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Silyl Triflate-Mediated Ring-Closure and Rearrangement in the Synthesis of Potential Bisfuran-Containing Intermediates of Aflatoxin Biosynthesis

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Abstract: The biosynthetic pathway to the potent mycotoxin aflatoxin B_1 is unusually long and complex, proceeding from anthraquinone to xanthone to coumarin nuclear types bearing fused tetrahydro- and bisdihydrofuran rings. A synthetic strategy is described involving two silyl triflate-mediated cyclization and rearrangement processes that have enabled both furofuran oxidation states to be readily achieved and undesired but thermodynamically favorable side reactions to be avoided in the preparation of these ring systems. In the first an *o*-methoxymethyl phenylacetaldehyde is cyclized directly to the five-membered, differentially protected hemiacetal, while in the second this group, appropriately substituted, can be rearranged to a 4-trialkylsilyloxy-2,5-methano-1,3-benzodioxepane. The latter masked dialdehyde is sufficiently stable to strong base, mild acid, and oxidants to allow all needed aryl ring systems to be constructed. Using these methods, total syntheses of (±)-versicolorin B, (±)-versicolorin A, its hemiacetal, and its 6-deoxy derivative, (±)-6-deoxyversicolorin A, have been achieved, and these are reported herein, as well as preparation of the methyl ester of a putative *o*-carboxybenzophenone biosynthetic intermediate. In work described elsewhere, incorporation experiments with ^{13}C-labeled forms of these compounds have made possible the complete elucidation of bisfuran biosynthesis characteristic of the first major phase of aflatoxin formation in vivo.

Elucidation of the biosynthesis of aflatoxin B_1 (AFB_1, **6**) has depended on the synthesis of advanced potential intermediates in the pathway, often in isotopically labeled form. Aflatoxin is a potent environmental carcinogen arising from the fungal infection of food grains and nuts by certain *Aspergillus* species and is one of the most highly rearranged polyketide natural products known.[1] It is formed in at least 15 enzymic steps from the first stable intermediate, norsolorinic acid (**1**), a C_{20} anthraquinone, through the cleavage, rearrangement, and methylation of dihydrobisfuran versicolorin A (**4**, C_{18}) to sterigmatocystin (**5**, R = CH_3, R′ = H; C_{17}) and, finally, further oxidative transformation to the substituted coumarin AFB_1 (**6**, C_{16}; Scheme 1). While synthetic methods developed previously to investigate the early steps between **1** and **3** have been described, these have been concerned with the construction of the anthraquinone nucleus, notably by regiospecific phthalide anion addition to a benzyne,[2−4] and the oxidative rearrangement of averufin (**2**) to hydroxyversicolorone (**3**).[5,6] In this paper we focus on the

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(1) Minto, R. E.; Townsend, C. A. *Chem. Rev.* **1997**, *97*, 2537−2555.
(2) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 839−861.
(3) Townsend, C. A.; Whittamore, P. R. O.; Brobst, S. W. *J. Chem. Soc., Chem. Commun.* **1988**, 726−728.
(4) Townsend, C. A. *Pure Appl. Chem.* **1986**, *58*, 227−238.

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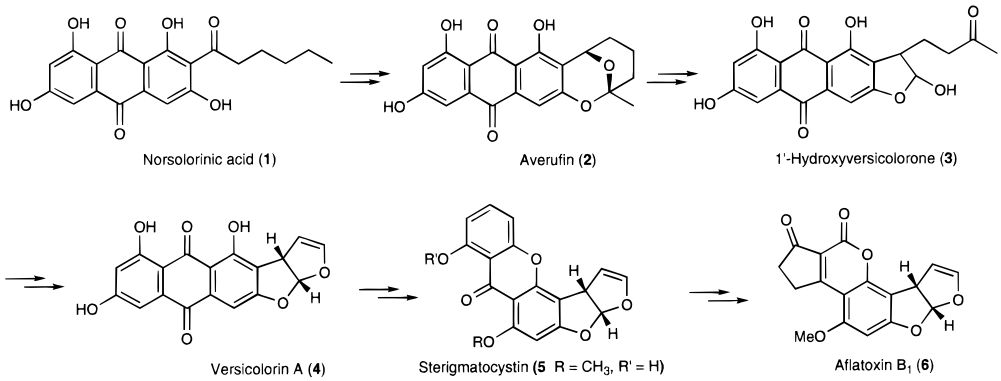
Scheme 1

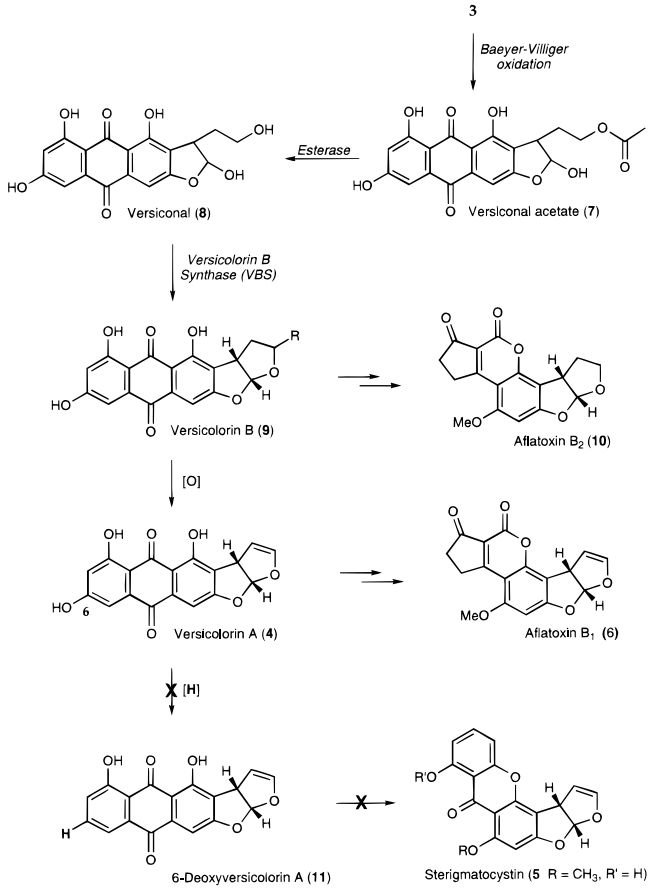


methods developed to synthesize tetrahydrobisfurans and the dihydrobisfuran ring system present in versicolorin A (**4**) and all later intermediates of the pathway. This characteristic structural element is rarely encountered among secondary metabolites and presents the synthetic task of introducing and preserving a labile masked dialdehyde. Solution of this and related problems is described in this paper, which has enabled delineation of the biochemical steps that occur in the formation of versicolorin A (**4**) and in its cleavage and rearrangement to xanthone products as sterigmatocystin (**5**, R = CH_3, R′ = H).

The biosynthesis of the dihydrobisfuran ring system in versicolorin A (**4**) is accomplished in five remarkably efficient steps, three of which are oxidative, as outlined in Scheme 2. The availability of synthetic materials was essential to unambiguously establishing the course of these biochemical events and in finally explaining misfounded and contradictory observations in the literature.[1,7−9] Oxidative rearrangement of averufin (**2**) gives hydroxyversicolorone (**3**),[3,10] and Baeyer−Villiger-like oxidation yields versiconal acetate (**7**).[11,12] Isolation of natural **3** and **7** revealed that each was a racemate (the 2′-center is benzylic and adjacent to a hemiacetal).[10] Cell-free experiments demonstrated the presence of an esterase[7,13,14] that releases the oxygen inserted into the carbon side chain to give (±)-versiconal (**8**), which is enzymically cyclized far faster than spontaneous chemical closure at neutral pH to the optically pure tetrahydrobisfuran, versicolorin B (**9**, R = H).[7,15] The enzyme that carries out this reaction, and sets the absolute configuration present in the eventual mycotoxin, is versicolorin B synthase (VBS), which has been purified,[16] characterized,[17] and cloned and overexpressed.[18]

Incorporation experiments with chemically pure, ^{13}C-labeled versicolorin B (**9**) and versicolorin A (**4**, Scheme 2) clearly

Scheme 2

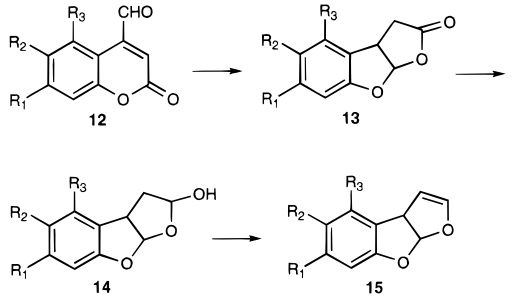


demonstrated that partitioning of tetrahydrobisfuran and dihydrobisfuran metabolites occurs in an irreversible oxidative step[7,9] that relates the former to the latter in a process believed now to be carried out by a P-450 oxygenase.[19] The double bond is not formed by dehydration of the oxidation product **9** (R = OH).[7]

The postbisfuran portion of the pathway beyond versicolorin A (**4**) is significantly less well-understood and is marked by nuclear rearrangements from the anthraquinone to the xanthone and coumarin structural types.[20,21] Demethylsterigmatocystin (**5** R = R′ = H, Scheme 2) has been implicated as the first

(5) Townsend, C. A.; Davis, S. G.; Koreeda, M.; Hulin, B. *J. Org. Chem.* **1985**, *50*, 5428−5430.
(6) Townsend, C. A.; Isomura, Y.; Davis, S. G.; Hodge, J. A. *Tetrahedron* **1989**, *45*, 2263−2276.
(7) McGuire, S. M.; Brobst, S. W.; Graybill, T. L.; Pal, K.; Townsend, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 8308−8309.
(8) Graybill, T. L.; Pal, K.; McGuire, S. M.; Brobst, S. W.; Townsend, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 8306−8308.
(9) Townsend, C. A.; Minto, R. E. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Eds.; Elsevier: Oxford, 1999; Vol. 1. (Sankawa, U., Volume Ed.), pp 443−471.
(10) Townsend, C. A.; Plavcan, K. A.; Pal, K.; Brobst, S. W.; Irish, M. S.; Ely, W. J.; Bennett, J. W. *J. Org. Chem.* **1988**, *53*, 2472−2477.
(11) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Am. Chem. Soc.* **1982**, *104*, 6154−6155.
(12) McGuire, S. M.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 653−656.
(13) Hsieh, D. P. H.; Wan, C. C.; Billington, J. A. *Mycopathologia* **1989**, *107*, 121−126.
(14) Hsieh, D. P. H.; Kusumoto, K.-I. *Can. J. Microbiol.* **1996**, *42*, 804−810.
(15) Yabe, K.; Hamasaki, T. *Appl. Environ. Microbiol.* **1993**, 2493−2500.
(16) Silva, J. C.; Townsend, C. A. *J. Biol. Chem.* **1996**, *272*, 804−813.
(17) McGuire, S. M.; Silva, J. C.; Casillas, E. G.; Townsend, C. A. *Biochemistry* **1996**, *35*, 11470−11486.
(18) Silva, J. C.; Minto, R. E.; Barry, C. E., III; Holland, K. A.; Townsend, C. A. *J. Biol. Chem.* **1997**, *271*, 13600−13608.
(19) Keller, N. P.; Segner, S.; Bhatnagar, D.; Adams, T. H. *Appl. Environ. Microbiol.* **1995**, *61*, 3628−3632.
(20) Chatterjee, M.; Townsend, C. A. *J. Org. Chem.* **1994**, *59*, 4424−4429.

Scheme 3



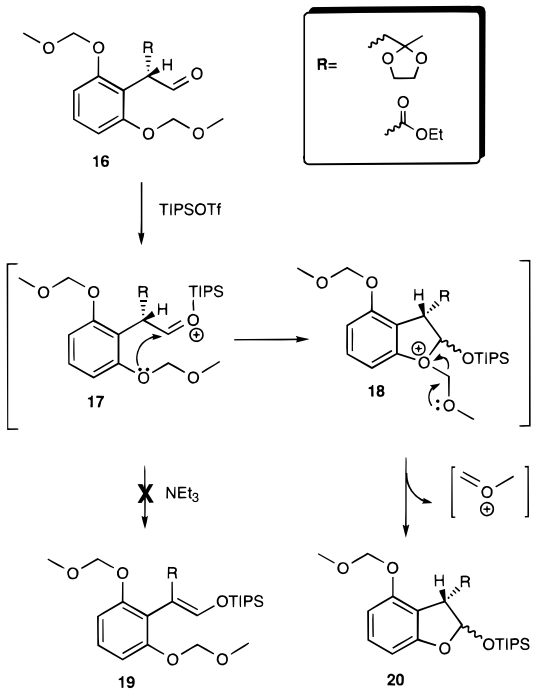
intermediate of these rearrangement reactions,[22,23] in which the 6-hydroxy group in **4** is no longer present in the xanthone. 6-Deoxyversicolorin A (**11**, Scheme 2), derived, in principle, from the precedented process of anthraquinone reductive dehydration,[24] could be invoked to explain this apparent deoxygenation. However, synthetic ^{13}C-labeled **11** failed to shown any detectable incorporation into AFB_1 under conditions where **4** was readily utilized. Another, as yet unknown, and more complex process must account for the skeletal reorganization and redox change between **4** and **5**.

Syntheses of Bisfuran-Containing Intermediates

The unique dihydrobisfuran structural element and environmental importance of AFB_1 have led to several partial syntheses and a limited number of total syntheses. The first construction of this ring system was carried out by Büchi (Scheme 3).[25−27] In that synthesis, reduction of the coumarin **12**, followed by acid-catalyzed rearrangement, gave the bisfuran lactone **13**. Reduction to the hemiacetal **14**, acetylation, and, finally, pyrolysis of the resulting acetate completed the first total synthesis of the aryl-fused dihydrobisfuran **15**. Several other laboratories have pursued analogous synthetic intermediates, some to complete formal total syntheses. These include Kuroda's quinone methide route to the aldehyde **12**;[28] Snieckus' aryl radical-induced ring closure of a phenolic butenolide,[29] as well as Snider's and Venkateswaran's cyclobutanone ring expansion approach to the bisfuranone **13**;[30,31] Pawlowski's Claisen rearrangement/oxidative cleavage approach to the hemiacetal **14**;[32] and Rapoport's enantiomeric oxaza-Cope route to the corresponding acetate.[33]

While these syntheses are efficient in the production of the dihydrobisfuran, the goal of this research was to devise a general procedure applicable to three nuclear types, including anthraquinone-, benzophenone-, or xanthone-fused dihydrobisfurans, as well as the introduction of isotopic label if desired.

Scheme 4



Silyl Triflate-Mediated Cyclization and Rearrangement

The dihydrobisfuran synthesis described in the following evolved from a series of observations and stepwise exploration of the chemical systems encountered. The first of these discoveries emerged during an earlier synthesis of 1′-hydroxyversicolorone (**3**).[3] As part of a routine effort to generate a silyl enol ether **19**, phenylacetaldehyde **16** was treated with triisopropylsilyl triflate (TIPSOTf) (Scheme 4). Presumed transient silylation of the aldehyde was followed by rapid intramolecular 5-*exo*-trig cyclization of the resultant oxonium ion **17** with one of the C_2-symmetric *ortho*-protected phenols rather than intermolecular deprotonation. Decomposition of the acetal protecting group **18** furnished 2-silyloxybenzofuran **20** as a mixture of geometric isomers. Thus, a fully differentiated benzofuran hemiacetal moiety was created and protected in a single step, with the concomitant removal of one methoxymethyl ether.

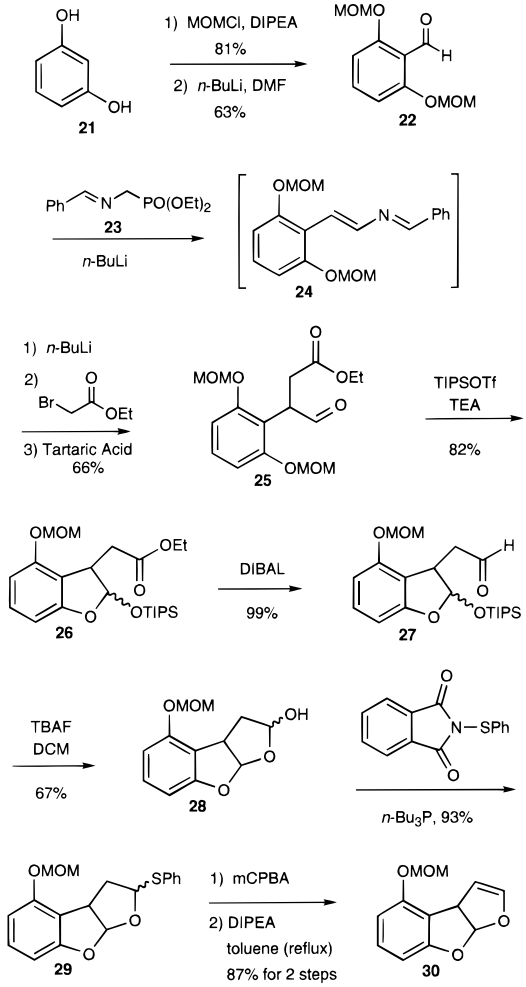
This discovery was turned to advantage in the synthesis of dihydrobisfuran-containing intermediates by modification of the alkyl substituent (Scheme 5). Intramolecular cyclization generated one furan ring, while the second was to be derived from a 2-alkanoate substituent. Therefore, the aryl-fused dihydrobisfuran **30** was pursued as the initial synthetic target, which could be incorporated into syntheses of several nuclear ring systems.

Preparation of **30** was initiated by protection of resorcinol (**21**) with methoxymethyl (MOM) chloride. In addition to their function as protecting groups, MOM ethers act as *ortho*-lithiation directors by inductively increasing the acidity of the *ortho* position while stabilizing the derived aryllithium in a six-membered chelate.[34−36] In this situation, *ortho*-lithiation followed by reaction with DMF and hydrolysis gave the benzaldehyde **22**.

