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Synthesis and structure–activity studies of schweinfurthin B analogs: Evidence for the importance of a D-ring hydrogen bond donor in expression of differential cytotoxicity

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Abstract—The synthesis and biological evaluation of several enantioenriched schweinfurthin B analogs were undertaken to develop structure–activity relationships and guide design of probes for their putative molecular target. The desired 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. Preparation 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 is described. Several of these analogs displayed cytotoxicity patterns well-correlated with the natural product and differences in activity of $\sim 10^3$ across the various cell lines. Together, these assay results indicate the importance of at least one free phenol group on the aromatic D-ring of this system for differential cytotoxicity.

1. Introduction

The schweinfurthins are a small set of natural stilbenes isolated from the African tree *Macaranga schweinfurthii* at the National Cancer Institute (NCI) in the late 1990s.[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**, Fig. 1) presented mean GI_{50}'s of 0.36 and 0.81 μM, respectively, but the more sensitive cell lines were affected by nanomolar concentrations, while the more resistant cell lines tolerated micromolar levels. Schweinfurthin D (**4**) was found to be equipotent with schweinfurthin B (**2**),[1b] while the fourth member of this family, schweinfurthin C (**3**), lacks the hexahydroxanthene system and displayed negligible cytotoxicity in initial screens. Vedelianin (**5**), a closely related natural product, has been shown to have cytotoxic activity similar to that of schweinfurthin A (**1**).[2]

The NCI has developed a bioinformatics algorithm known as COMPARE to identify correlations between patterns of cytotoxic activity in its 60 cell-line assay.[3] Compounds which act on the same molecular target typically display a high degree of correlation across the various cell lines and subpanels of the screen. The schweinfurthins were particularly potent inhibitors of CNS, renal, leukemia, and some breast cancer cell lines, 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; this may indicate that these compounds act via a novel cellular pathway or target.[4] However, we noted that the pattern of cell growth inhibition was strongly correlated to the cephalostatins, which also act at an as yet unknown target.[5] While considerably less potent than the most active cephalostatins, where mean GI_{50}'s as low as ~1 nM are known, the schweinfurthins are much more amenable to synthetic manipulation.[6] We have postulated that these two classes of compounds may act through a common pathway,

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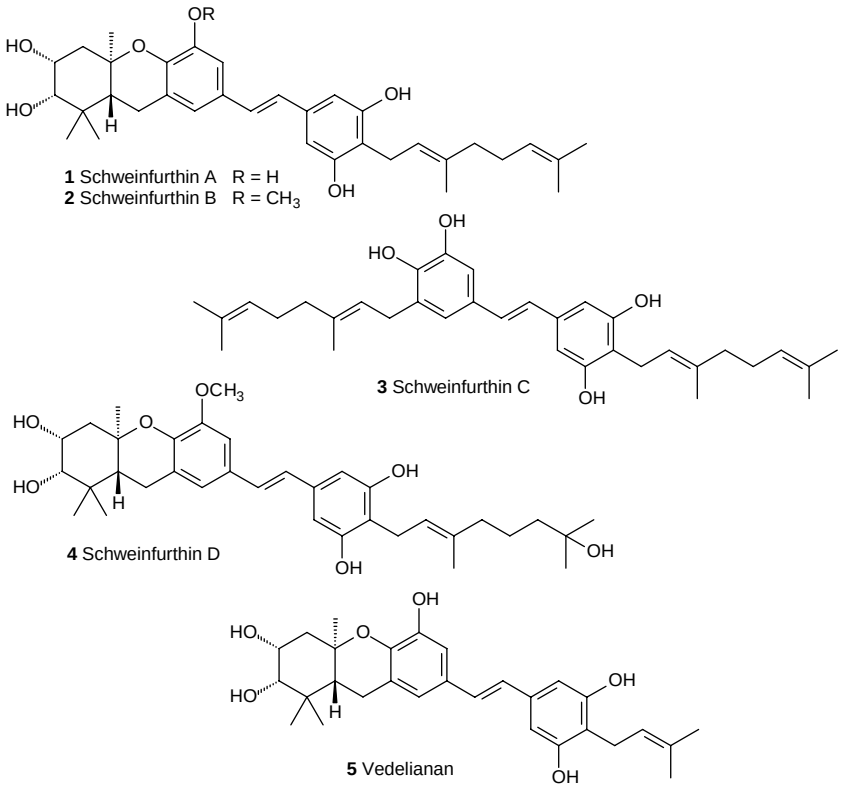


Figure 1. The schweinfurthin family and related natural products.

though not necessarily at the same point. All comparative studies of schweinfurthins and cephalostatins to date have found similar effects on cell morphology, time course of cell death, and a lack of effect on the cell cycle. Because of their intriguing activity as well as our ongoing interest in chemotherapeutic chemistry[7] and prenylated aromatics in general,[8] an effort to explore the activity of some schweinfurthin analogs was initiated. We hoped to identify themes in structure–activity relationships within the schweinfurthin class which could be used to design probes of the postulated molecular target responsible for growth inhibition in sensitive cell lines.