The one-pot procedure developed by Martin to achieve geminal disubstitution at a carbonyl center was employed utilizing iminophosphonate **23**.[37] The reagent was easily

(21) Watanabe, C. M. H.; Townsend, C. A. *J. Org. Chem.* **1996**, *61*, 1, 1990−1993.
(22) Watanabe, C. M. H.; Townsend, C. A. *J. Am. Chem. Soc.* **1998**, *120*, 6231−6239.
(23) Elsworthy, G. C.; Holker, J. S. E.; McKeown, J. M.; Robinson, J. B.; Mulheirn, L. J. *J. Chem. Soc., Chem. Commun.* **1970**, 1069−1070.
(24) Anderson, J. A.; Lin, B.-K.; Williams, H. J.; Scott, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 1623−1624 and references cited.
(25) Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F. *J. Am. Chem. Soc.* **1966**, *88*, 4534−4536.
(26) Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F.; Schneider, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 6745−6753.
(27) Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746−752.
(28) Matsumoto, M.; Kuroda, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 382−383.
(29) Sloan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685−4686.
(30) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194−2196.
(31) Mittra, A.; Biswas, S.; Venkateswaran, R. V. *J. Org. Chem.* **1993**, *58*, 8, 7913−7915.
(32) Pawlowski, N. E.; Jones, D. J.; Sinnhuber, R. O. *Tetrahedron Lett.* **1974**, *14*, 1321−1323.
(33) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775−3782.
(34) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1−360.

Scheme 5



prepared from *N*-bromomethylphthalimide, which undergoes exothermic Arbuzov reaction upon treatment with trimethyl phosphite to provide the corresponding phosphonate. The phthalimide was cleaved with hydrazine to yield a free amine, which was subsequently condensed with benzaldehyde to give the iminophosphonate **23**.

The geminal disubstitution was initiated by Horner−Emmons olefination, in which addition to the aldehyde **22** by the phosphonate precedes betaine elimination at or near room temperature. Reaction of the conjugated azadiene **24** with a further equivalent of *n*-butyllithium generated a metalloenamine intermediate, which reacted with ethyl bromoacetate. Hydrolysis of the resulting imine gave the desired phenylacetaldehyde **25**. This method allowed the protected benzaldehyde **22** to be elaborated in a single chemical operation to the more highly functionalized phenylacetaldehyde **25**. Some important modifications of the original Martin procedure improved the efficiency of the reaction in our hands. The Horner−Emmons step was performed at 0−25 °C for 1 h rather than at reflux in THF over 2 h as described, and final imine hydrolysis was completed under *mild* conditions (1 N aqueous tartaric acid, 1−2 h, 0 °C) to avoid the decomposition of the phenylacetaldehyde in acid. Finally, careful monitoring of the amount of *n*-butyllithium

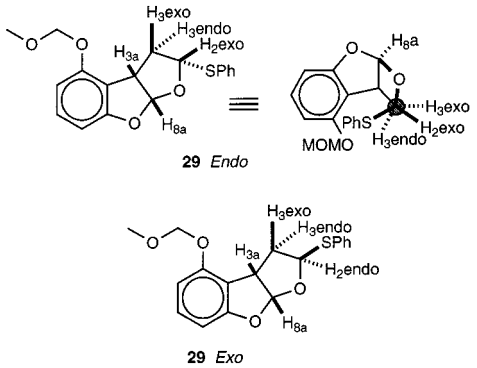


Figure 1. Structural assignment of the tetrahydrobisfuran *O,S*-acetal stereoisomers.

added to form the metalloenamine was essential to the success of this multistep reaction.

Attention was directed next toward the key cyclization expected to convert this labile aldehyde into the silyloxydihydrobenzofuran **26**. As anticipated, addition of TIPSOTf and TEA to a THF solution of the phenylacetaldehyde **25** at 0 °C rapidly promoted cyclization and monodeprotection. Chromatographic purification furnished the 2-triisopropylsilyloxydihydrobenzofuran products **26** in 80−85% yield in a 13:1 *trans*-to-*cis* ratio. The structural assignment of each isomer was secured on the basis of the coupling constant (<1 and 6 Hz, respectively) between the acetal and benzylic hydrogens. None of the enol ether product was ever detected.

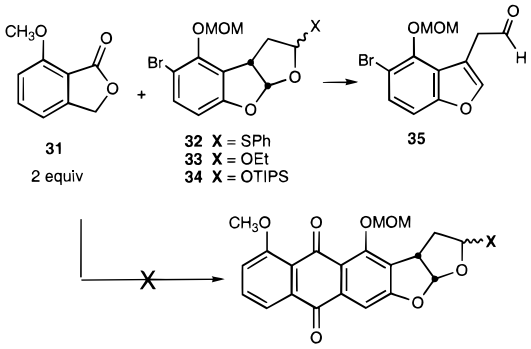
By analogy to Büchi's synthesis, an approach to hemiacetal **28** was pursued. DIBAL was employed to reduce ester **26** to the corresponding aldehyde **27** at −95 °C in nearly quantitative yield. Desilylation of the masked phenylacetaldehyde **27** at −43 °C using tetrabutylammonium fluoride in THF, followed by 5% aqueous sodium bicarbonate, produced the hemiacetal **28** in 67% yield. 1D and 2D ^{1}H NMR and ^{13}C spectral evidence suggested that the hemiacetal **28** exists in solution ($CDCl_3$) as a 3:1 mixture of interconverting *endo* and *exo* anomers.[38]

Because of the harsh conditions required for acetate pyrolysis and the inherent acid sensitivity of the bisfuran side chain and the MOM group, the Büchi method was bypassed in favor of a mild, essentially neutral, low-temperature protocol for conversion of the hemiacetal **28** to the corresponding *O,S*-acetal **29**. Using a Mitsunobu-like approach precedented by Walker,[39] the hemiacetal **28** was treated with tributylphosphine and *N*-thiophenylsuccinimide to give the desired mixed acetals in 92% yield as a 3.4:1 ratio of *exo* and *endo* isomers, respectively.

The relative stereochemical assignment of *exo*- and *endo*-*O,S*-acetals **29** was based on coupling constant analysis and on observed nuclear Overhauser enhancements (NOE) (Figure 1). For the *endo* diastereomer, the observed multiplicity (d, J = 6.9 Hz) of the H-2$_{exo}$ proton was consistent with H-2$_{exo}$−H-3$_{endo}$ and H-2$_{exo}$−H-3$_{exo}$ dihedral angles of approximately 90° and 30°, respectively. The observed multiplicity of H-3$_{endo}$ (d, J = 13.7 Hz) was in accord with a 90° dihedral angle for H-3$_{endo}$−H-3a and H-3$_{endo}$−H-2$_{exo}$, leaving the H-3$_{endo}$ to couple only to its geminal partner H-3$_{exo}$. For the *exo* diastereomer, only the H-3a−H-3$_{endo}$ dihedral angle would be approximately 90°, so that geminal and vicinal couplings were expected at the other positions. The observed multiplicity of H-2$_{endo}$ (dd, J = 10.7, 4.9 Hz) and H-3$_{endo}$ (dd, J = 13.5, 5.0 Hz) was in complete agreement with this prediction. NOE irradiation of the benzylic

(35) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923−3924.
(36) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885−6888.
(37) Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866−5872.
(38) Bujons, J.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1994**, *50*, 7597−7610.
(39) Walker, K. A. M. *Tetrahedron Lett.* **1977**, *51*, 4475−4478.

Scheme 6



hydrogen resulted in enhancement of the acetal hydrogen and H-3$_{exo}$. Additionally, irradiation of the H-3$_{endo}$ gave corresponding enhancement of H-2$_{endo}$ and H-3$_{exo}$. It should be noted that ring conformations in other 2-substituted tetrahydrobisfuran derivatives in the synthesis were found to be quite similar.

Low-temperature *m*-CPBA oxidation of *exo*-*O*,*S*-acetal furnished two diastereomeric sulfoxides that were heated to reflux in toluene to provide (±)-dihydrobisfuran **30** in 87% yield. The chemical shifts and multiplicities of the resonances for hydrogens on the dihydrobisfuran ring system closely paralleled those observed for the corresponding resonances of aflatoxin B_1 and other dihydrobisfuran-containing biosynthetic intermediates.[40]

The preceding sequence demonstrated an efficient route to the formation of the aryl-fused dihydrobisfuran in nine steps and 21% overall yield from the protected aldehyde **22**. However, the objective of this synthesis was to incorporate the bisfuran fragment into fully elaborated potential biosynthetic intermediates. The first attempt to employ this route in the total synthesis of versicolorin A (**4**) revealed some unforeseen limitations to the method. However, this initial setback afforded the opportunity to develop the silyl triflate-mediated chemistry further.

Development of the Silyloxybenzodioxepane

Any strategy to construct the anthraquinone found in versicolorin A must take account of the acid-sensitivity of the dihydrobisfuran. Therefore, a reliable alternative for anthraquinone formation was addition of a lithio-phthalide **31** to a benzyne intermediate, generated from a brominated derivative of the *O*,*S*-acetal **32** (Scheme 6). In practice, however, the addition of the strong, hindered base lithium tetramethylpiperidide did not give benzyne formation.[2] Rather, it promoted rapid E_2 elimination to form the thermodynamically stable dihydrobenzofuran **35**. Decomposition occurred in less than 5 min even at −78 °C, a temperature far lower than that required for in situ benzyne formation (−50 to −30 °C).

In an effort to salvage the benzyne annulation approach, the ethoxy derivative **33** and the sterically hindered triisopropylsilyloxy derivative **34** were prepared from the brominated analogue of *O*,*S*-acetal **29** and hemiacetal **36**, respectively. It became readily apparent that the aryl-fused tetrahydrobisfuran side chain would not withstand the highly basic reaction conditions necessary for in situ benzyne formation and that the thermodynamic driving force to aromatization would prevail.

The solution to this dilemma was realized while attempting to prepare the silyl derivative **34**. The dropwise addition of triisopropylsilyl triflate and triethylamine to a 0 °C solution of the hemiacetal **36** produced the desired *exo*-2-triisopropylsilyloxy-

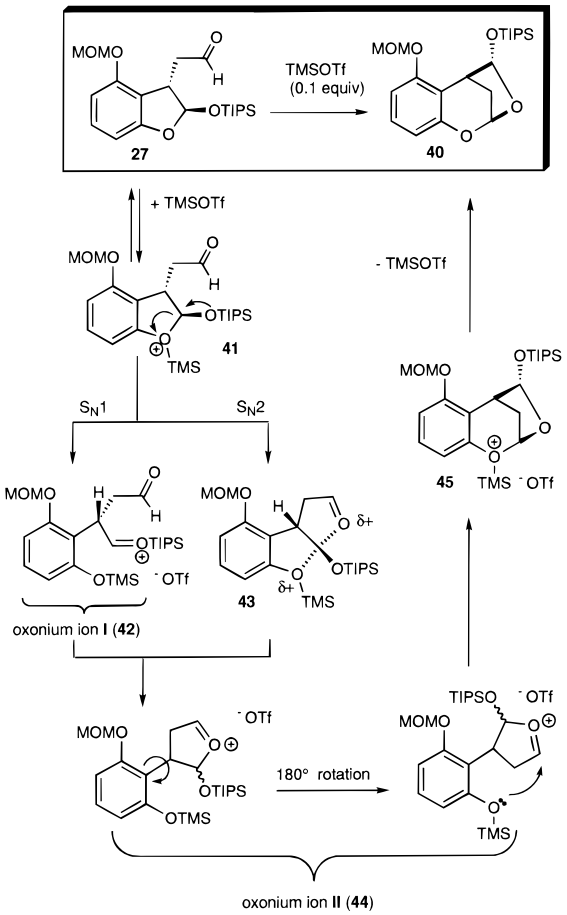


Figure 2. Proposed mechanism of the silyloxybenzodioxepane rearrangement.

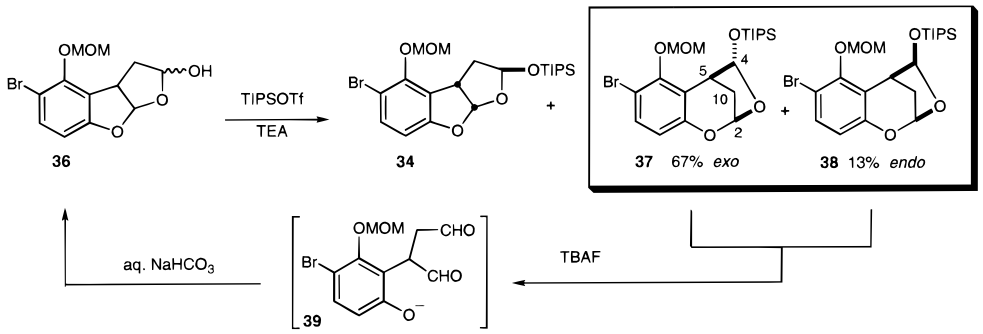
tetrahydrofurobenzofuran derivative **34**, but in less than 10% yield. The major, unanticipated products were identified as the *exo*- and *endo*-7-bromo-4-triisopropylsilyloxy-2,5-methano-1,3-benzodioxepane (**37**, Scheme 7, and **38**), in 67% and 13% yields, respectively. Previously, an altogether different experiment had given the same benzodioxepane. An effort to directly generate the *O*,*S*-acetal **29** from aldehyde **27** employing dithioacetalization conditions (PhSH, TMSCl[41] produced a mixture of the *O*,*S*-acetals directly in yields up to 45%. However, the major product had been the *exo*-2,5-methano-1,3-benzodioxepane analogous to **37**.

The structural characterization of benzodioxepanes **37** and **38** relied primarily on proton NMR decoupling experiments. The formation of a tricyclic acetal for the major product was suspected on the basis of the presence of a singlet (5.62 ppm) and a doublet (5.82 ppm, J = 3.3 Hz) at chemical shifts commonly observed for acetal methine protons. Homonuclear decoupling revealed that the hydrogen appearing at 5.82 ppm (H-2) was coupled to only one of the protons (H-10$_{anti}$, 2.55 ppm) of the methylene bridge. This observation is consistent with a Dreiding molecular model of **37** in which the dihedral angle between H-10$_{syn}$ and H-2 was found to be between 80 and 90°. The H-10$_{anti}$ proton (2.55 ppm) is coupled to H-2 (J = 3.3 Hz), H-10$_{syn}$ (J = 11.6 Hz), and H-5 (J = 3.8 Hz). The fact that the benzylic proton (H-5) was coupled neither to H-10$_{syn}$ nor to H-4 was also corroborated by molecular models, which indicated an orthogonal relationship for the three-spin

(40) Cole, R. J.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*; Academic Press: New York, 1981.

(41) Ong, B. S.; Chan, T. H. *Synth. Commun.* **1977**, *7*, 283−286.

Scheme 7



system. The otherwise similar, minor *endo* stereoisomer **39**, in contrast, showed vicinal coupling at H-4 (J = 3.2 Hz).

Optimization of the reaction conditions for benzodioxepane formation was undertaken. By removing thiophenol, but retaining a catalytic amount of the triisopropylsilyl triflate, it was found that aldehyde **27** (Figure 2) rapidly rearranged to the *exo*-benzodioxepane **40** in 96% yield at −43 °C. Under these conditions, only the *exo* diastereomer was produced, whose structure was easily deduced on the basis of the decoupling experiments above. Most importantly, this remarkably favorable rearrangement could be carried out easily on a multigram scale and thereby provided rapid and efficient access to the desired benzodioxepane **40** from the readily prepared aldehyde **27**.

It was now apparent that, if these benzodioxepane derivatives were sufficiently stable to LiTMP at low temperature, they might function ideally as masked tetrahydrobisfuran synthons during the benzyne annulation step. Following construction of the anthraquinone ring system, simple desilylation of the 2,5-methano-1,3-dioxepane side chain would unmask the base-sensitive tetrahydrobisfuran hemiacetal and ultimately lead to the desired dihydrobisfuran. Base stability of the dioxepane was tested by treatment of **40** with 4 equiv of LiTMP at −43 °C. Only limited decomposition was observed at temperatures above −43 °C. The greater stability of the 2,5-methano-1,3-benzodioxepane ring system compared to that of the tetrahydrobisfuran may reflect the difference in pK_a of a methylene (∼50) versus a benzylic hydrogen (∼40),[42] the substantial steric shielding of the H-10$_{anti}$ proton by the umbrella-like *exo*-triisopropylsilyloxy substituent at C-4, and a less favorable geometry for E2 elimination.

It was demonstrated in the course of the investigation that the silyloxybenzodioxepane protecting group **40** was capable of withstanding many conditions required for the envisioned synthesis: strongly basic (*s*-BuLi, −43 °C; *t*-BuLi, 0 °C), mildly acidic (acetic acid; catalytic HCl in acetic acid, 60 °C; camphorsulfonic acid, 60 °C), nucleophilic (TBAF, −78 °C; NaCN, 0 °C), reductive (DIBAL, −95 °C; LAH), oxidative ($KMnO_4$; DDQ; $BnEt_3NMnO_4$; $NaIO_4$; $Pb(OAc)_4$; PDC; CrO_3; NBS; SeO_2, 95 °C); or radical conditions (Ag_2O; NBS/$h\nu$, 75 °C).

The final criterion for the applicability of this method was the "unmasking" of the silyloxybenzodioxepane. Fluoride-induced (TBAF) removal of the triisopropylsilyl group of **37** and **38** gave a crimson solution, indicative of the phenolate intermediate **39** (Scheme 7), which was followed by rearrangement into the original tetrahydrofurobenzofuran hemiacetal **36** in nearly quantitative yield.

(42) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley and Sons: New York, 1992; pp 250−252.