Our synthetic strategy involves a late stage introduction of the central stilbene olefin via a Horner–Wadsworth–Emmons (HWE) olefination (Fig. 2). This allows maximum convergence and facilitates introduction of changes in the right-half architecture. Early work on the simplest member of the family, schweinfurthin C, required synthesis of the right-half phosphonate **6**[9] which also could serve as a synthon for schweinfurthins A and B. We targeted schweinfurthin B to derive the C-ring, including the methoxy group, from vanillin (**8**). Two routes that use cationic cascade cyclizations to effect formation of the A- and B-rings of the tricyclic system have been explored (Fig. 3). The first such process employed a phenylselenide substituent (i.e., compound **9**[10]) to direct a diastereoselective cascade,[8] ultimately leading to tricyclic olefin **10**. After some experimentation, a pathway involving a more biomimetic cyclization[11] of epoxide **11** was found to afford tricyclic aldehyde **12**.[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 similar enantiopurity.

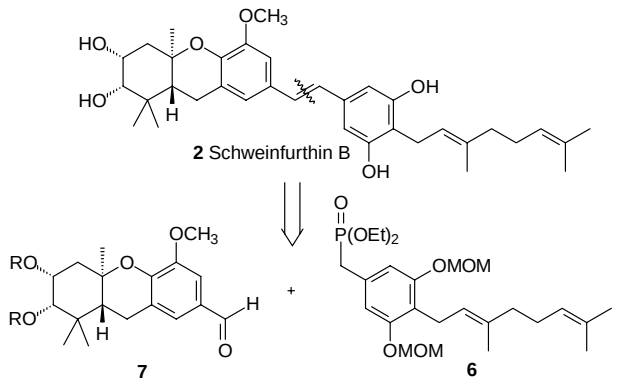


Figure 2. The HWE strategy.

To complete synthesis of a tetracyclic schweinfurthin, aldehyde **12** was condensed with the natural right-half synthon, phosphonate **6**. Final deprotection of the resulting stilbene afforded 3-deoxyschweinfurthin B (**13**), and this compound has shown biological activity comparable to that of the natural product (vide infra). Thus, the opportunity to explore the effect of right-half modifications on the bioactivity and physical properties of the schweinfurthins was presented. Such studies also might help to overcome a tendency toward oxidation noted during the isolation of the natural products and presumed to result from the resorcinol moiety. Finally,

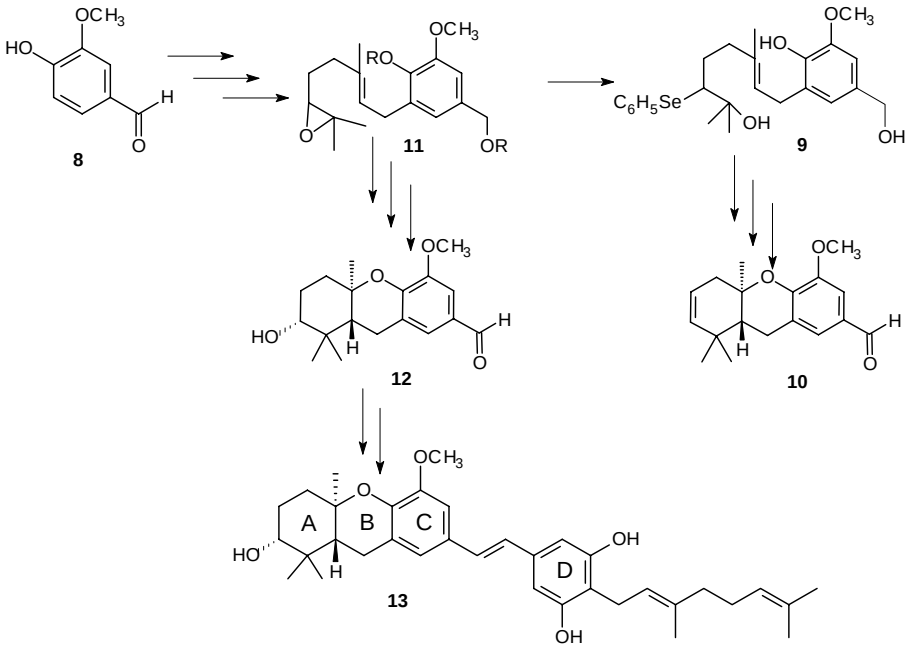


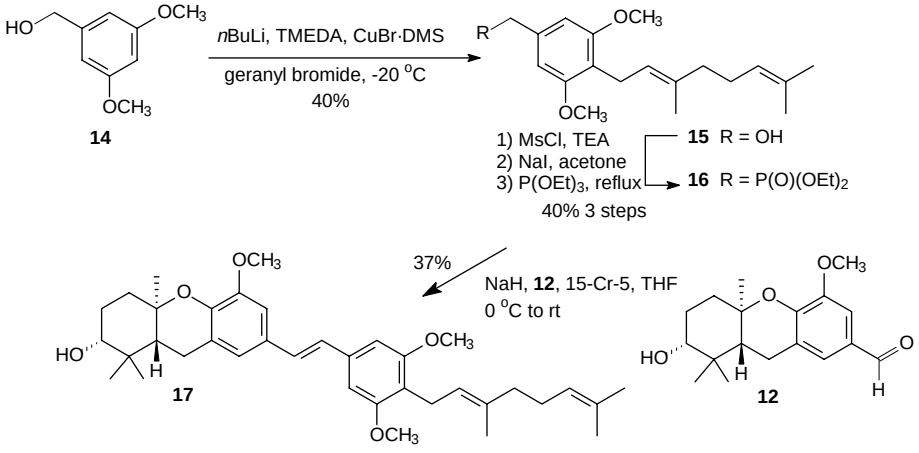
Figure 3. Previous synthetic work.

and most importantly, preparation of a series of analogs might allow identification of a position to introduce functionality for construction of affinity reagents or fluorescent analogs that would be useful in mechanism of action studies.[13]

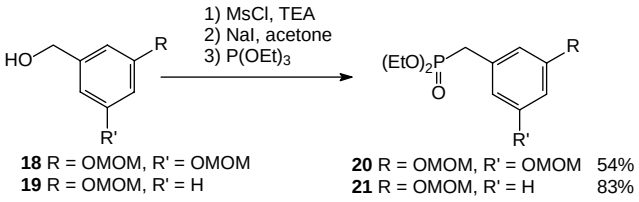
2. Chemical synthesis

Dimethoxy-3-deoxyschweinfurthin B (**17**) was selected as the first target of these studies, in order to block the potential of phenolic hydroxyls to become hydrogen bond donors. A path to the requisite phosphonate **16** commenced with the commercial 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.[14] 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[15] of phosphonate **16** with aldehyde **12** afforded the desired dimethoxy-3-deoxyschweinfurthin B (**17**) in modest yield.

Through very similar chemistry the phosphonates **20** and **21**, that both lack the geranyl chain, were prepared (Scheme 2). Thus, the methoxymethyl-protected benzylic alcohols **18**[16] and **19**[17] 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.



Scheme 1.

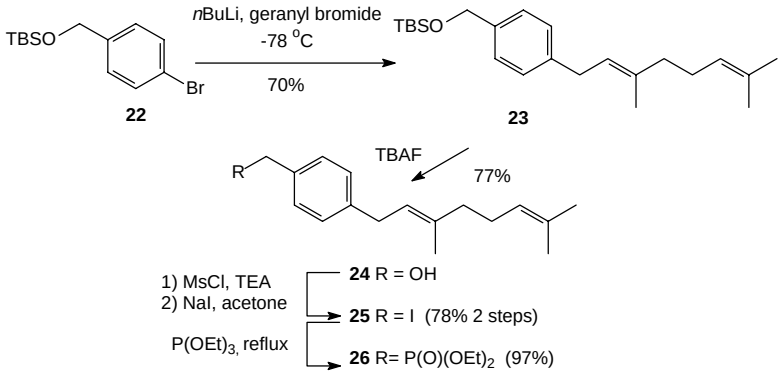


Scheme 2.

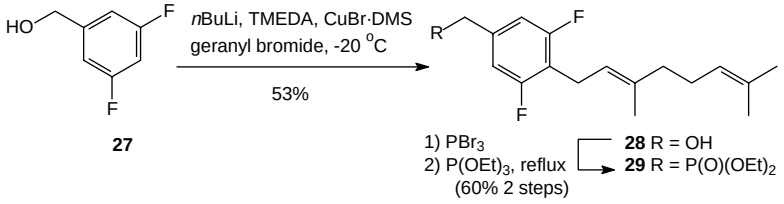
The phosphonate **26** (Scheme 3), which lacks both of the resorcinol hydroxyl groups while retaining the geranyl chain, was obtained by alkylation of the organolithium reagent derived by halogen metal exchange of known aryl bromide **22**.[18] The resulting geranylated arene **23** was then allowed to react with fluoride ion to remove the silyl ether-protecting group and afford benzylic alcohol **24**. A series of three steps parallel to those used in preparation of compound **16** was employed to convert alcohol **24** to phosphonate **26** in excellent yield.

Difluorophosphonate **29**, in which the phenolic groups are replaced by fluorine, was synthesized from the commercial alcohol **27** (Scheme 4). Treatment of this alcohol under the optimized directed *ortho* metalation (D*o*M) 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**.

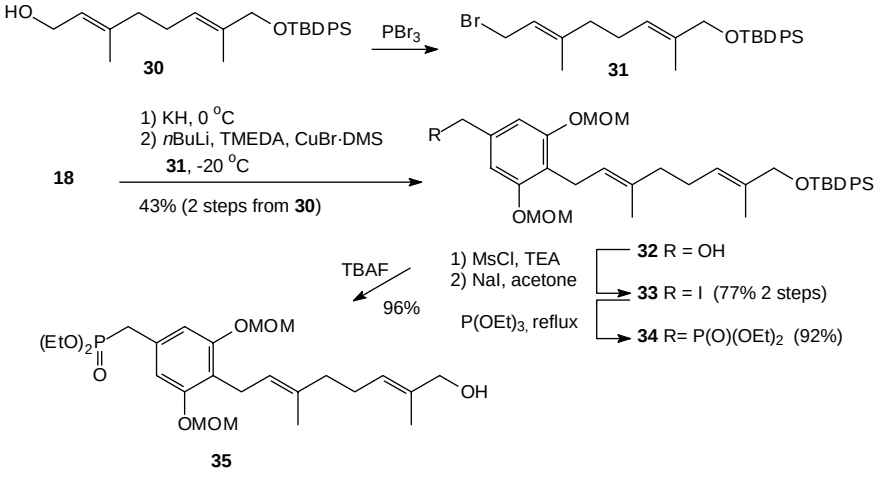
To obtain phosphonate **35**, which carries a terminal primary hydroxyl group, the requisite allyl bromide



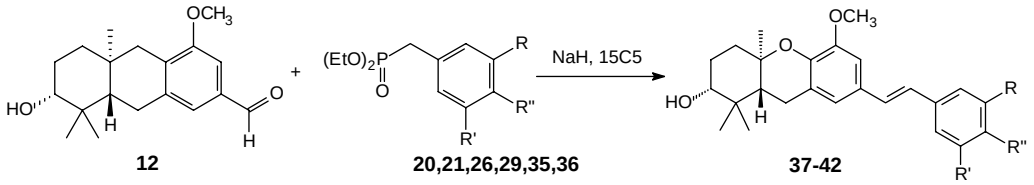
Scheme 3.