Mechanism of Silyl-Catalyzed Rearrangement

The mechanism of this intriguing rearrangement is proposed to occur as outlined in Figure 2. To clarify the fate of the catalytic silicon species throughout the rearrangement, TMSOTf was employed as a crossover catalyst. Rapid initial equilibrium of silyl triflate and acetal **27** produced a significant population of the activated acetal intermediate **41** prior to some rate-determining step. The chemoselectivity is consistent with superior Lewis basicity of the ether oxygen in contrast to the aldehyde carbonyl.[43] The enhanced reactivity of acetals over aldehydes (regarded as an *activating* group for the carbonyl moiety in the presence of a silyl triflate catalyst) was demonstrated in an intermolecular competition experiment by Noyori.[44] Acetal activation was succeeded by rapid, low-temperature acetal C−O bond cleavage. In a strict S_N1-type mechanistic interpretation, rate-determining endocyclic C−O bond cleavage of **41** would produce oxonium ion I **42**. Rapid nucleophilic attack by the intramolecular carbonyl group would then produce the cyclic tertiary oxonium ion II **44**. A plausible mechanistic alternative is the direct displacement of the TMS-activated furan oxygen, favored by neighboring group participation of the carbonyl oxygen to provide oxonium ion II **44** in a single step by way of an S_N2 transition state **43**.

Both the S_N1 and the S_N2 interpretations of this mechanism require selective acetal activation and kinetically favorable endocyclic C−O bond cleavage. The fact that ring-opened products (endocyclic C−O bond cleavage) are not observed with many other Lewis or Brönsted acids may reflect the instability of the kinetic ring-opened intermediates in competition with the thermodynamically favored (cyclic) product.[45−49] Increasing steric bulk of the alkoxy group in Lewis acid-mediated reactions with 2-alkoxytetrahydrofurans and pyrans is another factor known to favor endocyclic C−O bond cleavage[50−52] The sterically demanding triisopropylsilyl (TIPS) protecting group efficiently shields the lone-pair electrons of the exocyclic acetal

(43) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259−4275.

(44) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910.

(45) Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem.* **1988**, *60*, 1705−1714.

(46) Guindon, Y.; Anderson, P. C. *Tetrahedron Lett.* **1987**, *28*, 2485−2488.

(47) Guindon, Y.; Bernstein, M. A.; Anderson, P. C. *Tetrahedron Lett.* **1987**, *28*, 2225−2228.

(48) Normant, J. F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507−516.

(49) Cohen, N.; Schaer, B.; Saucy, G.; Borer, R.; Todaro, L.; Chiu, A.-M. *J. Org. Chem.* **1989**, *54*, 3282−3292.

(50) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973.

(51) Eliel, E. L.; Nowak, B. E.; Daignault, R. A.; Badding, V. G. *J. Org. Chem.* **1965**, *30*, 2441−2447.

(52) Diner, U. E.; Brown, R. K. *Can. J. Chem.* **1967**, *45*, 2547−2558.

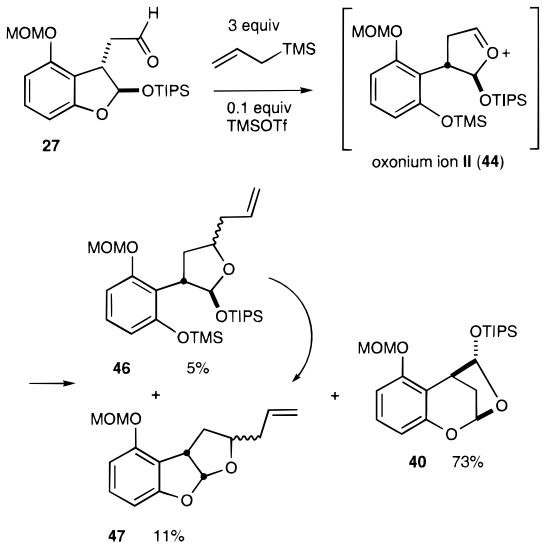


Figure 3. Oxonium ion trapping experiments.

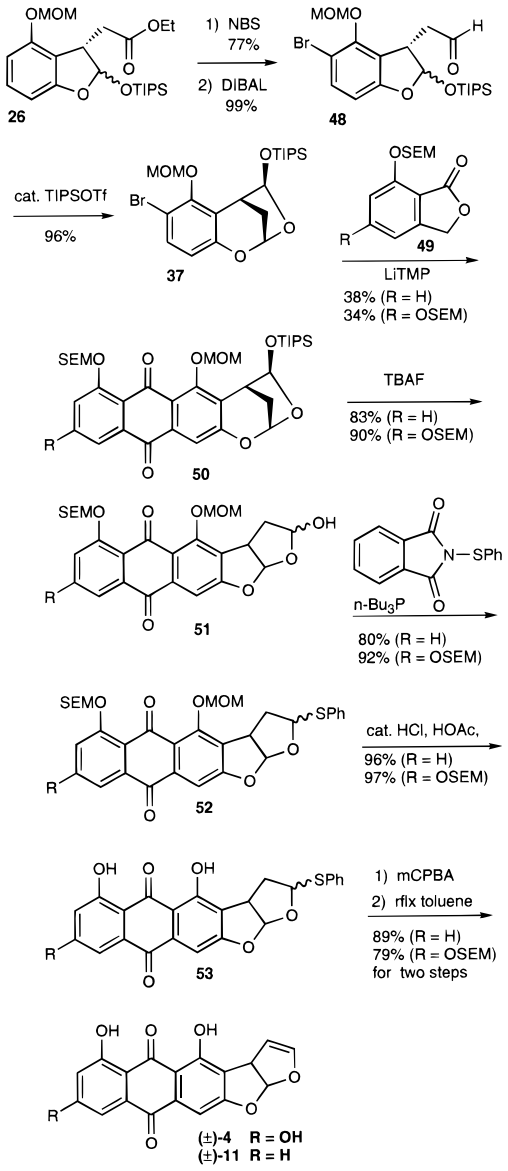
oxygen atom, hampering coordination by Lewis acids. The steric shielding by the TIPS group contributes, along with the apparent kinetic preference, to the selective cleavage of the endocyclic C−O bond. Once oxonium ion II has been generated by one of the preceding mechanisms, a 180° rotation around the benzylic bond, followed by intramolecular trapping by the silyl ether oxygen, provides the silylated benzodioxepane **45**. Regeneration of the TMSOTf catalyst furnishes the 2,5-methano-1,3-benzodioxepane **40**.

To gather experimental support for the transient existence of oxonium ions I **42** and II **44**, a trapping experiment was devised. Allylsilanes rapidly allylate oxonium ions, even at temperatures below −78 °C. Therefore, rearrangement of **27** (Figure 3) in the presence of excess trimethylallylsilane furnished the benzodioxepane **40** (73% yield) as the major product, accompanied by four allylated products. Two allylated diastereomers **46**, apparently derived from direct trapping of oxonium ion II **44** by allylsilane, were obtained. The other two products were the *exo*- and *endo*-2-allyltetrahydrofurobenzofuran derivatives **47**. Although not strictly proved, these tetrahydrofurobenzofuran derivatives were likely formed from the allylated furan intermediates **46** via a subsequent, less rapid intramolecular acetalization. In summary, under these oxonium ion trapping conditions, oxonium ion II **44** was trapped by the allylsilane about 16% of the time. Furthermore, an allylated intermediate derived from trapping of oxonium ion I **42** was never isolated, suggesting that the S_N2 endocyclic bond cleavage is the more likely mechanism.

In addition to silyl triflates, we have found that the rearrangement of aldehyde **27** to benzodioxepane **40** is catalyzed by protic acids such as trifluoromethanesulfonic acid (0.1 equiv, −43 °C). Although the rate of rearrangement was still rapid, the yield of the desired benzodioxepane was somewhat lower with these acid catalysts. Finally, the elevated sensitivity of aldehyde **27** to Lewis acid catalysis is probably due to the ability of the carbonyl oxygen to assist in the cleavage of the activated acetal in the transition state. Previous work has shown that participation of this sort is kinetically optimal through a five-membered transition state.[53] It is our conclusion, therefore, that the observed rearrangement is a Lewis acid-catalyzed cationic intramolecular transacetalization. The elevated rate of this skeletal reorganization is manifest in the intramolecular nature of the rearrangement and the apparent neighboring group participation of the carbonyl in the rate-determining endocyclic acetal cleavage step.

(53) Pasto, D. J.; Serve, M. P. *J. Am. Chem. Soc.* **1965**, *87*, 1515−1521.

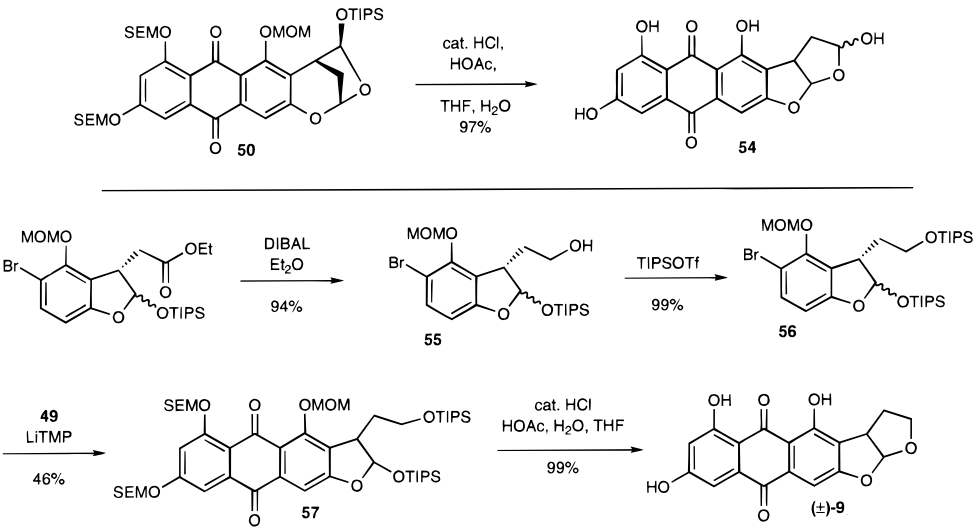
Scheme 8



Syntheses of Versicolorin A, Deoxyversicolorin A, Versicolorin A Hemiacetal, and Versicolorin C

To complete the synthesis of versicolorin A using the benzyne method, the corresponding 7-bromosilyloxybenzodioxepane **37** (Scheme 8) was required. Direct electrophilic halogenation of **40** using NBS was high-yielding but regioselective for the undesired bromo isomer. This difficulty was circumvented by bromination of its precursor, silyloxydihydrobenzofuran **26**, in the presence of 3-Å molecular sieves over 5 days at room temperature to give the desired bromide in 77% yield (6:1 regioselectivity observed). It is interesting to note that, in the absence of sieves, regioselectivity reversed (2:3) to provide the mainly undesired 7-bromo isomer. As before, the ester was reduced to the aldehyde **48** with DIBAL and treated with catalytic TIPSOTf to effect rearrangement into the benzodioxepane system **37** in 84% yield for two steps. Having now effectively constructed and masked the bisfuran, the stage was set for the benzyne coupling step.

Scheme 9



The phthalide coupling partner was easily prepared from 3,5-dimethoxybenzyl alcohol in a three-step sequence consisting of a dianionic Kolbe−Schmidt carboxylation and concomitant cyclization, removal of the methyl ethers, and reprotection with trimethylsilylethoxymethyl (SEM) chloride. The addition of excess LiTMP to a bromide **37**/phthalide **49** (R = OSEM) solution at low temperature resulted in regiospecific deprotonation of the phthalide as well as dehydrohalogenation to generate the benzyne. Regiospecific addition of the carbanion to the benzyne, followed by workup in air, provided the anthraquinone **50** (R = OSEM) in 34% yield.

The pivotal coupling step complete, unmasking of the bisfuran was triggered by the addition of TBAF, which induced rearrangement to the hemiacetal **51** (R = OSEM) in 90% yield. The Walker protocol followed to give the *O,S*-acetals **52** (R = OSEM) as a 5.6:1 mixture of *exo:endo* isomers in a combined 92% yield. Simultaneous removal of the SEM and MOM protecting groups with dilute aqueous acid furnished the trihydroxyanthraquinone **53** (R = OH) in 97% yield. Finally, oxidation of the sulfides, followed by pyrolysis of the resulting sulfoxides, furnished (±)-versicolorin A (**4**) in 79% yield for the combined two steps. Thus, the synthesis of versicolorin A was accomplished in 13 steps and 6.1% overall yield from **22**.

The synthesis of the analogous potential intermediate, (±)-6-deoxyversicolorin A (**11**), employed the identical sequence, but with phthalide **49** (R = H), which lacked the second SEM protected phenol. This sequence was completed in 13 steps and 5.7% overall yield from **22**.

Modifications of the versicolorin A synthesis also provided two other anthraquinone-containing targets required for the envisioned biochemical experiments. For the hemiacetal **54** (VAOH), benzodioxepane **50** (R = OSEM) underwent simultaneous acid-catalyzed unmasking of the benzofuran and deprotection of the MOM and SEM ethers, providing the target hemiacetal **54** in 97% yield (Scheme 9).

The synthesis of (±)-versicolorin B (**9**, Scheme 9) required adjustment of the oxidation state to provide the tetrahydrobisfuran. In contrast to the versicolorin A synthesis, the bromoester was reduced to the alcohol **55** and protected as its TIPS ether **56**. The bromide was carried through the benzyne protocol, employing phthalide **49** (R = OSEM), and furnished the corresponding anthraquinone **57** in 46% yield. Aqueous acid was again used to simultaneously deprotect the TIPS, MOM, and SEM ethers while effecting cyclization of the diol to the tetrahydrobisfuran **9** in 99% yield. By its longest linear route, (±)-VAOH and (±)-versicolorin B were prepared in nine steps each and in 13% and 10% overall yield, respectively, from the protected aldehyde **22**.

Synthesis of a Putative *o*-Carboxybenzophenone Cleavage Product

As briefly summarized in the introduction, the availability of chemically pure and fully characterized tetrahydro- and dihydrobisfurans in labeled and unlabeled form, and their use in conventional incorporation studies and in transformation experiments with blocked mutants, unambiguously established the partition of the biosynthetic pathway as outlined in Scheme 2. The oxidative desaturation of versicolorin B (**9**) to versicolorin A (**4**) is the pivotal reaction, giving rise to parallel later reactions to AFB_2 (**10**, tetrahydrobisfuran) and AFB_1 (**6**, dihydrobisfuran) from these intermediates.[1,7,9] The next mechanistic issue is the cleavage and rearrangement of **4** to give demethylsterigmatocystin (**5**, R = R′ = H), a process in which the 6-hydroxyl group of **4** is reduced, cleavage of the anthraquinone nucleus occurs, and reclosure to the xanthone takes place with loss of a carbon.

A first attempt to answer this question relied upon the preparation of 6-deoxyversicolorin A (**11**, Scheme 2), as described above. This material, however, was not incorporated into AFB_1 under any of several conditions tried. Thus, a global sequence of events involving reduction followed by oxidative cleavage, while precedented in other systems,[24] does not appear to operate in the biosynthesis of aflatoxin. Reversal of these major oxidation and reduction steps is indirectly exemplifed in the biosynthesis of griesofulvin/geodin[54] and is proposed to take place by way of oxidative cleavage to *o*-carboxybenzophenone **58** (Figure 4), which could be envisoned to couple to spirocyclohexadienone **59**. Reduction of the enone, dehydration, decarboxylation, and rearrangement can be invoked to give demethylsterigmatocystin (**5**, R = R′ = H). Extension, then, of the methods developed thus far for the preparation of anthraquinone bisfurans was to be applied to a new nuclear system.

The synthesis of the benzophenone cleavage product **58** also took advantage of the benzodioxepane method, but to construct the dihydrobisfuran, several adaptations were required. For

(54) Fujii, I.; Iijima, H.; Tsukita, S.; Ebizuka, Y.; Sankawa, U. *J. Biochem.* **1987**, *101*, 11−18.

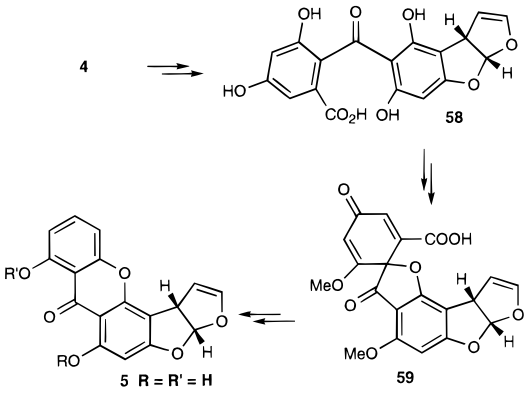


Figure 4. Alternative biogenetic route to desmethylsterigmatocystin (**59**) from versicolorin A (**4**).

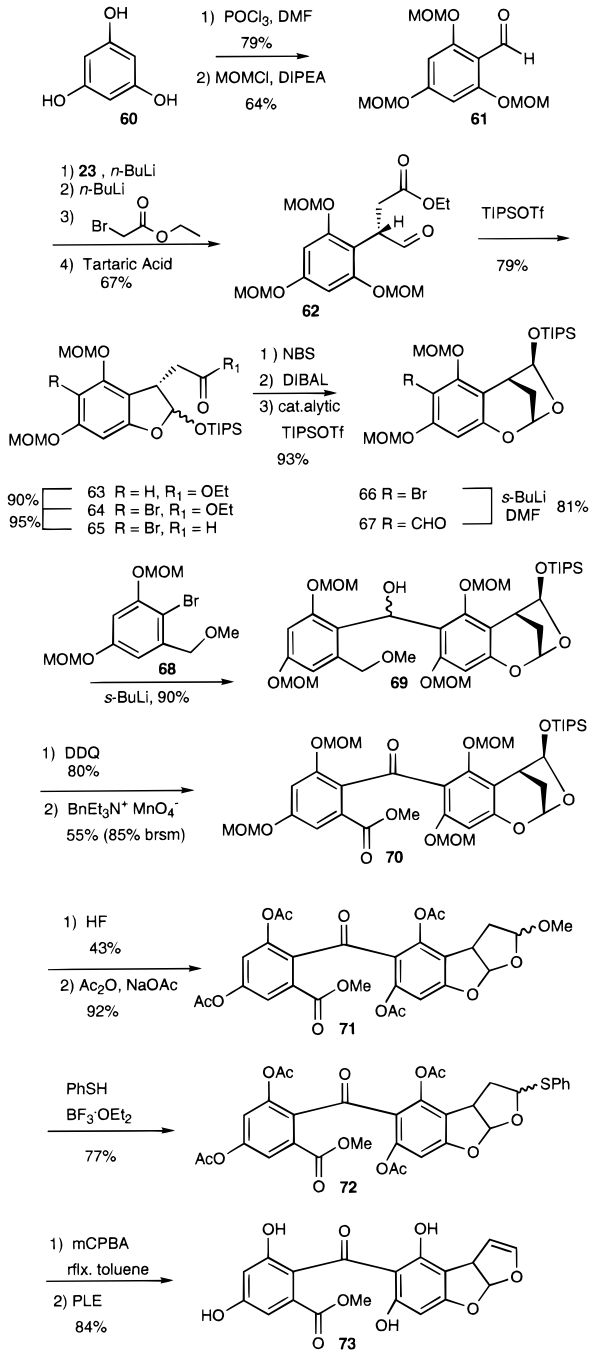
example, the bisfuran remained in the masked benzodioxepane form for most of the synthesis, while the benzophenone linkage was created by addition of an aryl anion to a formyl-substituted benzodioxepane **67** (Scheme 10).