Scheme 4.



Scheme 5.



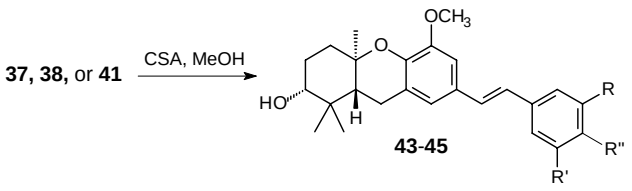
Scheme 6.

Table 1. HWE coupling reactions

Phosphonate	R	R′	R″	Stilbene	Yield (%)
20	OMOM	OMOM	H	**37**	91
21	OMOM	H	H	**38**	62
26	H	H	$C_{10}H_{17}$	**39**	55
29	F	F	$C_{10}H_{17}$	**40**	85
35	OMOM	OMOM	$C_{10}H_{16}OH$	**41**	60
36	H	H	H	**42**	90

31 was synthesized from the known silyl ether **30**[19] by treatment with PBr_3. The benzylic alcohol **18** (Scheme 5) then was treated with KH followed by D*o*M 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.

With a representative group of phosphonates in hand, exploration of the required HWE couplings was initiated. Phosphonates **20**, **21**, **26**, **29**, and **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[20] to free the phenolic hydroxyl groups (Scheme 7, Table 2) and afford the desired compounds **43**–**45**.



Scheme 7.

Table 2. Removal of MOM ether protecting groups

Protected stilbene	R	R′	R″	Product	Yield (%)
37	OH	OH	H	**43**	93
38	OH	H	H	**44**	63
41	OH	OH	$C_{10}H_{16}OH$	**45**	42

3. Biological data and discussion

Synthetic 3-deoxyschweinfurthin B has been tested in the 60 cell-line assay and was found to have activity very much comparable to that of the natural products (mean GI_{50} = 0.74 μM). Even more importantly the differential activity across the cell lines was correlated with the natural schweinfurthin B (correlation coefficient = 0.75, Fig. 4), suggesting that the synthetic compound was operating at the same, and as yet unknown, molecular or cellular target.

The seven new analogs (**17**, **39**, **40**, and **42**–**45**) were tested in the NCI 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 terminal primary hydroxyl group, compound **45**. While the mean GI_{50} values suggest weakly toxic compounds, the more sensitive cell lines were affected at nanomolar levels, and the unique pattern of schweinfurthin activity was observed in several of the analogs. The schweinfurthins are effective over 3 orders of magnitude in concentration, with the most sensitive cells including the CNS-derived lines SF-295, SNB-75, and U-251, while the entire lung, colon, and ovarian panels show very little sensitivity.

Our initial hypothesis was that the basis for differential activity resided within the left half of the structure. The dimethoxy derivative **17** was targeted with the expectation that it would be more stable than the parent resorcinols but still retain the cytotoxic profile of the family. Unfortunately, this proved not to be the case, since dimethoxy-3-deoxyschweinfurthin B (**17**) was ~10-fold less cytotoxic than the parent 3-deoxyschweinfurtin B. More intriguing was the differential cytotoxicity displayed by this analog. While some differential activity across the tested cell lines was observed, 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 3). Clearly this result shows that methylation of the phenols is not well tolerated, but these findings also raise a question of how these groups function.

To probe the activity of a compound without H-bond acceptors in the D-ring, the difluorinated compound **40** was tested. This compound was found to have the

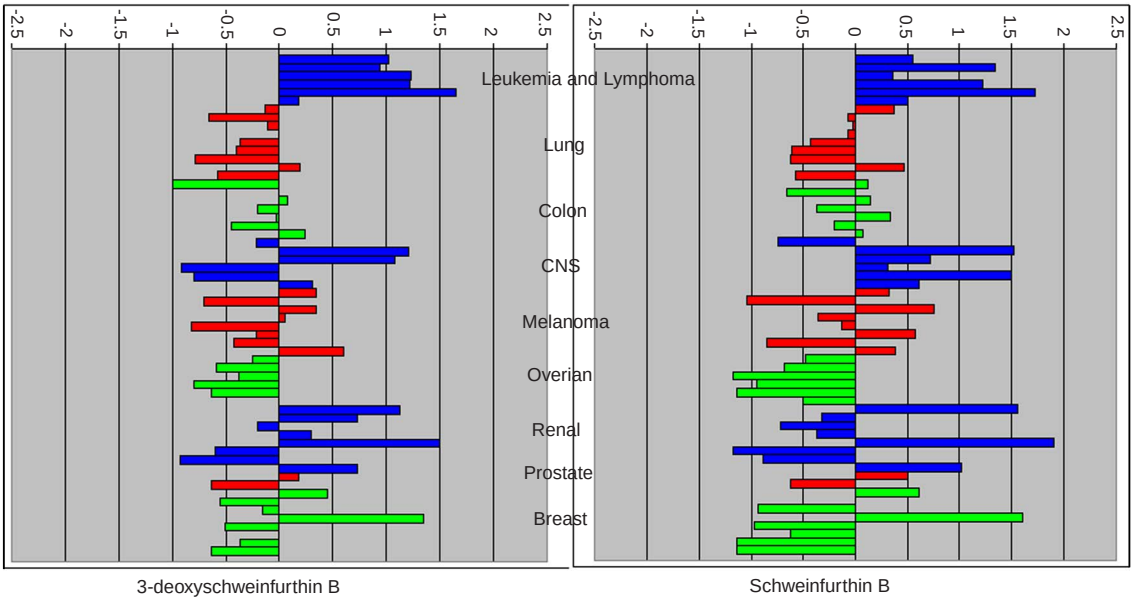


Figure 4. Mean graph comparison of 3-deoxyschweinfurthin B (**13**) and schweinfurthin B (**2**). Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI_{50} level, data are presented so that positive deviations indicate more potent cytotoxicity. Approximate regions of several subpanels are indicated. Complete 60 cell-line data are presented in the Supplemental material.