Accordingly, the synthesis began with the Vilsmeier−Haack formylation of phloroglucinol (**60**) to give a 79% yield of the desired benzaldehyde, followed by methoxymethyl ether protection to provide the fully MOM-protected benzaldehyde **61** in 64% yield. From this point, the silyloxybenzodioxepane methods developed above could be employed. The Martin geminal disubstitution protocol readily afforded the racemic aldehyde **62** in 67% overall yield and concomitantly established the carbon framework of the bisfuran.[37] The aldehyde **62** was combined with TIPSOTf, effecting cyclization to the desired silyloxydihydrobenzofuran **63** in 79% yield; this was treated with NBS to give a quantitative yield of monobrominated product **64** and its regioisomer in >9:1 ratio. The regiochemistry of the major product could not be determined without ambiguity by an NOE difference experiment, so the sequence was carried through the DIBAL reduction and TIPSOTf-catalyzed rearrangement in 95% and 93% yields, respectively. The NOE difference experiment of the benzodioxepane **66** clearly showed that the correct bromide regioisomer had, indeed, been established. Irradiation of the single aromatic resonance gave a positive NOE enhancement in only *one* MOM group, diagnostic for the desired bromide. Unlike the corresponding earlier NBS reaction (Scheme 8), >90% yield of the desired bromide **64** was obtained without need for molecular sieves or long reaction times. Metal−halogen exchange with *sec*-BuLi, followed by immediate addition to DMF, provided an 81% yield of the desired benzaldehyde **67**. A final NOE difference experiment confirmed the regiochemistry of the formyl substituent.

Construction of the resorcylic acid ring system was straightforward. Fischer esterification of α-resorcylic acid was followed by protection of the phenols as MOM ethers in a combined 72% yield. Methoxymethyl ethers were again employed to both protect the phenols and to direct *ortho* lithiation.[34−36] Benzyl alkyl ethers are moderate *ortho*-lithiation directors for aryl anion formation, a necessity in the presence of two MOM ethers that would direct lithiation to the undesired site.[55] Therefore, $LiAlH_4$ reduction of the methyl ester to the benzylic alcohol, and methylation with iodomethane, gave 3,5-bis(O-methoxymethyl)-benzyl methyl ether in 81% yield for two steps. NBS treatment proceeded regiospecifically to afford the desired bromide **68** in 95% yield. Addition of the aryl anion derived from bromide **68** by metal−halogen exchange to the formylbenzodioxepane **67** furnished the two benzhydrol diastereomers **69** in 90% yield. None of the regioisomeric product derived from metalation at the alternative site was ever observed. Subsequent DDQ oxidation, reportedly effective for benzylic alcohols, converted the benzhydrols **69** to the benzophenone in 86% yield.[56,57] The benzylic ether-to-ester oxidation employing $BnEt_3NMnO_4$, a DCM-soluble permanganate salt,[58] provided the desired ester **70** in 55% yield (85% based on recovered starting material).[59]

The earlier protocol to unmask the bisfuran involving TBAF desilylation and rearrangement, followed by Walker *O*,*S*-acetal

Scheme 10



(55) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195−1198.

(56) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021−3028.

(57) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1983**, *48*, 749−751.

(58) Schmidt, H.-J.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 68−69.

(59) Schmidt, H.-J.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 69−70.

formation,[39] proceeded in high yield. However, the increased activity of the phloroglucinol nucleus made the phenol deprotection under a number of acidic conditions extremely troublesome. Polymerization or hydroxymethylation with the formaldehyde released during MOM deprotection was most often the outcome. Alternatively, it was considered that conditions that provided both fluoride and protic acid, namely methanolic HF, would consolidate desilylation/rearrangement and acetalization into one step. It was found that these conditions removed the MOM ethers of **70** and provided the bisfuran methyl acetal in up to 43% yield. Considering that desilylation, rearrangement, mixed acetal formation, and four MOM deprotections occurred in one step, the net yield was deemed sufficient to proceed with the synthesis.

In preparation for construction of the dihydrobisfuran ring system, the phenols were reprotected by treatment with acetic anhydride in the presence of NaOAc to provide the deactivated tetraacetate **71** in 92% yield.[60] The acetate-protected methyl acetal **71**, when treated with the $BF_3{\cdot}OEt_2$/PhSH, gave a 77% yield of both epimers (~1:1 ratio) of the *O*,*S*-acetal **72**.[61] The diastereomers of **72** were separated and treated individually with *m*-CPBA to provide two polar, diastereomeric sulfoxides. The sulfoxides were worked up in sodium sulfite to remove excess oxidant, dissolved in dry toluene, and placed in a preheated 110 °C oil bath. The *exo* isomer required 1.5 h for oxidation and 50 min for pyrolysis, while for the *endo* isomer oxidation proceeded in 2 h, but pyrolysis for 2.5 h was necessary. Nonetheless, the final conditions furnished the desired dihydrobisfuran in 84% yield from the sulfide.

A representative panel of esterases and lipases was screened to gently remove the protecting groups. The aryl acetates were readily hydrolyzed by most of the enzymes tested, but the methyl ester was invariably unaffected. All further attempts to accomplish this final deprotection by chemical means to the hypothetical biosynthetic intermediate **58** failed. Efforts by either acyl substitution or nucleophilic displacement methods without destruction of the fragile dihydrobisfuran or its immediate precursors were thwarted. Alternative synthetic routes to **58**, however, can be visualized that will avoid late deprotection of a hindered and electronically deactivated ester. For the moment, an answer to the question of the intermediacy of an oxidatively cleaved tetrahydroxyanthraquinone proposed in Figure 4 will have to be deferred.

Nonetheless, from the perspective of synthesis, the use of simple benzenoid precursors having *O*-methoxymethyl substituents at the biogenetically correct positions can be seen to allow elaboration to more complex ring systems rapidly and efficiently. This has been illustrated in the preparation of anthraquinones bearing the fused bisfuran in various oxidation states and of the corresponding *o*-carboxybenzophenone nucleus. In other work in this laboratory, these methods have been extended to xanthones with fused dihydrobisfurans, thus completing the three nuclear structural types sought.[62] The unstable bisfuran, especially its dihydro form (a masked dialdehyde), is prone to elimination reactions to the derived benzofuran and renders access to this skeletal class difficult. A particularly effective solution to this synthetic problem has been devised in two silyl triflate-mediated transformations, illustrated in Scheme 5 and Figure 2. In the first, a 2,6-bis(*O*-methoxymethyl)phenylacetaldehyde is cyclized to a silyl-protected dihydrobenzofuran (e.g., **25** → **26**, Scheme 5). Second, an equally rapid and high-yielding rearrangement of this ring system can be carried out in a seemingly contrathermodynamic manner to give a benzodioxepane (e.g., **27** → **40**, Figure 2), stable to strong base and mild acid but containing the sensitive bisfuran in masked form and at the correct oxidation state. Using these methods, the central steps of aflatoxin biosynthesis have been established, as illustrated in Scheme 2, and the groundwork has been put in place to examine the poorly understood nuclear rearrangement events (anthraquinone → xanthone → coumarin) that mark the end of the pathway.

Experimental Section

General Methods. All air- or moisture-sensitive reactions were run under an argon or nitrogen atmosphere in flame-dried or oven-dried glassware with magnetic stirring. Moisture-sensitive reagents were added to reaction vessels by oven-dried syringes through rubber septa. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl; dichloromethane, acetonitrile and pentane were distilled from P_2O_5 or CaH_2 just prior to use. *N*,*N*-Dimethylformamide was sequentially dried over 4-Å molecular sieves. All other solvents and reagents for air- or moisture-sensitive reactions were dried by standard procedures.[63] ^1H NMR spectra were measured with a Varian XL/VXR-400 or a Bruker AMX300 NMR spectrometer. Chemical shifts are reported on the δ scale downfield from TMS, and coupling constants are reported in hertz. Unambiguous proton assignments were determined using difference nuclear Overhauser effect experiments (diff. NOE). Carbon NMR spectra were obtained at 100 MHz using solvent resonances as the internal reference ($CDCl_3$, 77.0 ppm; d_6-DMSO, 39.5 ppm; d_6-acetone, 29.8 ppm). Low- and high-resolution mass spectral data were obtained on a VG Instruments 70-S GC/MS at 70 eV and are tabulated as *m*/*z* (intensity expressed as percent of base peak). IR spectra were obtained on a Perkin-Elmer 1600 series FT spectrophotometer ($CHCl_3$ solution or KBr disk). Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. All column chromatography was carried out using Merck Kieselgel 60 (230−400 mesh). Radial chromatography was accomplished with a Harrison Laboratories Chromatotron, using 1-, 2-, or 4-mm rotors coated with EM Science PF_{254} silica containing gypsum. Analytical and preparative TLC analyses were performed using Analtech Uniplate TLC plates (catalog no. 21521) with $KMnO_4$, phosphomolybdic acid (PMA), dinitrophenylhydrazine (DNP), or aqueous $PdCl_2$/HCl visualization. Reagents and solvents were purchased from Aldrich Chemical Co., Lancaster Synthesis, Cambridge Isotopes, and Trans World Chemicals. Enzymes were purchased from Sigma. Novazyme 435 was the generous gift of Novartis.

(±)-Ethyl γ-Formyl-2,6-bis(methoxymethoxy)benzenepropanoate (25) (Martin Aldehyde). *n*-BuLi (25.2 mL, 40.4 mmol) in 180 mL of dry THF was cooled to −70 °C in a flame-dried 500-mL three-neck flask equipped with an internal thermometer. A solution of the Martin reagent[64,65] (35.8 mL, 40.04 mmol, 1.13 M THF solution) was added dropwise over 25 min and then stirred at −78 °C for 1 h. A 20-mL THF solution containing 2,6-bis(*O*-methoxymethyl)benzaldehyde[36] (**22**) (8.01 g, 35.1 mmol) was added over 15 min. The reaction was kept at −78 °C for 30 min and then warmed slowly to 15 °C over the next 1.5 h. The temperature was allowed to rise until the Martin reagent/benzaldehyde adduct (0.2 R_f, 100% EtOAc) eliminated to the higher R_f azadiene intermediate **24**. The temperature was lowered to −78 °C, and a solution of *n*-BuLi (26.3 mL, 42.1 mmol, 1.6 M solution in hexanes) was added dropwise over 15 min. The mixture was stirred for 2 h at −65 °C. Ethyl bromoacetate (9.15 g, 56.2 mmol, 6.1 mL) was added dropwise to the −78 °C reaction mixture over 45 min, and then the mixture was warmed to room temperature over a period of

(60) Rance, M. J.; Roberts, J. C. *J. Chem. Soc. (C)* **1971**, 1247−1252.
(61) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766−1775.
(62) Casillas, L. K.; Townsend, C. A. *J. Org. Chem.* **1999**, *64*, 4050−4059.
(63) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboroatory Chemicals*; Pergamon Press: New York, 1988.
(64) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2531−2534.
(65) Yamauchi, K.; Mitsuda, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3285−3286.

1 h. The entire reaction mixture was then poured into 150 mL of a 1 M aqueous tartaric acid at 0 °C and stirred vigorously for 1 h. The resulting suspension was poured into 200 mL of brine and extracted four times with ether. The ether phase (600 mL) was then quickly washed twice with ice-cold 1 N HCl. The ether phase was washed with 5% $NaHCO_3$, water, and brine and then dried over anhydrous $MgSO_4$. The crude reaction product was quickly chromatographed (10- × 20-cm column, 2−10% EtOAc/hexanes) to separate the desired aldehyde from the bulk of the lower and higher R_f impurities. Fractions containing the desired aldehyde were collected and rechromatographed until 7.53 g (66%) of pure aldehyde **25** was obtained as a light yellow oil: TLC R_f 0.33 in 30% Et_2O/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.21 (t, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 5.16 (s, 4H), 4.60 (dd, J = 8.4, 5.2 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.45 (s, 6H), 3.17 (dd, J = 16.0, 8.4 Hz, 1H), 2.42 (dd, J = 16.0, 5.2 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 172.3, 156.1, 129.6, 114.6, 107.8, 94.5, 60.5, 56.3, 44.7, 32.8, 14.1; IR ($CHCl_3$) 2931, 2866, 1726, 1611, 1486, 1459, 1258, 1154, 1044 cm^{-1}; MS m/z 326 (M^+, 1.2) 298 (1), 264 (15), 232 (14), 207 (3), 174 (12); exact mass m/z calcd for $C_{16}H_{22}O_7$ 326.1366, found 326.1371.

***trans*-(±)-Ethyl 2,3-Dihydro-4-(methoxymethoxy)-2-[[tris(1-methylethyl)silyl]oxy]-3-benzofuranacetate (26).** Triisopropylsilyl triflate (7.9 g, 24.9 mmol) was added dropwise over 5 min to an ice-cold THF solution (170 mL) of aldehyde **25** (7.41 g, 22.7 mmol) and TEA (3.68 g, 36.3 mmol) under argon. The reaction was quenched with *N*,*N*-dimethylethanolamine (0.51 g, 5.7 mmol) and stirred for an additional 30 min. The reaction mixture was poured into 200 mL of ether and 100 mL of water. After multiple ether extractions of the aqueous phase, the combined organic phase (∼400 mL) was washed with water, cold 1 N HCl, 5% $NaHCO_3$, brine and dried over $MgSO_4$. Chromatography (5- × 25-cm column, 500 mL of hexanes, 500 mL of 2.5% ether/hexane, and 500 mL of 5% ether/hexane) allowed isolation of the pure *trans*-acetal **26** as a colorless viscous oil: 8.14 g (82%); TLC R_f 0.7 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 8.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 5.88 (s, 1H), 5.19 (2H, ABq, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 9.8 Hz), 4.15 (m, 2H), 3.65 (dd, J = 10.4, 3.4 Hz, 1H), 3.48 (s, 3H), 2.82 (dd, J = 15.7, 3.4 Hz, 1H), 2.40 (dd, J = 15.7, 10.4 Hz, 1H), 1.24 (t, J = 8.2 Hz, 3H), 1.13−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.4, 154.3, 129.6, 116.1, 106.4, 105.4, 104.1, 94.2, 60.6, 56.2, 46.6, 35.6, 17.9, 17.8, 12.2; FTIR ($CHCl_3$) 2928, 2866, 1728, 1610, 1461, 1258, 1155 cm^{-1}; MS m/z 395 (M^+ − *i*-Pr, 41), 363 (19), 349 (4), 317 (11), 289 (13), 275 (5), 251 (7); exact mass m/z calcd for $C_{23}H_{38}O_6Si$ (M^+ − *i*-Pr 395.1890, found 395.1893.

***trans*-(±)-2,3-Dihydro-4-(methoxymethoxy)-2-[[tris(1-methylethyl)silyl]oxy]3-benzofuranacetaldehyde (27).** A 1.0 M DIBAL solution in hexanes (5.48 mL, 3.66 mmol) was added dropwise to a −95 °C ether (17 mL) ester **26** (1.600 g, 3.66 mmol) solution. The reaction was stirred for 15 min and then quenched with methanol (700 mg, 21.9 mmol, 0.88 mL). The mixture was warmed to −15 °C and then poured into a separatory funnel containing 75 mL of ether. The organic layer was washed with 100 mL of cold 1 N HCl, 5% $NaHCO_3$, brine, and dried over $MgSO_4$. Column chromatography (2- × 10-cm column, 20% EtOAc/hexane) furnished aldehyde **27** (1.401 g, 99%) as a colorless oil: TLC R_f 0.2 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (dd, J = 2.0, 1.6 Hz, 1H), 7.09 (t, J = 8.2 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.72 (d, J = 1.2 Hz, 1H), 5.18 (2H, ABq, J_{AB} = 5.6 Hz, $\Delta\nu_{AB}$ = 9.7 Hz), 3.69 (br dd, J = 8.8, 5.2 Hz, 1H), 2.83 (ddd, J = 17.2, 5.2, 2.0 Hz, 1H), 2.59 (ddd, J = 17.2, 8.8, 1.6 Hz, 1H), 1.2−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 159.3, 154.1, 129.7, 115.8, 106.4, 105.7, 104.1, 94.1, 56.2, 45.2, 44.4, 17.8, 17.8, 17.7, 12.1; FTIR ($CHCl_3$) 2946, 2868, 1724, 1610, 1488, 1462 cm^{-1}; MS m/z 394 (M^+, 0.1), 351 (9), 333 (1), 319 (14), 301 (4), 289 (19), 247 (21), 219 (13), 192 (21), 147 (13); exact mass m/z calcd for $C_{21}H_{34}O_5Si$ 394.2176, found 394.2174.

2,3,3a,8a-Tetrahydro-4-(methoxymethoxy)furo[2,3-*b*]benzofuran-2-ol (28). TBAF was added dropwise (4.1 mL, 4.1 mmol, 1 M THF solution) to a stirred 0.1 M THF solution of aldehyde **27** (1.30 g, 3.39 mmol) at −43 °C under argon. After 35 min, the reaction mixture was poured into 50 mL of 5% $NaHCO_3$ and extracted three times with ether. The extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography (2- × 20-cm column, 20−40% EtOAc/hexane) provided pure hemiacetal **28** (0.511 g, 67%), which was recrystallized from ether/hexanes: mp 78−80 °C; TLC R_f 0.2 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$), for 2α,3a*β*,8a*β*-*endo*, δ 7.12 (t, J = 8.2 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 8.2 Hz, 1H), 6.38 (d, J = 6.1 Hz, 1H), 5.66 (t, J = 5.1 Hz, 1H), 5.2 (2H, ABq, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 12.3 Hz), 4.04 (dd, J = 9.2, 6.1 Hz, 1H), 3.49 (s, 3H), 3.01 (d, J = 6.1 Hz, 1H), 2.45 (d, J = 13.1 Hz, 1H), 2.35 (ddd, J = 13.1, 9.2, 6.1 Hz, 1H), and for 2α,3aα,8aα-*exo*, δ 7.1 (t, J = 8.2 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.35 (d, J = 6.1 Hz, 1H), 5.58 (q, J = 5.2 Hz, 1H), 5.20 (m, 2H), 4.10 (ddd, J = 8.8, 6.0, 2.8 Hz, 1H), 2.42 (d, J = 5.2 Hz, 1H), 2.43 (m, 1H), 2.20 (ddd, J = 13.2, 9.2, 5.6 Hz, 1H); FTIR ($CHCl_3$) 3590, 3422, 3019, 2957, 1609, 1487, 1461, 1261, 1155 cm^{-1}; MS m/z 238 (M^+, 10), 179 (2), 176 (8), 165 (3), 149 (3), 148 (9), 147 (18); exact mass m/z calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0840.

2,3,3a,8a-Tetrahydro-4-(methoxymethoxy)-2-(phenylthio)furo-[2,3-*b*]benzofuran (29). Distilled Bu_3P (58 mg, 0.28 mmol, 72 μL) in 6 mL of dry THF was cooled to −78 °C. *N*-Phenylthiosuccinimide (60 mg, 0.28 mmol) in 1 mL of THF was then cannulated into the flask dropwise. One hour later, hemiacetal **28** (57.0 mg, 0.24 mmol) in 1 mL of THF was transferred to the colorless −78 °C solution of thiophosphonium intermediate. The reaction was then warmed to 0 °C, poured into water, and extracted three times with ether. The ether phase was washed with water and brine and then dried over K_2CO_3. Rotary chromatography (1-mm rotor, 2−10% ether/hexane) provided both the *exo*- and *endo*-*O*,*S*-acetals **29** as colorless oils in 72% and 21% yields, respectively. Both diastereomers were crystallized from ether/hexane at low temperature (−78 °C). 2α,3aα,8aα-*exo*: mp 25−28 °C; TLC R_f 0.6 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5−7.2 (m, 5H), 7.10 (t, J = 8.1 Hz, 1H,), 6.64 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.41 (d, J = 5.8 Hz, 1H), 5.32 (dd, J = 10.7, 4.9 Hz, 1H), 5.22 (s, 2H), 4.09 (dd, J = 7.3, 5.8 Hz, 1H), 3.50 (s, 3H), 2.64 (dd, J = 13.5, 5.0 Hz, 1H), 2.27 (ddd, J = 13.5, 10.7, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 154.1, 133.8, 131.4, 130.1, 128.9, 127.4, 114.8, 111.2, 106.7, 103.6, 94.2, 85.8, 56.3, 44.8, 37.4; FTIR ($CHCl_3$) 3010, 2957, 2904, 1609, 1585, 1486, 1461, 1442, 1405, 1048 cm^{-1}; MS m/z 330 (M^+, 2.3), 221 (11), 190 (4), 161 (17), 147 (14); exact mass m/z calcd for $C_{18}H_{18}O_4S$ 330.0926, found 330.0928. 2α,3a*β*,8a*β*-*endo*: mp 92−93 °C; TLC R_f 0.5 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.8 Hz, 2H), 7.3−7.2 (m, 3H), 7.17 (t, J = 8.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 6.41 (d, J = 6.0 Hz, 1H), 5.75 (d, J = 6.9 Hz, 1H), 5.26 (2H, ABq, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 5.0 Hz), 4.14 (dd, J = 8.6, 6.0 Hz, 1H), 3.52 (s, 3H), 2.80 (ddd, J = 13.7, 8.6, 6.9 Hz, 1H), 2.58 (d, J = 13.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 153.8, 135.6, 131.7, 130.1, 128.8, 127.1, 115.8, 112.5, 106.5, 103.9, 94.1, 88.4, 56.2, 44.8, 38.1; FTIR ($CHCl_3$) 3010, 2957, 2849, 1611, 1583, 1484, 1462, 1048 cm^{-1}; MS m/z 330 (M^+, 4), 221 (10), 189 (32), 161 (19), 147 (12); exact mass m/z calcd for $C_{18}H_{18}O_4S$ 330.0926, found 330.0925.

***cis*-(±)-3a,8a-Dihydro-4-(methoxymethoxy)furo[2,3-*b*]benzofuran (30).** *m*-CPBA (39 mg, 0.226 mmol; 80−85%) was quickly added in one portion to a −78 °C solution of *O*,*S*-acetals **29** (67.9 mg, 0.20 mmol, 3.4:1 ratio, respectively) in 5 mL of CH_2Cl_2 and stirred for 2 h. Four diastereomeric sulfoxides were detected by TLC analysis (R_f 0.2−0.1, 30% EtOAc/hexanes). The reaction was warmed to −43 °C for 10 min and then poured into 5% $NaHCO_3$ and ether. The combined ether phase was washed with 10% Na_2SO_3, 5% $NaHCO_3$, and brine, dried over K_2CO_3, filtered, and concentrated. The residual light yellow oil was dissolved in 10 mL of distilled toluene and TEA (72.6 mg, 0.6 mmol, 0.1 mL), lowered into a 115 °C oil bath, and stirred for 30 min. The reaction mixture was concentrated and the oil passed down a short column of silica gel (1 × 10 cm, 20% EtOAc/hexane) to provide the crude bisfuran product. Final separation by rotary chromatography (1-mm rotor, 2−5% ether/hexanes) gave 39.0 mg (87%) of pure dihydrofurobenzofuran **30** as a clear viscous oil: TLC R_f 0.15 in 5% Et_2O/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 8.0 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.45 (t J = 2.4 Hz, 1H), 5.34 (t, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.62 (ddd, J = 7.2, 2.6, 2.4 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 159.0, 153.6, 144.9, 129.5, 116.0, 111.8, 107.0, 104.0, 102.6, 94.2, 56.2, 48.8; FTIR ($CHCl_3$) 3010, 2957, 2931, 2828, 1621, 1610, 1488, 1459, 1047 cm^{-1}; MS *m*/*z* 220 (M^+, 19), 188 (13), 187 (18), 160 (6), 147 (6); exact mass *m*/*z* calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0741.

***trans*-(±)-Ethyl 5-Bromo-2,3-dihydro-4-(methoxymethoxy)-2-[[tris(1-methylethyl)silyl]oxy]-3-benzofuranacetate.** Activated powdered molecular sieves (26 g, 3 Å, Aldrich, 3−5 $\mu\mu$) were mixed with neutralized $CHCl_3$ (80 mL, passed through basic alumina) and cooled to 0 °C. A 20-mL solution of acetal **26**(2.54 g, 5.79 mmol) in neutral $CHCl_3$ was cannulated into the flask. NBS (3.09 g, 17.4 mmol) was added quickly in one portion. The solution was allowed to warm to 25 °C. After the starting material was consumed (3−6 days), the suspension was filtered through a pad of Celite and washed with 400 mL of ether. The filtrate was concentrated, and the succinimide and excess NBS were crystallized with hexane (300 mL) and filtered. The resulting light yellow oil was loaded onto a 4- × 20-cm silica gel column in hexane and eluted with 300 mL of hexanes, 300 mL of 3% ether/hexanes, and finally 5% ether/hexanes. Purification in this manner furnished bromide 2.29 g (77%) of as a clear viscous oil: TLC R_f 0.33 in 100% toluene; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 5.84 (s, 1H), 5.16 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.72 (dd, J = 10.8, 3.2 Hz, 1H), 3.60 (s, 3H), 2.84 (dd, J = 15.6, 3.2 Hz, 1H), 2.36 (dd, J = 15.6, 10.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.1−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.8, 151.5, 133.1, 123.1, 107.8, 107.2, 105.5, 99.2, 60.8, 57.6, 47.4, 35.7, 17.7, 14.1, 12.0; FTIR ($CHCl_3$) 2946, 2866, 1728, 1605, 1590, 1452, 1158 cm^{-1}; MS *m*/*z* 518 (M^+, 1), 516 (1), 475 (21), 473 (21), 443 (8), 441 (8), 397 (10), 395 (10), 357 (4), 355 (4), 331 (6), 329 (6); exact mass calcd for $C_{23}H_{37}BrO_6Si$ 516.1543, found 516.1537. Anal. ($C_{23}H_{37}BrO_6Si$) C, H.

***trans*-(±)-5-Bromo-2,3-dihydro-4-(methoxymethoxy)-2-[[tris(1-methylethyl)silyl]oxy]-3-benzofuranacetaldehyde (48).** Comparable to the preparation of **27**, a 99% yield of aldehyde **48** obtained as a colorless oil: TLC R_f 0.2 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 5.69 (s, 1H), 5.14 (s, 2H), 3.81 (dd, J = 10.4, 4.0 Hz, 1H), 3.55 (s, 3H), 2.98 (dd, J = 18.0, 4.0 Hz, 1H), 2.62 (ddd, J = 18.0, 10.4, 1.6 Hz, 1H), 1.1−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 158.8, 151.4, 133.1, 123.1, 107.9, 107.3, 105.8, 99.3, 57.7, 45.0, 44.9, 17.7, 17.6, 12.0; FTIR ($CHCl_3$) 2945, 2870, 2719, 2355, 2340, 1724, 1605, 1588, 1441, 1158, 1141 cm^{-1}; MS *m*/*z* 474 (M^+, 0.6), 472 (0.5), 431 (6), 429 (6), 399 (8), 397 (8), 369 (13), 367 (11), 327 (10), 325 (10), 299 (5), 297 (6), 272 (4), 270 (4), 227 (8), 225 (8); exact mass calcd for $C_{21}H_{33}BrO_5Si$ 472.1281, found 472.1282. Anal. ($C_{21}H_{33}BrO_5Si$) C, H.

***exo*-(±)-[7-Bromo-2,5-methano-6-(methoxymethoxy)-1,3-benzodioxepan-4-yloxy]tris(1-methylethyl)silane (37).** Triisopropylsilyl triflate (140 mg, 0.46 mmol, 127 μL) was added to a −43 °C solution of freshly chromatographed bromoaldehyde **48** (2.102 g, 4.44 mmol) in 25 mL of dry CH_2Cl_2 under argon. After being stirred for 5 min, the reaction was quenched with *N*,*N*-dimethylethanolamine (61.5 mg, 0.69 mmol), warmed to room temperature, and partitioned between 100 mL ether and 30 mL of 0.15 N HCl. The aqueous phase was then extracted three times with ether. The ether phase was washed with 0.15 N HCl, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (3- × 10-cm column, 0−2% ether/hexanes). In this manner, benzodioxepane **37** (2.025 g, 96%) was obtained as a clear viscous oil: mp 34−35 °C; TLC R_f 0.5 in 10% Et_2O/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.82 (d, J = 3.3 Hz, 1H), 5.62 (s, 1H), 5.10 (2H, ABq, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 8.8 Hz), 3.62 (s, 3H), 3.58 (d, J = 3.8 Hz, 1H), 2.55 (ddd, J = 11.6, 3.8, 3.3 Hz, 1H), 1.94 (d, J = 11.6 Hz, 1H), 1.1−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.7, 132.2, 121.3, 114.5, 107.9, 104.8, 100.3, 99.1, 57.9, 39.1, 28.5, 17.9, 17.8, 12.1; FTIR ($CHCl_3$) 2946, 2866, 1596, 1574, 1456, 1035 cm^{-1}; MS *m*/*z* 474 (M^+, 1), 472 (M^+, 1), 431 (8), 429 (8), 399 (10), 397 (9), 369 (13), 367 (11), 327 (7), 325 (7), 227 (11), 225 (12); exact mass calcd for $C_{21}H_{33}BrO_5S$ 472.1281, found 472.1282. Anal. ($C_{21}H_{33}BrO_5S$) C, H.

***exo*-(±)-2,5-Methano-6-(methoxymethoxy)-8-[[2-(trimethylsilyl)ethoxy]methoxy]-4-[[tris(1-methylethyl)silyl]oxy]anthra[2,3-*d*]-1,3-dioxepane-7,12-dione (50, R = H).** Distilled tetramethylpiperidine (1.943 g, 13.75 mmol) in 15 mL of dry THF was cooled to −43 °C. *n*-BuLi (8.6 mL, 13.75 mmol, 1.6 M solution in hexanes) was added dropwise and stirred for 15 min. The temperature was lowered to −78 °C, and then a 5-mL THF solution of 7-[[(trimethylsilyl)ethoxy]-methoxy]phthalide **49** (R = H)[66] (1.542 g, 5.52 mmol) was added dropwise by cannula over no longer than 5−8 min. The temperature was raised to −43 °C after addition. Dropwise addition of bromide **37** (1.321 g, 2.75 mmol in 5 mL of THF) using a double-ended needle was begun immediately upon warming of the solution to −43 °C and resulted in a color change from yellow to dark red. The reaction mixture was stirred for 2 h and then quenched with 2.0 M acetic acid/THF (5.5 mL, 11 mmol). Compressed air was bubbled through the solution until the color became light orange. The mixture was poured into 100 mL of water and extracted with ether. The yellow ether phase was washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, concentrated, and chromatographed (5- × 12-cm column, 2% EtOAc/hexanes). Anthraquinone (**50**, R = H) was crystallized from a ether/hexanes: 0.699 g (38%); mp 46−47 °C; TLC R_f 0.3 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.3 Hz, 1H), 7.62−7.55 (m, 2H), 7.46 (s, 1H), 5.91 (d, J = 3.0 Hz), 5.66 (s, 1H), 5.40 (s, 2H), 5.27 (d, J = 6.9 Hz, 1H, A of ABq), 5.20 (d, J = 6.9 Hz, 1H, B of ABq), 3.85 (dd, J = 8.3, 8.1 Hz, 2H), 3.81 (d, J = 3.7 Hz, 1H), 3.61 (s, 3H), 2.65 (ddd, J = 11.6, 3.8, 3.1 Hz, 1H), 1.99 (d, J = 11.6 Hz, 1H), 1.1−1.0 (m, 21H), 0.98 (dd, J = 8.3, 8.1 Hz, 2H), −0.003 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 181.9, 157.4, 156.6, 155.9, 135.1, 134.8, 133.8, 126.4, 124.5, 123.1, 120.9, 120.5, 111.5, 104.6, 102.4, 99.4, 93.9, 66.9, 57.7, 38.7, 28.5, 18.1, 17.8, 17.7, 12.1, −1.4; FTIR ($CHCl_3$) 3015, 2949, 2870, 1672, 1588, 1468, 1301, 1120 cm^{-1}; MS *m*/*z* 670 (M^+, 0.05), 655 (0.09), 627 (3), 597 (44), 570 (12), 569 (29), 537 (60), 508 (16), 465 (23), 395 (17), 365 (17); exact mass calcd for $C_{32}H_{43}O_9Si_2$ (M^+ − *i*-Pr) 627.2446, found 627.2456. Anal. ($C_{35}H_{50}O_9Si_2$) C, H.

(2α,3a*β*,12a*β*)-2,3,3a,12a-Tetrahydro-2-hydroxy-4-(methoxymethoxy)-6-[[2-(trimethylsily)ethoxy]methoxy]anthra[2,3-*b*]-furo-[3,2-*d*]furan-5,10-dione (51, R = H). Tetrabutylammonium fluoride (1.06 mL, 1.06 mmol) was added dropwise to a −78 °C 25-mL THF solution of acetal **50** (R = H) (0.649 g, 0.97 mmol), causing it to become dark violet. The solution was warmed to −20 °C over 2.5 h and then cooled to −50 °C before addition of 2 N AcOH/THF (0.56 mL, 1.1 mmol). The reaction mixture was then partitioned between water and ether. The combined ether phase was washed with 5% $NaHCO_3$, water, and brine and then dried over Na_2SO_4. Column chromatography (2- × 20-cm column, 5−50% EtOAc/hexane) furnished 0.411 g (83%) of hemiacetal **51** (R = H) as a yellow oil that crystallized from ether/hexanes as a bright yellow solid: mp 102−103 °C (dec); TLC R_f 0.3 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$), for 2α,3a*β*,12a*β*, δ 7.88 (d, J = 5.7 Hz, 1H), 7.6−7.5 (m, 2H), 7.45 (s, 1H), 6.49 (d, J = 6.1 Hz, 1H), 5.76 (d, J = 2.8 Hz, 1H), 5.4−5.2 (m, 4H, 2 overlapping ABq, J = 7.0 Hz), 4.23 (dd, J = 9.2, 6.1 Hz, 1H), 3.84 (t, J = 8.3 Hz, 2H), 3.60 (s, 3H), 2.6 (d, J = 13.2 Hz, 1H), 2.4 (m,1H), 0.962 (t, J = 8.3 Hz, 2H), 0.003 (s, 9H), distinctive 2α,3aα,12aα-resonances at δ 5.62 (t, J = 2.8 Hz), 4.30 (ddd, J = 8.8, 6.0, 2.8 Hz, 1H), distinctive *exo*-benzodioxepanylhemiacetal resonances at δ 5.95 (d, J = 3.2 Hz, 1H), 5.67 (s, 1H), 2.02 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), downfield distinctive peaks with intensities >12% but <35%, δ 183.2, 183.0, 162.4, 157.3, distinctive peaks with intensities >35%, δ 133.8, 133.7, 123.0, 120.5, 112.8, 110.7, 104.5, 101.6, 100.2, 99.9, 93.4, 66.9, 57.2, 44.4, 38.3, 18.1; FTIR ($CHCl_3$) 3589, 3013, 1666, 1586, 1318, 1249 cm^{-1}; MS *m*/*z* 441 (M^+, 0.9), 384 (5), 338 (2), 323 (4), 322 (5), 312 (3), 311 (6), 294 (19), 293 (20), 283 (8); exact mass calcd for $C_{22}H_{21}O_8Si$ (M^+ − 73) 441.1006, found 441.1011. Anal. ($C_{26}H_{30}O_9Si$) C, H.