Table 3. Cytotoxic activity of the schweinfurthin analogs and the correlation matrix for the 60 cell-line assay, both at the GI_{50} level

Compound	**1**	**13**	**2**	**45**	**44**	**17**	**43**	**42**	**39**	**40**	Mean GI_{50} (μM)	Range at GI_{50} (log units)
1	1.00										0.40	3.14
13	0.75	1.00									0.74	2.63
2	0.91	0.75	1.00								0.79	3.08
45	0.74	0.80	0.78	1.00							1.0	2.39
44	0.64	0.65	0.72	0.62	1.00						3.8	1.94
17	0.46	0.39	0.42	0.34	0.18	1.00					6.6	2.52
43	0.38	0.50	0.46	0.42	0.45	0.42	1.00				7.8	2.41
42	0.31	0.31	0.29	0.50	0.25	0.15	0.24	1.00			15	1.20
39	0.12	0.01	0.05	0.15	−0.08	0.34	0.10	0.30	1.00		19	0.79
40	−0.07	−0.05	−0.17	0.02	−0.08	0.08	0.04	0.00	0.59	1.00	42	1.63

Pearson correlation coefficients were calculated based on comparisons of common cell lines for each pair of compounds. The range represents the differential in log10 units between the least and most sensitive cell lines in the experiment.

weakest antitumor activity of all the analogs tested so far, as well as a 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 both of the resorcinol oxygens. The compounds show very weak cytoxicity (mean GI_{50}'s of 19 and 15 μM, respectively) and virtually no differential cytotoxicity (i.e., a ∼10-fold concentration differential between most and least sensitive cell lines, also reflected in the poor correlation to compound **2**).

Once the importance of the phenolic hydrogen was clear, implicating this substructure as a hydrogen bond donor, it was intriguing to ascertain the requirements for the geranyl chain. Schweinfurthin D (**4**), which shows cytotoxicity similar to that of 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 toward deciphering the role of the geranyl chain it seemed appropriate to test whether or not simple deletion of this substructure would affect the activity.

Compound **43**, which lacks the geranyl chain, was shown to be ∼10 times less active (mean GI_{50} = 7.8 μM) than 3-deoxyschweinfurthin B (**13**). It does however show a modest degree of correlation in its pattern of differential activity (correlation coefficient = 0.46 vs **2**) with the natural product. This result supports installation of other motifs at this position to identify an affinity probe. Compound **43** still shows the same propensity for degradation as other stilbenes bearing the resorcinol hydroxyl groups. Because a formal deletion of one of the D-ring hydroxyl groups might be expected to improve stability, the phenol **44** was tested and found to be twofold more cytotoxic than resorcinol **43** (mean GI_{50} = 3.8 μM). Even more importantly, phenol **44** was found to have differential activity highly correlated with that of the natural product (correlation coefficient = 0.72).

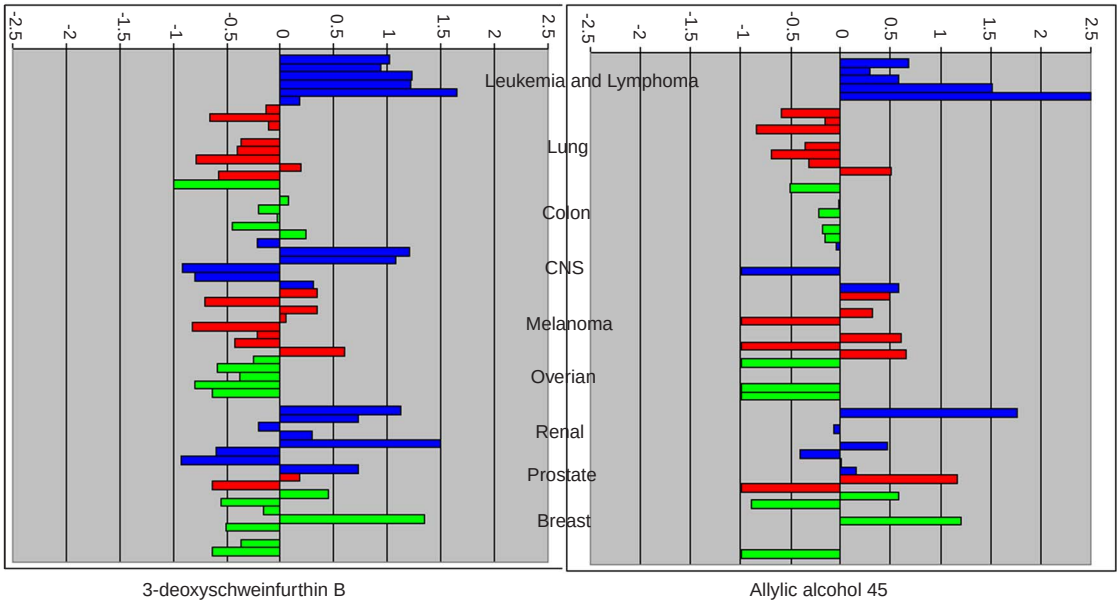


Figure 5. Mean graph comparison of 3-deoxyschweinfurthin B (**13**) and allylic alcohol **45**. Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI_{50} level, data are presented so that positive deviations indicate more potent cytotoxicity. Complete 60 cell line data are available in the Supplemental material.