(2α,3aα,12aα)-2,3,3a,12a-Tetrahydro-4-(methoxymethoxy)-2-(phenylthio)-6-[[2-(trimethylsilyl)ethoxy]methoxy]anthra[2,3-*b*]furo-[3,2-*d*]furan-5,10-dione (52, R = H). *N*-Phenylthiosuccinimide (0.323 g, 1.49 mmol) in THF (10 mL) was cooled to −78 °C, and tributylphosphine (0.303 g, 1.49 mmol, 0.37 mL) was added quickly, stirred for 5 min, and then warmed to 0 °C. The light pink thiophos-

(66) Dodsworth, D. J.; Calcagno, M. P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120−2124.

phonium intermediate was added dropwise to a −78 °C THF solution (20 mL) of the fully protected hemiacetal **51** (R = H) (0.386 g, 0.747 mmol). The mixture was slowly warmed to −25 °C over 2.5 h and then poured directly onto a 2- × 10-cm column of silica gel and eluted with 20% EtOAc/hexane. The partially purified *O,S*-acetals were placed on a 2-mm Chromatotron rotor, separated (10% EtOAc/hexane), and crystallized from ether/hexanes to give an 80% combined yield of crystallized (2α,3aα,12aα)- and (2α,3a*β*,12a*β*)-*O,S*-acetal products (**52**, R = H) in a 5.6:1 ratio, respectively. 2α,3aα,12aα: mp darkens at 80−100 °C and then melts at 110−110.5 °C (open capillary); TLC R_f 0.4 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.3, 1.1 Hz, 1H), 7.61 (t, J = 8.3 Hz, 1H), 7.56 (dd, J = 8.5, 1.1 Hz, 1H), 7.50 (d, J = 6.9 Hz, 2H), 7.47 (s, 1H,), 7.35−7.25 (m, 3H), 6.51 (d, J = 5.8 Hz, 1H), 5.39 (2H, ABq, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 12.8 Hz), 5.34 (d, J = 7.0 Hz, 1H, A of AB), 5.28 (dd, J = 10.8, 5.2 Hz, 1H), 5.18 (d, J = 7.0 Hz, 1H, B of ABq), 4.27 (dd, J = 8.4, 5.8 Hz, 1H), 3.84 (t, J = 8.3 Hz, 2H), 3.61 (s, 3H), 2.82 (dd, J = 12.8, 5.2 Hz, 1H), 2.36 (ddd, J = 12.8, 10.8, 8.4 Hz, 1H), 0.961 (t, J = 8.3 Hz, 2H), 0.006 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 181.8, 163.1, 157.4, 155.7, 137.2, 134.7, 133.8, 133.2, 131.7, 129.1, 128.1, 127.7, 124.2, 123.1, 122.4, 120.6, 112.1, 104.3, 101.5, 93.9, 86.2, 66.9, 57.3, 45.4, 37.4, 18.1, −1.4; FTIR ($CHCl_3$) 2954, 2904, 1670, 1595, 1588, 1399, 1331, 1296, 1249 cm^{-1}; MS *m*/*z* 606 (M$^+$, 0.04), 590 (0.3), 548 (0.35), 533 (5), 439 (9), 407 (22), 395 (5), 379 (9), 335 (25), 323 (8), 293 (6); exact mass calcd for $C_{32}H_{34}O_8SSi$ 606.1744, found 606.1750. Anal. ($C_{32}H_{34}O_8SSi$) C, H. 2α,3a*β*,12a*β*: mp darkens at 50−150 °C and then melts at 150−153 °C (open capillary); TLC R_f 0.25 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.1, 1.7 Hz, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.57 (dd, J = 7.1, 1.7 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 5.8 Hz, 2H), 7.3−7.2 (m, 3H), 6.52 (d, J = 6.2 Hz, 1H), 5.78 (d, J = 7.6 Hz, 1H), 5.41 (2H, ABq, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 16.4 Hz), 5.39 (d, J = 7.0 Hz, 1H, A of ABq), 5.23 (d, J = 7.0 Hz, 1H, B of ABq), 4.34 (ddd, J = 9.2, 6.4, 0.8 Hz, 1H), 3.86 (t, J = 8.3 Hz, 2H), 3.63 (s, 3H), 2.88 (ddd, J = 13.6, 9.2, 6.4 Hz, 1H), 2.75 (d, J = 13.6 Hz, 1H$_o$), 0.97 (t, J = 8.3 Hz, 2H), 0.008 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 182.1, 163.5, 157.4, 155.5, 137.3, 134.8, 134.2, 133.8, 132.2, 129.5, 128.9, 127.6, 124.3, 123.1, 122.9, 120.6, 113.3, 104.6, 101.7, 94.0, 88.4, 66.9, 57.3, 45.6, 38.1, 18.1, −1.3; FTIR ($CHCl_3$) 3001, 2954, 1669, 1595, 1588, 1343, 1250 cm^{-1}; MS *m*/*z* 606 (M$^+$, 0.28), 590 (0.3), 548 (0.4), 533 (4), 439 (7), 407 (18), 379 (10), 335 (22), 294 (5), 293 (5); exact mass *m*/*z* calcd for $C_{32}H_{34}O_8$-SSi 606.1744, found 606.1756. Anal. ($C_{32}H_{34}O_8SSi$) C, H.

(2α,3aα,12aα)-2,3,3a,12a-Tetrahydro-4,6-dihydroxy-2-(phenylthio)anthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione (53, R = H). *exo-O,S*-Acetal **52** (R = H) (0.285 g, 0.469 mmol) was dissolved in 10 mL of THF, 1 mL of water, 1 mL of acetic acid, and 6 drops of 6 N HCl and then warmed to 65 °C. After 5 h, the deprotected *exo-O,S*-acetal **53** (R = H) was collected by filtration, washed with ether, and dried under reduced pressure (186 mg, 92%). The mother liquor was partitioned between EtOAc and water, and the organic phase was washed with 5% $NaHCO_3$ (until the pH >7) and brine and then dried over $MgSO_4$. The preadsorbed reaction products (1 g of silica gel) were chromatographed on a 2- × 10-cm silica gel column, eluting with 10% EtOAc/hexane + 0.5% AcOH. Purification in this manner furnished additional deprotected *exo-O,S*-acetal **53** (R = H) (5.6 mg, 2.8%) as well as partially deprotected starting materials. The latter were resubjected to the deprotection conditions, which allowed an additional 3.6 mg (2%) to be collected. The total yield of *exo-O,S*-acetal **53** (R = H) was 96%.

Unfortunately, *endo-O,S*-acetal **53** (R = H) (43 mg, 0.071 mmol) was moderately soluble under the deprotection conditions, and the product did not precipitate from the solution as above. Isolation and column purification afforded 8.6 mg (28%) of the desired *endo-O,S*-acetal **53** (R = H). 2α,3aα,12aα: 0.1953 g (96.3%); mp 253 °C; TLC R_f 0.3 in 20% EtOAc/hexanes + several drops AcOH; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H), 12.06 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 9.5 Hz, 1H), 7.29−7.26 (m, 3H), 6.58 (d, J = 6.0 Hz, 1H), 5.32 (dd, J = 10.7, 4.7 Hz, 1H), 4.17 (t, J = 8.5 Hz, 1H), 2.74 (dd, J = 13.2, 5.2 Hz, 1H), 2.33 (ddd, J = 13.2, 10.7, 8.5 Hz, 1H); FTIR ($CHCl_3$) 3423 br, 3060, 3000, 1671, 1623, 1466, 1393, 1236 cm^{-1}; MS *m*/*z* 432 (M$^+$, 3), 324 (20), 323 (100), 322 (7), 295 (16), 294 (19), 293 (12), 281 (5); exact mass calcd for $C_{24}H_{16}O_6S$ 432.0668, found 432.0671. Anal. ($C_{24}H_{16}O_6S$) H, C: calcd, 66.65%; found, 65.87%. 2α,3a*β*,12a*β*: 8.6 mg (28%); mp 220−231 °C (dec); TLC R_f 0.25 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H), 12.06 (s, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.43 (d, J = 6.9 Hz, 2H), 7.39 (s, 1H), 7.36−7.20 (m, 4H), 6.56 (d, J = 6.2 Hz, 1H), 5.80 (d, J = 7.6 Hz, 1H), 4.22 (dd, J = 8.6, 6.0 Hz, 1H), 2.84 (ddd, J = 14.0, 9.2, 7.6 Hz, 1H), 2.68 (d, J = 14.0 Hz, 1H); MS *m*/*z* 432 (M$^+$, 5), 324 (20), 323 (100), 295 (18), 294 (16), 281 (6); exact mass calcd for $C_{24}H_{16}O_6S$ 432.0668, found 432.0679.

(±)-6-Deoxyversicolorin A. (±)-(3a*S*-*cis*)-3a,12a-Dihydro-4,6-dihydroxyanthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione (11). *m*-CPBA (81.9 mg, 0.40 mmol; 80−85%) was added in one portion to a stirred −15 °C solution of *O,S*-acetal **53** (R = H) (0.159 g, 0.366 mmol) in 300 mL of reagent-grade $CHCl_3$. The solution was stirred 2 h at −15 °C, during which time two lower R_f diastereomeric sulfoxides were produced (R_f 0.21 and 0.25, 30% EtOAc/hexane). When the starting material was fully consumed, the reaction was poured into 30 mL of a 10% Na_2SO_3 solution and shaken to reduce the excess *m*-CPBA. The chloroform layer was then washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and removal of solvent resulted in a yellow powder (0.170 mg, 104%). The crude sulfoxides were transferred to 100 mL of reagent-grade toluene, and the flask was fitted with a reflux condenser, lowered into a preheated 120 °C oil bath, and heated to reflux for 45 min. The reaction mixture quickly became homogeneous. After cooling, the toluene solution was washed with 5% $NaHCO_3$, water, and brine and dried over $MgSO_4$. The crude reaction products were preadsorbed onto silica gel (2 g), placed on a 2- × 15-cm column of silica gel, and eluted with a 55:40:3:2 mixture of CH_2Cl_2/hexane/EtOAc/AcOH. Isolation in this way allowed most of the 6-deoxyversicolorin A to be separated from the sulfone derivative (0.4 R_f). Impure fractions were combined and rechromatographed. The resulting yellow-orange solids were triturated with pentane five times to remove a strongly UV-active contaminant. Residual water and acetic acid were removed as their water−toluene azeotropes. After further drying (high vacuum, 10 h), (±)-6-deoxyversicolorin A **11** (104.9 mg, 89%) was obtained as an orange crystalline solid that was homogeneous by TLC and ^{1}H NMR: mp 251−252 °C (lit.[23] mp 245−246 °C from acetone); TLC R_f 0.5 in 30% EtOAc/hexanes + a few drops of AcOH; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 12.12 (s, 1H), 7.81 (dd, J = 7.3, 1.1 Hz, 1H), 7.65 (t, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.28 (dd, J = 8.5, 1.1 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 6.51 (t, J = 2.5 Hz, 1H), 5.46 (t, J = 2.6 Hz, 1H), 4.74 (ddd, J = 7.2, 2.5, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 181.4, 165.3, 162.4, 159.8, 145.6, 136.7, 136.1, 133.4, 124.7, 120.4, 120.2, 115.6, 113.1, 112.0, 103.7, 101.7, 48.2; FTIR ($CHCl_3$) 3500 br, 3001, 1670, 1636, 1618, 1610, 1466, 1381, 1363, 1303, 1283, 1272, 1225 cm^{-1}; UV λ_{max} (ϵ) 219 (11,800), 270 (10,300), 430 (4,180); MS *m*/*z* 323 (M^{+1}, 25), 322 (M$^+$, 100), 295 (17), 294 (88), 293 (95), 265 (13), 163 (6), 152 (5), 147 (9). Exact mass calcd for $C_{18}H_{10}O_6$ 322.0477, found 322.0481. Anal. ($C_{18}H_{10}O_6$) H,C: calcd, 67.08%; found, 66.01%.

***exo*-(±)-2,5-Methano-6-(methoxymethoxy)-8,10-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4-[[tris(1-methylethyl)silyl]oxy]anthra[2,3-*d*]-1,3-dioxepane-1,12-dione (50, R = OSEM).** Preparation was comparable to that of **50** (R = H). A 34% yield of anthraquinone **50** (R = OSEM) was obtained as a yellow oil: TLC R_f 0.2 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.5 Hz, 1H), 7.44 (s, 1H), 7.16 (d, J = 2.5 Hz, 1H), 5.88 (d, J = 3.0 Hz, 1H), 5.64 (s, 1H), 5.35 (s, 2H), 5.30 (s, 2H), 5.24 (d, J = 7.0 Hz, 1H, A of ABq), 5.17 (d, J = 7.0 Hz, 1H, B of ABq), 3.83 (t, J = 8.5 Hz, 2H), 3.79 (d, J = 3.9 Hz, 1H), 3.75 (t, J = 8.5 Hz, 2H), 3.59 (s, 3H), 2.62 (dt, J = 11.9, 3.4 Hz), 1.96 (d, J = 11.8 Hz), 1.1−1.0 (m, 21H), 0.97−0.92 (m, 4H), −0.02 (s, 9H), −0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 180.9, 161.4, 159.5, 156.2, 155.9, 136.1, 135.0, 126.5, 120.6, 119.0, 111.5, 110.8, 107.1, 104.6, 102.5, 99.3, 94.0, 92.7, 66.8, 57.7, 38.7, 28.5, 17.8, 17.7, 12.1, −1.43; FTIR ($CHCl_3$) 2959, 2927, 2870, 1731, 1669, 1593, 1463, 1249, 1122, 1031 cm^{-1}; MS *m*/*z* 816 (M$^+$, 0.21), 773 (1.4), 743 (11), 715 (4), 685 (7), 643 (4), 625 (6), 439 (5); exact mass calcd for $C_{41}H_{64}O_{11}Si_3$ 816.3757, found 816.3768. Anal. ($C_{41}H_{64}O_{11}Si_3$) C, H.

(2α,3a*β*,12a*β*)-2,3,3a,12a-Tetrahydro-2-hydroxy-4-(methoxy-

methoxy)-6,8-bis[[2-(trimethylsilyl)ethoxy]methoxy]anthra[2,3-*b*]-furo[3,2-*d*]furan-5,10-dione (51, R = OSEM). Preparation was comparable to that of **51** (R = H). A 90% yield of the hemiacetal as a yellow crystalline solid was obtained: mp 78−79 °C. Data for the (2α,3a*β*,12a*β*)-hemiacetal (major isomer): TLC R_f 0.3 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.5 Hz, 1H), 7.42 (s, 1H), 7.15 (d, J = 2.5 Hz, 1H), 6.46 (d, J = 6.2 Hz, 1H), 5.72 (dd, J = 4.7, 2.8 Hz, 1H), 5.35 (2H, ABq J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 16.1 Hz), 5.32 (d, J = 7.2 Hz, 1H, B of ABq), 5.30 (s, 2H), 5.17 (d, J = 7.1 Hz, 1H, B of ABq), 4.21 (dd, J = 9.8, 6.3 Hz), 3.82 (t, J = 8.2 Hz, 2H), 3.74 (t, J = 8.4 Hz, 2H,), 3.58 (s, 3H), 2.61 (d, J = 13.2 Hz, 1H), 2.39 (m, 1H), 0.944 (t, J = 8.2 Hz, 2H), 0.938 (t, J = 8.4 Hz, 2H), −0.03 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 181.0, 162.1, 161.3, 159.4, 155.2, 136.9, 136.1, 130.8, 122.0, 118.8, 112.8, 110.7, 107.2, 104.5, 101.7, 100.2, 94.0, 92.7, 66.9, 57.2, 44.4, 38.4, 18.1, −1.4; FTIR ($CHCl_3$) 3589, 3013, 2942, 2896, 1666, 1596, 1314, 1211 cm^{-1}; MS m/z 660 (M^+, 0.15), 529 (2), 382 (7); exact mass calcd for $C_{32}H_{44}O_{11}Si_2$ 660.2422, found 660.2430. Anal. ($C_{32}H_{44}O_{11}Si_2$) C, H.

(2α,3aα,12aα)-2,3,3a,12a-Tetrahydro-4-(methoxymethoxy)-2-(phenylthio)-6,8-bis[[2-(trimethylsilyl)ethoxy]methoxy]anthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione (52, R = OSEM). To a 4-mL solution of tri-*n*-butylphosphine (0.443 g, 2.19 mmol) in THF at −78 °C was added a solution of *N*-phenylthiosuccinimide (0.454 g, 2.19 mmol) in 6 mL of tetrahydrofuran in one portion. The mixture was stirred at −78 °C for 15 min and then warmed to 0 °C. The hemiacetal (0.33 g, 0.5 mmol) was dissolved in 3 mL of THF and then cooled to −100 °C. Four milliliters of the thiophosphonium intermediate solution was added to produce a bright red-colored solution that was warmed to −20 °C over 2 h. The reaction mixture was poured into brine and extracted with ether. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to produce a yellow oil. Column chromatography (2 × 10 cm, 10−30% EtOAc/hexanes) afforded 0.305 g of the (2α,3aα,12aα)-*O*,*S*-acetal and 0.035 g of the (2α,3a*β*,12a*β*)-*O*,*S*-acetal as yellow oils **52** (R = OSEM) in a combined yield of 92% (8.7:1 ratio). 2α,3a*β*,12a*β*-*O*,*S*-acetal: recrystallized from acetone to obtain a yellow crystalline solid; mp 56−57 °C; TLC R_f 0.6 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.5 Hz, 1H), 7.50−7.47 (m, 2H), 7.44 (s, 1H), 7.31−7.25 (m, 3H), 7.16 (d, J = 2.3 Hz, 1H), 6.48 (d, J = 5.9 Hz, 1H), 5.37 (d, J = 7.0 Hz, 1H, A of ABq), 5.33 (d, J = 7.0 Hz, 1H, B of ABq), 5.31 (d, J = 7.1 Hz, 1H, A of ABq), 5.30 (s, 2H), 5.26 (dd, J = 10.7, 5.0 Hz, 1H), 5.15 (d, J = 7.1 Hz, 1H, B of ABq), 4.25 (dd, J = 8.2, 5.9 Hz, 1H), 3.82 (t, J = 8.3 Hz, 2H), 3.74 (t, J = 8.3 Hz, 2H), 3.58 (s, 3H), 2.81 (dd, J = 12.8, 5.0 Hz), 2.34 (ddd, J = 12.8, 10.7, 8.2 Hz), 0.95 (t, J = 8.3 Hz, 2H), 0.94 (t, J = 8.3 Hz, 2H), −0.02 (s, 9H), −0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 180.9, 162.8, 161.5, 159.5, 137.2, 136.1, 133.3, 131.7, 129.1, 128.2, 127.7, 122.2, 118.7, 112.1, 110.8, 107.2, 104.4, 101.7, 94.0, 92.7, 86.3, 66.9, 57.3, 45.5, 37.4, 18.1, −1.38; FTIR ($CHCl_3$) 3013, 2943, 2896, 1661, 1596, 1567, 1478, 1460, 1308, 1243, 1155 cm^{-1}; MS m/z 752 (M^+, 0.04), 679 (3), 621 (2), 585 (3), 527 (4), 495 (6), 423 (5); exact mass calcd for $C_{38}H_{48}O_{11}SSi_2$ 752.2507, found 752.2517. (0.4%) 2α,3a*β*,12a*β*: TLC R_f 0.4 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.4 Hz, 1H), 7.49 (s, 1H), 7.41 (m, 2H), 7.27−7.21 (m, 3H), 7.18 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 6.1 Hz, 1H), 5.75 (dd, J = 7.6, 1.1 Hz, 1H), 5.39 (d, J = 7.1 Hz, 1H, A of ABq), 5.36 (d, J = 7.1 Hz, 1H, B of ABq), 5.35 (d, J = 7.1 Hz, 1H, A of ABq), 5.31 (s, 2H), 5.20 (d, J = 7.1 Hz, 1H, B of ABq), 4.31 (ddd, J = 9.3, 6.2, 1.0 Hz, 1H), 3.84 (m, 2H), 3.75 (m, 2H), 4.60 (s, 3H, OCH_3), 2.85 (ddd, J = 13.8, 9.5, 7.7 Hz, 1H), 2.73 (d, J = 13.9 Hz, 1H), 0.96 (t, J = 8.3 Hz, 2H), 0.94 (t, J = 8.3, 2H), −0.01 (s, 9H), −0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 181.1, 163.2, 161.4, 159.6, 155.6, 137.2, 136.2, 134.3, 132.2, 129.6, 128.8, 127.6, 122.0, 118.8, 113.3, 110.8, 107.2, 104.7, 101.8, 94.1, 92.7, 88.3, 66.9, 57.2, 45.6, 38.1, 18.1, −1.35; FTIR ($CHCl_3$) 3001, 2954, 1660, 1596, 1471, 1436, 1317, 1246, 1157 cm^{-1}.

(2α,3aα,12aα)-2,3,3a,12a-Tetrahydro-4,6,8-trihydroxy-2-(phenylthio)anthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione (53, R = OH). Preparation was comparable to that of **53** (R = H) in 97% yield as a dark orange solid: mp 253−254 °C (dec); TLC R_f 0.3 in 20% EtOAc/hexanes + 1% AcOH; ^{1}H NMR (400 MHz, DMSO) δ 12.46 (s, 1H), 12.08 (s, 1H), 11.37 (br s, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.37−7.29 (m, 3H), 7.13 (m, 2H), 6.60 (d, J = 5.9 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 5.34 (dd, J = 10.7, 4.9 Hz, 1H), 4.26 (dd, J = 8.9, 7.4, Hz, 1H), 2.59 (dd, J = 12.9, 4.7 Hz, 1H), 2.28 (ddd, J = 12.9, 10.7, 8.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 189.0, 180.7, 165.2, 164.6, 164.2, 159.0, 135.5, 134.6, 133.1, 130.8, 129.0, 127.4, 119.6, 112.6, 111.0, 108.8, 108.3, 107, 101.6, 85.4, 43.3, 35; FTIR (KBr) 3000 br, 1631, 1616, 1464, 1440, 1328, 1287 cm^{-1}; MS m/z 448 (M^+, 3), 388 (3), 340 (21), 339 (100), 311 (19), 310 (18); exact mass calcd for $C_{24}H_{16}O_7S$ 448.0617, found 448.0622.

(±)-Versicolorin A (4). (±)-(3a*S*-*cis*)-3a,12a-dihydro-4,6,8-trihydroxyanthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione. *O*,*S*-Acetal **53** (R = OH) (0.252 g, 0.56 mmol) was brought up in 350 mL of ethyl acetate and cooled to −30 °C. *m*-CPBA (0.242 g, 1.12 mmol) was added in one portion and the mixture stirred for 2 h, during which time the temperature rose to −15 °C. The excess oxidant was reduced by the addition of methyl sulfide (0.4 mL) with stirring for 30 min. The reaction mixture was washed with two portions of 10% aqueous Na_2SO_3 and brine. After back extraction with two portions of ethyl acetate, the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a yellow solid. The crude sulfoxides were then preadsorbed onto 5 g of silica, placed atop a 3- × 15-cm column, and eluted with 20−90% EtOAc/hexanes. The desired sulfoxide derivatives (0.205 g) were isolated in 79% yield. The sulfoxides (0.205 g, 0.44 mmol) were dissolved in ca. 10 mL of DMSO and 40 mL of toluene and heated at reflux (125 °C) for 1 h. After the reaction mixture had cooled, the solution was diluted with 300 mL of ethyl acetate and washed three times with water. The extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to a volume of ca. 100 mL. Column chromatography on silica gel (3 × 20 cm, 15−30% EtOAc/hexanes + 0.5% AcOH) resulted in the isolation of 0.148 g (100%) of the desired (±)-versicolorin A (**4**) as an orange powder: mp 282 °C (darkens ca. 270 °C then dec; lit.[64] mp 289 °C from acetone); TLC R_f 0.4 in 30% EtOAc/hexanes + 0.5% AcOH; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.29 (s, 1H), 12.00 (s, 1H), 11.12 (br s, 1H), 7.18 (s, 1H), 7.14 (br d, J = 2.5 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 6.72 (t, J = 2.4 Hz, 1H), 6.59 (br d, J = 2.5 Hz, 1H), 5.41 (t, J = 2.4 Hz, 1H), 4.77 (dt, J = 7.1, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 189.0, 180.8, 165.2, 164.2, 163.6, 158.3, 145.8, 135.3, 134.8, 120.6, 113.0, 111.4, 108.9, 108.5, 107.9, 101.8, 101.5, 47.4; MS m/z 338 (M^+, 100), 310 (95), 309 (92), 281 (23); exact mass calcd for $C_{18}H_{10}O_7$ 338.0427, found 338.0426.

Versicolorin C Synthesis. *trans*-(±)-5-Bromo-2,3-dihydro-4-(methoxymethoxy)-2-[[tris(1-methylethyl)silyl]oxy]-3-benzofuranethanol (55). A solution of ester **48** (0.387 g, 0.748 mmol) in 9 mL of THF was cooled to −43 °C, and 1.0 M DIBAH in hexanes (1.87 mL, 1.87 mmol) was added dropwise over 30 s. The reaction mixture was stirred at −43 °C for 30 min and then heated to 0 °C for an additional 30 min. The reaction was quenched by addition of excess MeOH (0.24 g, 7.5 mmol) at 0 °C, and the mixture was partitioned between ether and 1 N HCl. The ether extracts were washed with 0.15 N HCl, 5% $NaHCO_3$, and brine and dried over $MgSO_4$. Removal of the ether resulted in a cloudy, colorless oil, which was chromatographed on silica gel (2 × 10 cm) using 10% EtOAc/hexanes. Purification in this manner furnished alcohol **55** (0.332 g, 94%) as a colorless viscous oil: TLC R_f 0.2 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 5.78 (s, 1H), 5.22 (d, J = 5.8 Hz, 1H), 5.10 (d, J = 5.8 Hz), 3.73 (m, 2H), 3.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 1H), 2.10 (t, J = 5.9 Hz, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.1−1.0 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.3, 132.8, 124.0, 107.9, 107.1, 106.6, 99.4, 60.4, 57.9, 47.9, 34.6, 17.8, 17.7, 12.0; FTIR ($CHCl_3$) 3618, 3524 br, 2943, 2866, 1605, 1587, 1450, 1392, 1160, 1129 cm^{-1}; MS m/z 475 (0.15), 473 (M^+ − 1, 0.06), 431 (0.2), 429 (0.3), 401 (4), 399 (4), 371 (6), 369 (6), 301 (46), 299 (46); exact mass calcd for $C_{21}H_{35}BrO_5Si$ 476.1417, found 476.1417. Anal. ($C_{21}H_{35}BrO_5Si$) C, H.

***trans*-(±)-[5-Bromo-4-(methoxymethoxy)-3[2-[[tris(1-methylethyl)silyl]oxy]ethyl]benzofuran-2-yloxy]tris(1-methylethyl]silane (56).** Triisopropylsilyl triflate (0.263 g, 0.833 mmol) was added dropwise to a −43 °C solution of alcohol **55** (0.329 g, 0.694 mmol) and 2,6-lutidine (0.104 g, 0.971 mmol) in 7 mL of dry CH_2Cl_2. After being stirred for 2 h at −43 °C, the reaction was quenched by the

dropwise addition of *N*,*N*-dimethylethanolamine (0.031 g, 0.35 mmol). After 30 min, the reaction mixture was concentrated, loaded onto a silica gel column (1 × 15 cm), and eluted with 1% ether/hexanes, affording alcohol **55** (0.433 g) as a clear viscous oil in 99% yield: TLC R_f 0.5 in 2% ether/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 5.85 (br s, 1H), 5.17 (2H, ABq, J_{AB} = 6.1 Hz, $\Delta\nu_{AB}$ = 14.8 Hz), 3.79 (ddd, J = 10.4, 6.4, 5.2 Hz, 1H), 3.74 (ddd, J = 10.4, 8.6, 5.2 Hz, 1H), 3.59 (s, 3H), 3.51 (dd, J = 9.6, 4.0 Hz, 1H), 2.02 (dddd, J = 14.4, 8.4, 6.4, 4.0 Hz, 1H), 1.69 (dddd, J = 14.4, 10.0, 9.2, 5.2 Hz, 1H), 1.1−1.0 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 151.0, 132.6, 123.9, 107.4, 107.0, 105.8, 98.6, 60.9, 57.8, 48.3, 34.5, 18.0, 17.87, 17.75, 12.1, 12.0; FTIR ($CHCl_3$) 2945, 2867, 1605, 1587, 1451, 1390, 1158, 1133, 1105 cm^{-1}; MS *m*/*z* 632 (0.4), 630 (M^+, 0.3), 589 (9), 587 (8), 557 (4), 555 (4), 415 (8), 413 (8), 383 (26), 381 (24), 157 (22), 145 (44); exact mass calcd for $C_{30}H_{55}BrO_5Si_2$ 630.2771, found 630.2779.

***trans*-(±)-2,3-Dihydro-4,6,8-tri(methoxymethoxy)-3-[2-[[tris-(1-methylethyl)silyl]oxy]ethyl]-2-[[tris(1-methylethyl)silyl]oxy]-anthra[2,3-*b*]furan-5,10-dione (57).** Distilled tetramethylpiperidine (TMP, 0.593 g, 4.19 mmol) in 6.5 mL of dry THF was cooled to −30 °C. *n*-BuLi in hexanes (2.62 mL, 4.19 mmol) was added dropwise over 15 min. The temperature was lowered to −78 °C before 5,7-bis-(methoxymethoxy)phthalide (**49**, R = OSEM) (0.329 g, 1.29 mmol, dissolved in 3 mL of THF) was added dropwise *in less than 5−8 min* by cannula. The temperature was increased to −30 °C *2 min* after completion of phthalide addition. Dropwise addition of bromide **56** (0.407 g, 0.644 mmol in 3 mL of dry THF) through a double-ended needle was begun immediately upon warming of the solution to −30 °C. The mixture was stirred for 2 h and quenched by the addition of 2 M acetic acid/THF (1.93 mL, 3.86 mmol) to the −30 °C reaction mixture. Compressed air was bubbled through the reaction mixture until the reaction color was light orange. The reaction mixture was poured into 5% $NaHCO_3$, and the aqueous phase was extracted with ether until no yellow color was seen in the organic phase. The ether extracts were washed with 5% $NaHCO_3$ and brine and dried over Na_2SO_4. Purification of the red oil by Chromatotron (2-mm rotor, 10−30% EtOAc/hexanes) produced anthraquinone **57** (0.237 g, 46%) as a viscous orange oil: TLC R_f 0.1 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.5 Hz, 1H), 7.46 (s, 1H), 7.12 (d, J = 2.5 Hz, 1H), 6.03 (d, J = 1.0 Hz, 1H), 5.35−5.15 (m, 6H, 3 overlapping ABq), 3.82 (m, 1H), 3.75 (m, 1H), 3.60 (dd, J = 9.2, 4.0 Hz, 1H), 3.56 (s, 6H), 3.50 (s, 3H), 2.17 (m, 1H), 1.78 (m, 1H), 1.2−1.0 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 181.4, 162.5, 161.0, 159.1, 155.6, 136.6, 136.3, 131.0, 122.0, 119.5, 111.0, 107.2, 106.7, 104.7, 101.0, 95.7, 94.3, 61.0, 57.6, 56.6, 56.5, 48.1, 18.0, 17.8, 17.7, 12.1, 12.0; FTIR ($CHCl_3$) 3011, 2946, 2868, 1667, 1597, 1464, 1314, 1148, 1085 cm^{-1}; MS *m*/*z* 802 (M^+, 1), 771 (22), 760 (11), 759 (19), 727 (13), 716 (15), 715 (30), 684 (28), 683 (54), 627 (5); exact mass calcd for $C_{42}H_{66}O_{11}Si_2$ 802.4144, found 802.4151.

(±)-Versicolorin B (9). (±)-(3a*S*-*cis*)-2,3,3a,12a-tetrahydro-4,6,8-trihydroxyanthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione. Anthraquinone **57** (0.237 g, 0.294 mmol) was dissolved in THF (5 mL), water (0.3 mL), and acetic acid (0.3 mL). Two drops of 6 N HCl were added to the homogeneous reaction mixture. The reaction was heated at 60 °C until (±)-versicolorin B (lowest R_f material, 0.3 in 30% EtOAc/hexanes + 1% AcOH) was the major product. The reaction mixture was poured directly into brine, and the aqueous phase was extracted with ether. The extracts were washed with water, a small amount of 5% $NaHCO_3$, and brine and dried over $MgSO_4$. The crude anthraquinones were preadsorbed onto 3 g of silica gel, loaded onto a column of silica gel (2 × 10 cm), and eluted with 20−50% EtOAc/hexanes containing ∼0.5% AcOH. Fractions containing partially protected anthraquinones were collected and concentrated; the residue was then resubjected to acidic conditions to effect complete deprotection. The chromatographed versicolorin B **9** was then recrystallized from acetone/hexane as a fine orange powder: 0.099 g (98.9%); mp 335 °C (dec) (lit.[64] mp > 310 °C); TLC R_f 0.3 in 30% EtOAc/hexanes + 1% AcOH; ^{1}H NMR (d_6-DMSO) δ 12.34 (s, 1H), 12.01 (s, 1H, 11.01 (br s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.09 (s, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 5.6 Hz, 1H), 4.16 (ddd, J = 8.0, 5.6, 2.0 Hz, 1H), 4.10 (ddd, J = 8.8, 7.2, 1.6 Hz, 1H), 3.56 (ddd, J = 10.8, 8.8, 6.4 Hz, 1H), 1.75 (dddd, J = 12.8, 10.8, 8.0, 7.2 Hz, 1H), 1.69 (dddd, J = 12.8, 6.4, 2.0, 1.6 Hz, 1H); ^{13}C NMR (d_6-DMSO) δ 189.1, 180.9, 165.3, 165.2, 164.3, 159.0, 135.4, 134.8, 120.2, 113.3, 110.9, 108.8, 108.5, 108.0, 101.3, 67.2 43.5, 30.2; FTIR (KBr) 3400 br, 2978, 2896, 1624, 1610, 1579, 1472, 1391, 1317, 1165 cm^{-1}; UV λ_{max} (ϵ) in MeOH 203.5 (13 640), 222 (22 910), 264.5 (13 610), 290.0 (21 310), 314.0 (10 840), 452.5 (6370); MS *m*/*z* 341 (M + 1, 15), 340 (M^+, 100), 325 (50), 312 (8), 311 (32), 298 (15), 297 (85); exact mass calcd for $C_{18}H_{12}O_7$ 340.0583, found 340.0586.