Based on these results at least one of the D-ring hydroxyl groups appeared to be crucial to activity, whereas the geranyl chain clearly was amenable to some modification. In order to test our hypothesis that the terminus of the geranyl system could be used as a point of attachment to some form of affinity reagent, it would be necessary to append a 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, and this compound showed very good activity (Fig. 5). It was nearly as potent (mean GI_{50} = 1.0 μM) as schweinfurthin B or 3-deoxyschweinfurthin B, and its activity was highly correlated to the natural product (correlation coefficient = 0.78 vs **2**) and the 3-deoxy analog (0.80). Of special interest, compound **45** shows activity at nanomolar levels against the leukemia-derived RPMI-8226 and the renal-derived 786-0 cell lines (3.2 and 17 nM, respectively), which suggests that it may be a useful mechanistic probe in these lines.

4. Conclusions

The schweinfurthins offer 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 study of these compounds by making available synthetic analogs with high activity and more favorable chemical properties than the natural products. The discovery of 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, may be suitable for 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.

5. Experimental

5.1. General experimental conditions

THF was freshly distilled from sodium/benzophenone, while CH_2Cl_2 and Et_3N were freshly distilled from CaH. All reactions in non-aqueous solvents were conducted in oven-dried glassware under positive pressure of argon, with magnetic stirring. Methanesulfonyl chloride was purchased commercially and distilled from P_2O_5. NMR spectra were recorded at 300 MHz for ^1H, and 75 MHz for ^{13}C with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards unless otherwise noted. Correlation coefficients were calculated using Excel with the Pearson method excluding data points for cell lines which were not present for both compounds being compared. High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed at an outside facility.

5.2. [4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxy-phenyl]-methanol (15)

*n*BuLi (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

1 N NH_4Cl, the aqueous layer was neutralized to pH 7 with 1 N HCl, and this layer was 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 chromatography (20% EtOAc in hexanes) afforded alcohol **15** (76 mg, 40%) as a clear oil. ^1H NMR δ 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 δ 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.

5.3. [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_3N (0.3 mL 1.9 mmol) in CH_2Cl_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 H_2O, and extracted with EtOAc. The combined organic layers were washed with NH_4Cl (sat), brine, dried ($MgSO_4$), 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 $NaHCO_3$ and then with $Na_2S_2O_3$ until the color faded, it was extracted with ether and the combined organic layers were dried ($MgSO_4$) 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 ($MgSO_4$), 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, $J_{PH} = 21.5$ 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); ^{13}C NMR δ 160.9 (d, $J_{CP} = 3.1$ Hz, 2C), 137.5, 134.1, 132.9 (d, $J_{CP} = 9.0$ Hz), 127.5, 125.7 (d, $J_{CP} = 2.9$ Hz), 120.1 (d, $J_{CP} = 3.4$ Hz), 108.6 (d, $J_{CP} = 6.7$ Hz, 2C), 65.1 (d, $J_{CP} = 6.7$ Hz, 2C), 58.7 (2C), 42.8, 37.1 (d, $J_{CP} = 137.3$ Hz), 29.7, 28.6, 24.9, 20.6, 19.4 (d, $J_{CP} = 6.0$ Hz, 2C), 18.9; ^{31}P NMR δ +26.4; HRMS (EI) calcd for $C_{23}H_{37}O_5PNa$ [M^++Na], 447.2276; found 447.2265.

5.4. Dimethoxy-3-deoxyschweinfurthin 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 h. The solution was quenched with water, extracted (ether), and the combined organic layers were washed with brine. The residual organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Final purification by column chromatography (50% EtOAc in hexanes) afforded the target schweinfurthin analog **17** (6.4 mg, 37%) as a clear oil: ^1H 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.

5.5. (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 Et_3N (2.2 mL 15.76 mmol) in CH_2Cl_2 (150 mL). 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 NH_4Cl (sat), brine, dried ($MgSO_4$), 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 $NaHCO_3$ and then with $Na_2S_2O_3$ until the color faded, it was extracted with ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Final purification of the residue by flash chromatography (30% EtOAc in hexanes) afforded compound iodide (1.12 g, 84%) as a yellow oil: ^1H 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 (EI) calcd for $C_{11}H_{15}O_4I$ [M^+], 338.0015; found 338.0016. A stirred solution of this iodide (1.11 g, 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: ^1H NMR δ 6.58–6.55 (m, 3H), 5.06 (s, 4H), 3.97 (m, 4H), 3.39 (s, 6H), 3.01 (d, $J_{PH} = 21.6$ Hz, 2H), 1.20 (tm, $J = 7.1$ Hz, 6H); ^{13}C NMR δ 158.2 (d, $J_{CP} = 3.2$ Hz, 2C), 133.8 (d, $J_{CP} = 8.8$ Hz), 111.2 (d, $J_{CP} = 6.5$ Hz, 2C), 103.5 (d, $J_{CP} = 3.4$ Hz), 94.4 (2C), 62.1 (d, $J_{CP} = 6.6$ Hz, 2C), 55.9 (2C), 33.9 (d, $J_{CP} = 138.1$ Hz), 16.3 (d, $J_{CP} = 6.1$ Hz, 2C); ^{31}P NMR δ +25.7. Anal. Calcd for $C_{15}H_{25}O_7P$: C, 51.72; H, 7.23. Found: C, 51.55; H, 7.27.

5.6. (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_3N (0.5 mL 3.6 mmol) in CH_2Cl_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_2O, and extracted with EtOAc. The combined organic layers were washed with NH_4Cl (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 $Na_2S_2O_3$ until the color faded, it was extracted with ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was added to triethyl phosphite (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 ($MgSO_4$), 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: ^{1}H 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, J_{PH} = 21.6 Hz, 2H), 1.27–1.22 (m, 6H); ^{13}C NMR δ 157.1 (d, J_{CP} = 3.2 Hz), 132.9 (d, J_{CP} = 8.9 Hz), 129.2 (d, J_{CP} = 3.1 Hz), 123.1 (d, J_{CP} = 6.5 Hz), 117.5 (d, J_{CP} = 6.5 Hz), 114.5 (d, J_{CP} = 3.5 Hz), 94.1, 61.8 (d, J_{CP} = 6.7 Hz, 2C), 55.6, 33.4 (d, J_{CP} = 137.2 Hz), 16.1 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ +25.8. Anal. Calcd for $C_{13}H_{21}O_5P$: C, 54.16; H, 7.34. Found: C, 53.98; H, 7.35.

5.7. tert-Butyl-[4-(3,7-dimethyl-octa-2,6-dienyl)-benzyloxy]-dimethyl-silane (23)

*n*BuLi (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, quenched by addition of H_2O, and then extracted with ether. The combined organic layers were washed with NH_4Cl (sat), brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by flash chromatography (hexanes) afforded compound **23** (2.61 g, 70%) as a light yellow oil: ^{1}H 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); ^{13}C 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.

5.8. [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_4Cl (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 chromatography (20% EtOAc in hexanes) afforded compound **24** (1.35 g, 77%) as a light yellow oil: ^{1}H NMR δ 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_2O), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR δ 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 (EI) calcd for $C_{17}H_{24}O$ [M^+], 244.1827; found 244.1832.

5.9. 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_3N (3 mL 21.5 mmol) in CH_2Cl_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_4Cl (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 $NaHCO_3$ and then with $Na_2S_2O_3$ until the color faded, the aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Final purification of the residue by flash chromatography (20% EtOAc in hexanes) afforded compound **25** (1.44 g, 78%) as a yellow oil: ^{1}H 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); ^{13}C 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 (EI) calcd for $C_{17}H_{23}$ [M^+−I], 227.1800; found 227.1801.

5.10. Diethyl[4-(3,7-dimethyl-octa-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: ^{1}H NMR δ 7.22–7.18 (m, 2H), 7.12–7.09 (m, 2H), 5.33–5.29 (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, J_{PH} = 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); ^{13}C NMR δ 140.6 (d, J_{CP} = 3.8 Hz),

136.5, 131.7, 129.8 (d, J_{CP} = 6.5 Hz, 2C), 128.9 (d, J_{CP} = 9.3 Hz), 128.7 (d, J_{CP} = 3.1 Hz, 2C), 124.5, 123.1, 62.2 (d, J_{CP} = 6.8 Hz, 2C), 39.9, 34.4, 32.6 (d, J_{CP} = 138.2 Hz), 26.8, 26.0, 17.9, 16.6 (d, J_{CP} = 6.1 Hz, 2C), 16.3; ^{31}P NMR δ +26.6. Anal. Calcd for $C_{21}H_{33}O_3P$: C, 69.21; H, 9.13. Found: C, 69.09; H, 9.16.

5.11. [4-(3,7-Dimethyl-octa-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 *n*BuLi (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 1 N NH_4Cl, 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 ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded alcohol **28** (68 mg, 53%) as a clear oil: ^{1}H 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 D_2O 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); ^{13}C 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 $C_{17}H_{22}F_2O$ [M^+], 280.1639; found 280.1639.

5.12. [4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-benzyl]-phosphonic acid diethyl ester (29)

PBr_3 (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 ($MgSO_4$) 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 ($MgSO_4$), 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: ^{1}H 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); ^{13}C 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; ^{31}P NMR δ +24.8 (t, J_{PF} = 2.3 Hz). Anal. Calcd for $C_{21}H_{31}F_2O_3P$: C, 62.99; H, 7.80. Found: C, 63.22; H, 7.98.

5.13. {4-[8-(tert-butyl-diphenyl-silanyloxy)-3,7-dimethyl-octa-2,6-dienyl]-3,5-bis-methoxymethoxy-phenyl}-methanol (32)

PBr_3 (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 ($MgSO_4$) and concentrated in vacuo to give a yellow residue, bromide **31**. A solution of benzylic alcohol **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 *n*BuLi (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 1 N NH_4Cl, and the aqueous layer was neutralized to pH 7 with 1 N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash chromatography (20% EtOAc in hexanes) afforded compound **32** (341 mg, 43% from alcohol **30**) as a clear oil: ^{1}H 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); ^{13}C 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 $C_{37}H_{50}O_6Si$: C, 71.81; H, 8.14. Found: C, 71.72; H, 7.98.

5.14. tert-Butyl-[8-(4-iodomethyl-2,6-bis-methoxymethoxy-phenyl)-2,6-dimethyl-octa-2,6-dienyloxy]-diphenylsilane (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 Et_3N (0.2 mL 1.4 mmol) in CH_2Cl_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 H_2O, and extracted with EtOAc. The combined organic layers were washed with NH_4Cl (sat) and brine, dried ($MgSO_4$), 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 $NaHCO_3$ and then with $Na_2S_2O_3$ 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 chromatography (30% EtOAc in hexanes) afforded the iodide **33** (347 mg, 77%) as a yellow oil: ^{1}H NMR δ 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 δ 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 $C_{37}H_{49}IO_5Si$ [M^+], 728.2394; found 728.2395.

5.15. {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 a light yellow oil: ^{1}H NMR δ 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 (trm, 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 (trm, J = 7.08 Hz, 6H), 1.06 (s, 9H); ^{13}C NMR δ 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 δ +26.2. Anal. Calcd for $C_{41}H_{59}O_8PSi$: C, 66.64; H, 8.05. Found: C, 66.58; H, 8.32.

5.16. [4-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-3,5-bis-methoxymethoxy-benzyl]-phosphonic acid diethyl ester (35)

TBAF (0.3 mL, 1 M 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 chromatography (gradient, 60–100% EtOAc in hexanes) afforded compound **35** (36 mg, 96%) as a clear oil: ^{1}H NMR δ 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 (trm, J = 6.8 Hz, 6H); ^{13}C NMR δ 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 δ +26.2; HRMS (EI) calcd for $C_{25}H_{41}O_8P$ [M^+], 500.2539; found 500.2531.

5.17. 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) were added phosphonate **20** (25 mg, 0.12 mol) and aldehyde **12** (20 mg, 0.066 mmol) at 0 °C. 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 ($MgSO_4$), and concentrated in vacuo, final purification by flash 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 (EI) calcd for $C_{29}H_{38}O_7$ [M^+], 498.2618; found 498.2608.

5.18. 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 were 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 ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by flash 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 $C_{27}H_{34}O_5$ $(M+H)^+$, 439.2484; found 439.2475.

5.19. 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 mixture was allowed to warm to rt and stir for 19 h. Water was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine and dried ($MgSO_4$). Concentration in vacuo afforded a yellow oil and final purification by column chromatography (50% EtOAc in hexanes) gave the stilbene **39** (26 mg, 55%) as a clear oil: ^{1}H 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); ^{13}C 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 $C_{35}H_{46}O_3$ (M^+) 514.3447; found 514.3447.

5.20. 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) were 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 ($MgSO_4$), and concentrated in vacuo. Final purification of the residue by flash chromatography (50% EtOAc in hexanes) afforded compound **40** (30.9 mg, 85%) as a clear oil: ^{1}H 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); ^{13}C NMR δ 163.4–160.0 (dd, J_{CF} = 241.8 Hz, J_{CF} = 9.8 Hz, 2C), 149.3, 143.4, 137.9, 136.8, 131.7, 130.5, 124.5 (t, J_{CF} = 9.5 Hz), 124.3, 123.0, 121.1, 120.8, 115.9 (t, J_{CF} = 23.4 Hz), 110.0, 108.7 (dd, J_{CF} = 26.6 Hz, J_{CF} = 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, J_{CF} = 2.0 Hz), 20.1, 17.8, 16.2, 14.5; HRMS (EI) calcd for $C_{35}H_{44}O_3F_2$ [M^+], 550.3259; found 550.3256.

5.21. 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 (5 mL) were 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 ($MgSO_4$), and concentrated in vacuo. Purification of the resulting oil by flash chromatography (50% EtOAc in hexanes) afforded compound **41** (20.5 mg, 60%) as a clear oil: ^{1}H 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); ^{13}C NMR δ 156.1 (2C), 149.2, 142.8, 137.0, 134.9, 134.4, 129.1, 128.6, 126.6, 126.2, 123.3, 122.8, 120.8, 119.7, 107.1, 106.3 (2C), 94.8 (2C), 78.3, 77.4, 69.2, 56.2 (2C), 47.0, 39.6, 38.6, 37.9, 28.5, 27.6, 26.3, 23.4, 22.9, 20.1, 16.3, 14.5, 14.3, 13.9; HRMS (EI) calcd for $C_{39}H_{54}O_8$ [M^+], 650.3819; found 650.3812.

5.22. 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 μL, 3 mol %) in THF (5 mL) were 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 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 $C_{25}H_{30}O_3$ [M^+], 378.2195; found 378.2195.

5.23. 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 chromatography (60% EtOAc in hexanes) afforded compound **43** (23 mg, 93%) as a clear oil: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 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_3OD) δ 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.

5.24. 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 chromatography (60% EtOAc in hexanes) afforded compound **44** (9 mg, 63%) as a clear oil: ^{1}H NMR δ 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_2O), 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_2O), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 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 $C_{25}H_{30}O_4$ ($M+H^+$), 395.2222; found 395.2237.

5.25. 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 ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (80% EtOAc in hexanes) afforded compound **45** (6 mg, 42%) as a clear oil: ^{1}H NMR δ 6.94–6.73 (m, 4H), 6.49 (s, 2H), 5.40 (s, 2H, exchangeable with D_2O), 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 D_2O), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C 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 $C_{35}H_{46}O_6$ [M^+], 561.3216; found 561.3214.

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Supplementary data

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **16**, **17**, **24**, **25**, **28**, **33**, **35**, and **37**–**45**, a table of elemental analyses, and complete assay data from the 60 cell line screen for compounds **17**, **39**, **40**, and **42**–**45** can be found here. This material is available free of charge via the Internet. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2005.10.025.

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