Versicolorin A Hemiacetal (54). (2α,3a*β*,12a*β*)-2,3,3a,12a-Tetrahydro-2,4,6,8-tetrahydroxy-anthra[2,3-*b*]furo[3,2-*d*]furan-5,10-dione. Anthraquinone **50** (115.8 mg, 0.142 mmol) was dissolved in THF (4 mL), water (0.3 mL), acetic acid (0.3 mL), and 2 drops of 6 N HCl. The mixture was heated at 60 °C until versicolorin A hemiacetal (lowest R_f material, 0.3 in 20% EtOAc/hexanes + 0.5% AcOH) was the major product visible by TLC analysis. After the mixture was poured into brine, the aqueous phase was extracted four times with ether. The ether extracts were washed with water, 5% $NaHCO_3$, and brine and dried over $MgSO_4$. The crude versicolorin A hemiacetal was preadsorbed onto 10 g of silica gel, loaded onto a column of silica gel (5 × 15 cm), and eluted with 20−50% EtOAc/hexanes with ∼1% AcOH. Any partially deprotected anthraquinones were resubjected to the acidic conditions. Recrystallization from acetone produced versicolorin A hemiacetal **54** as a fine orange crystalline powder: 48.9 mg (96.6%); mp 264−265 °C (dec) (lit.[67] mp 269−270 °C from acetone); TLC R_f 0.2 in 30% EtOAc/hexanes + 1% AcOH. Once VAOH is dissolved in DMSO, it is free to slowly isomerize to the linear *exo*-hemiacetal and to the angular *endo*- and *exo*-hemiacetal forms as well. If the sample is prepared and the NMR spectrum is taken within 30 min of sample preparation, the NMR spectrum indicates a roughly 8:1 ratio of the linear *endo* and *exo* forms, respectively: ^{1}H NMR (400 MHz, DMSO), for the linear *endo* isomer (∼6−8:1 *endo:exo*), δ 12.34 (s, 1H), 12.26 (s, 1H, 11.32 (br s, 1H), 7.11 (d, J = 2.2 Hz, 1H), 7.05 (s, 1H), 6.58 (d, J = 2.2 Hz), 6.52 (d, J = 6.3 Hz, 1H), 5.62 (br t, J = 4.0 Hz, 1H), 4.10 (dd, J = 9.5, 6.4 Hz, 1H), 2.26 (ddd, J = 13.1, 9.5, 4.6 Hz, 1H), 2.14 (d, J = 13.1 Hz, 1H); FTIR (KBr) 3463 br, 3258 br, 2982, 2873, 1621, 1609, 1445, 1382, 1319, 1289, 1182, 1164 cm^{-1}; UV λ_{max} (ϵ) in MeOH 203.5 (16 500), 222.0 (26 400), 263.5 (16 100), 291.0 (22 400), 457 (7400); MS *m*/*z* 356 (M^+, 23), 338 (18), 329 (14), 328 (60), 311 (29), 310 (95), 309 (85), 300 (77), 299 (100), 285 (42); exact mass calcd for $C_{18}H_{12}O_8$ 356.0532, found 356.0537.

2,4,6-Trihydroxybenzaldehyde. *N*,*N*-Dimethylformamide (25.50 g, 0.3489 mol) was cooled in a 0 °C bath, and distilled $POCl_3$ (53.49 g, 0.3489 mol) was added. The orange solution was stirred for 20 min until the reagent solidified. Distilled acetonitrile (320 mL, 1.1 M) was added until the white solid dissolved. The reaction mixture was stirred a further 45 min at room temperature under argon. Phloroglucinol **60** (40.00 g, 0.3172 mol) in acetonitrile (320 mL, 1.0 M) was cannulated into the flask ,and the mixture was stirred for 18 h at room temperature. Imine hydrolysis using 2:1 MeOH/H_2O took place over 4 h at room temperature. The solution was concentrated and chromatographed on a short column of silica gel, topped by a 1:1 Norit/silica mixture to remove the colored impurities and baseline material. The filtrate was concentrated and rechromatographed using 50% EtOAc/hexanes as the eluent. The 2,4,6-trihydroxybenzaldehyde was obtained (38.58 g) as a reddish solid (79.2%). This color could be removed for reactions run on a small scale (∼1 g) by this chromatographic method: mp 183 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 10.00 (s, 1H), 5.76 (s, 2H).

2,4,6-Tris(*O*-methoxymethyl)benzaldehyde (61). 2,4,6-Trihydroxybenzaldehyde (38.58 g, 250.4 mmol) in dry DCM (0.6 M, 400 mL) was treated with MOMCl (100.8 g, 1.252 mol) and the dropwise addition of DIPEA (169.9 g, 1.315 mol) over 1.5 h. The red/black solution was stirred overnight at 0 °C. Solvent and any excess MOMCl were removed under reduced pressure, leaving a solid yellow residue, which was dissolved in ethyl acetate and partitioned with distilled H_2O. The aqueous layer was extracted with ethyl acetate (4×). The extracts were pooled and washed with cold 0.5 N HCl (1×), 2 N NaOH (2×), and brine (1×) and then dried over $MgSO_4$. The oily residue was

(67) Chen, P. N.; Kingston, D. G. I.; Vercellotti, J. R. *J. Org. Chem.* **1977**, *42*, 3599−3605.

purified by silica gel chromatography (7 × 20 cm, 20% EtOAc/hexanes, loaded with 20% EtOAc/hexanes and DCM). The desired triprotected aldehyde (45.9 g, 64.1%) was isolated as white crystals prone to decomposition to the 2,4-diprotected aldehyde: mp 60 °C; TLC R_f 0.31 (50:50 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 6.52 (s, 2H), 5.26 (s, 4H), 5.20 (s, 2H), 3.51 (s, 6H), 3.50 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 187.6, 163.3, 161.1, 111.0, 96.8, 94.9, 94.2, 56.5; IR ($CDCl_3$) 1679, 1604, 1578, 1392, 1223, 1154, 1144, 1051 cm^{-1}; MS *m*/*z* 286 (2), 241 (2), 224 (6), 209 (1); exact mass calcd for $C_{13}H_{18}O_7$ 286.1053, found 286.1056. Anal. ($C_{13}H_{18}O_7$) C, H.

Ethyl 3-[Tris-2′,4′,6′-(*O*-methoxymethyl)phenyl]-4-oxobutanoate (62). A 0.645 M THF solution (12.5 mL, 8.04 mmol) of phosphonate **23** was cooled to −78 °C with stirring, and *n*-BuLi (2.38 M solution in hexanes, 8.04 mmol) was added dropwise over 5 min. An additional 35 mL of THF was added, and the solution was stirred for 1 h under an inert atmosphere. A 20-mL solution of phloroglucinaldehyde **61** (2.00 g, 6.99 mmol) in THF was cannulated into the ylide flask, stirred at −78 °C for 30 min, and then warmed to room temperature over 2.5 h. The resulting yellow azadiene solution was cooled to −78 °C, treated with another equiv of *n*-BuLi (3.8 mL, 9.09 mmol), and stirred for 2 h. Ethyl bromoacetate (1.87 g, 11.18 mmol) was rapidly added by syringe and stirred for 2.5 h as the reaction mixture warmed to room temperature. Approximately 30 mL of a 1 M aqueous tartaric acid solution was added with stirring for 1 h at 25 °C. The reaction mixture was poured into brine and extracted with ether (4×). The extracts were pooled,washed with ice-cold 5% HCl (2×), 5% $NaHCO_3$ (1×), H_2O (1×), and brine (1×), and dried over $MgSO_4$. Purification of the residue by silica gel column chromatography (3 × 20 cm, loaded and run with 15% EtOAc/hexanes) afforded 1.82 g of **62** as a yellow oil (67.4%): TLC R_f 0.44 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 6.55 (s, 2H), 5.15 (s, 2H), 5.14 (s, 4H), 4.52 (dd, J = 8.3, 5.4 Hz, 1H), 4.14 (qt, J = 7.1 Hz, 2H), 3.48 (s, 3H), 3.45 (s, 6H), 3.15 (dd, J = 16.2, 8.3 Hz, 1H), 2.40 (dd, J = 16.2, 5.4 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.0, 172.4, 158.6, 156.7, 108.2, 96.7, 94.6, 94.5, 60.5, 56.4, 56.2, 44.5, 33.0 14.2; IR ($CHCl_3$) 3024, 2960, 2935, 2829, 1725, 1609, 1595, 1396, 1155, 1052 cm^{-1}; MS *m*/*z* 386 (M^+, 1), 357 (1), 325 (1), 324, (7); exact mass calcd for $C_{18}H_{26}O_9$ 386.1577, found 386.1581.

Ethyl [2,3-Dihydro-4,6-bis(*O*-methoxymethyl)-2-{[tris(1-methylethyl)silyl]oxy}-3-benzofuranacetate (63). Aldehyde **62** (2.20 g, 5.70 mmol) in dry THF (38 mL, 0.15 M) was cooled to 0 °C, and triethylamine (0.127 g, 1.43 mmol) was added, followed by TIPSTf in a dropwise manner over 2 min. The resulting solution was stirred for 2 h at 0 °C. TLC showed the presence of starting material, so another 0.2 equiv of TIPSTf (0.026 g, 0.030 mmol) was added, and stirring was continued for 1 h. The reaction mixture was partitioned between ether and H_2O, and three extractions of the aqueous phase were performed with ether, which were pooled and washed with H_2O (1×), ice-cold 5% HCl (1×), 5% $NaHCO_3$ (1×), and brine (1×) and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving a pale yellow oil. The oil was purified by silica gel chromatography (3.5 × 24 cm, 10% EtOAc/hexanes). The ester **63** was isolated (2.23 g) as a light yellow oil (78.5%): TLC R_f 0.42 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 1.9 Hz, 1H, 6.25 (d, J = 1.9 Hz, 1H), 5.87 (s, 1H), 5.16 (2H, ABq, J_{AB} = 3.0 Hz, $\Delta\nu_{AB}$ = 9.6 Hz), 5.11 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 5.8 Hz), 4.13 (qt, J = 7.2 Hz, 2H), 3.58 (dd, J = 10.6, 3.8 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 2.77 (dd, J = 15.7, 3.9 Hz, 1H), 2.37 (dd, J = 15.7, 10.5 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.05−1.12 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.6, 159.9 159.2, 154.3, 109.6, 106.0, 95.8, 94.8, 94.2, 92.8, 60.5, 56.2, 56.0, 46.2, 35.9, 17.8, 17.7, 14.2, 12.1; IR ($CHCl_3$) 3011, 2959, 2868, 1728, 1610, 1498, 1249, 1155, 1133 cm^{-1}; MS *m*/*z* 498 (M^+, 3), 455 (19), 423 (12), 377 (20), 324 (18); exact mass calcd for $C_{25}H_{42}O_8Si$ 498.2649, found 498.2656. Anal. ($C_{25}H_{42}O_8Si$) C, H.

Ethyl 5-Bromo-2,3-dihydro-4,6-bis(*O*-methoxymethyl)-2-{[tris-(1-methylsilyl]oxy}-3-benzofuranacetate (64). Ester **63** (12.85 g, 25.77 mmol) in chloroform (258 mL, 0.1 M; dried by filtration through alumina) was treated with *N*-bromosuccinimide (5.045 g, 28.34 mmol) and stirred at 0 °C for 3.5 h. The resulting yellow-orange solution was treated with hexanes to precipitate the succinimides, allowed to stand overnight, and then filtered. The filtrate was concentrated and placed directly on a silica gel column. The desired bromide **64** (13.87 g) was isolated as a pale yellow oil (93.2%): TLC R_f 0.53 (85:15 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 5.84 (s, 1H), 5.20 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 13.4 Hz), 5.16 (2H, ABq, J_{AB} = 6.2 Hz, $\Delta\nu_{AB}$ = 3.6 Hz), 4.14 (qt, J = 7.1 Hz, 2H), 3.68 (dd, J = 10.9, 3.5 Hz, 1H), 3.60 (s, 3H), 3.51 (s, 3H), 2.81 (dd, J = 15.7, 3.3 Hz, 1H), 2.34 (dd, J = 15.8, 11.0 Hz, 1H), 1.24 (t, J = 7.3 Hz, 3H), 1.05 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.3, 158.9, 155.4, 152.0, 115.7, 105.9, 99.1, 98.6, 95.5, 95.4, 60.7, 57.6, 56.4, 47.3, 35.9, 17.8, 17.7, 14.1; IR ($CHCl_3$) 2944, 2861, 1727, 1614, 1591, 1466, 1389, 1154, 1098 cm^{-1}; MS *m*/*z* 578 (M^+, 3), 576 (2), 533 (11), 501 (4), 457 (5); exact mass calcd for $C_{25}H_{41}O_8SiBr$ 576.1754, found 576.1759. Anal. ($C_{25}H_{41}O_8SiBr$) C, H. *cis*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.22 (d, J = 6.2 Hz, 1H), 5.19 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 7.5 Hz), 5.09 (2H, ABq, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 9.3 Hz), 4.13 (qt, J = 7.3 Hz, 2H), 4.00 (ddd, J = 11.3, 6.2, 3.3 Hz, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.12 (dd, J = 17.5, 3.2 Hz, 1H), 2.87 (dd, J = 17.6, 11.4 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.05 (m, 21H).

5-Bromo-2,3-dihydro-4,6-bis(*O*-methoxymethyl)-2-{[tris(1-methylethyl)silyl]oxy}-3-benzofuranacetaldehyde (65). The procedure used was comparable to the preparation of **27**, giving *cis*- and *trans*-aldehydes **65** as a colorless oil in 94.5% yield: TLC R_f 0.24 (90:10 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J = 1.2 Hz, 1H), 6.55 (s, 1H), 5.70 (d, J = 0.9 Hz, 1H), 5.20 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 14.6 Hz), 5.14 (2H, ABq, J_{AB} = 6.2 Hz, $\Delta\nu_{AB}$ = 7.4 Hz), 3.76 (dd, J = 9.9, 3.7 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 2.94 (ddd, J = 18.0, 3.8, 1.0 Hz, 1H), 2.62 (ddd, J = 18.0, 10.0, 1.5 Hz, 1H), 1.04−1.08 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.2, 159.0, 155.4, 151.9, 115.5, 106.1, 99.2, 98.7, 95.7, 95.4, 57.7, 56.4, 45.4, 44.8, 17.8, 17.7, 12.1; IR ($CHCl_3$) 2944, 2870, 1724, 1617, 1589, 1463, 1389, 1156, 1040 cm^{-1}; MS *m*/*z* 534 (1), 532 (1), 459 (2), 457 (1), 429 (3), 427 (3), 387 (3), 332 (15), 330 (15), 300 (3), 298 (3); exact mass calcd for $C_{23}H_{37}O_7SiBr$ 532.1492, found 532.1489. Anal. ($C_{23}H_{37}O_7BrSi$) C, H, Br. *cis*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 6.52 (s, 1H), 6.22 (d, J = 6.3 Hz, 1H), 5.20 (2H, ABq, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 8.1 Hz), 5.08 (2H, ABq, J_{AB} = 6.1 Hz, $\Delta\nu_{AB}$ = 15.5 Hz), 3.76 (ddd, J = 9.9, 3.7, 1.8 Hz, 1H), 3.56 (s, 3H), 3.51 (s, 3H), 3.11 (m, 1H), 3.10 (m, 1H), 1.04−1.08 (m, 21H).

[7-Bromo-2,5-methano-6,8-bis(*O*-methoxymethyl)-1,3-benzodioxepan-4-yloxy]tris(1-methylethylsilane). The procedure was comparable to the preparation of **37**, giving desired acetal **66** as a colorless oil in 93% yield: TLC R_f 0.48 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 5.81 (d, J = 3.2 Hz, 1H), 5.61 (s, 1H), 5.17 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 5.4 Hz), 5.10 (2H, ABq, J_{AB} = 6.2 Hz, $\Delta\nu_{AB}$ = 8.6 Hz), 3.63 (s, 3H), 3.51 (d, J = 3.5 Hz, 1H), 3.48 (s, 3H), 2.53 (ddd, J = 11.5, 3.8, 3.7 Hz, 1H), 1.92 (d, J = 11.5 Hz, 1H), 1.1−1.2 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.4, 152.6, 152.1, 114.4, 104.9, 101.3, 100.3, 99.5, 99.2, 95.1, 57.9, 56.4, 38.7, 28.8, 17.9, 17.8, 12.1; IR ($CHCl_3$) 2943, 2872, 1608, 1572, 1467, 1390, 1155 cm^{-1}; MS *m*/*z* 534 (M^+, 4), 532 (3), 429 (3), 427 (3), 332 (26), 330 (26), 300 (5), 298 (5), 287 (4), 285 (4), 219 (3); exact mass calcd for $C_{23}H_{37}O_7SiBr$ 532.1492, found 532.1499. Anal. ($C_{23}H_{37}O_7SiBr$) C, H, Br.

[7-Formyl-2,5-methano-6,8-bis(*O*-methoxymethyl)-1,3-benzodioxepan-4-yloxy]tris(1-methylethylsilane) (67). The bromide **66** (0.973 g, 1.82 mmol) in dry pentane (0.08 M, 23.0 mL) was cooled to −43 °C, and *s*-BuLi in cyclohexanes (3.04 mL, 3.19 mmol) was added, followed 10 s later by dry DMF (0.670 g, 9.17 mmol; speed is important). The solution was stirred at −43 °C for 80 min under argon. A 1 M solution of acetic acid (3.19 mmol) in ether was added to quench the reaction, which was quickly chromatographed on a silica gel (3.5 × 16 cm). Separation was performed with a 5% to 20% EtOAc/hexanes gradient to provide 0.7113 g of the aldehyde **67** as white crystals (80.8%): mp 73.5−75.0 °C; TLC R_f 0.28 (90:10 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 6.45 (s, 1H), 5.82 (d, J = 3.3 Hz, 1H), 5.58 (s, 1H), 5.19 (s, 2H), 5.07 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 22.9 Hz), 3.57 (m, 4H), 3.46 (s, 3H), 2.56 (ddd, J = 11.6, 3.6, 3.6 Hz, 1H), 1.91 (d, J = 11.6 Hz, 1H), 1.0−1.1 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 187.7, 161.5, 158.5, 156.6, 113.5, 112.6, 104.9, 102.3, 99.6, 94.8, 57.7, 56.5, 37.7, 29.1, 17.9, 17.8, 12.4; IR

($CHCl_3$) 3002, 2863, 1674, 1606, 1573, 1468, 1124, 1046 cm^{-1}; MS *m*/*z* 451 (M^+, 1), 439 (1), 409 (3), 407 (7), 363 (3), 281 (3), 280 (19), 236 (4), 235 (11), 234 (6), 220 (9), 218 (5), 204 (6). Exact mass calcd for $C_{24}H_{38}O_8Si$ 482.2336, found 482.2331. Anal. ($C_{24}H_{38}O_8Si$) H,C: calcd 59.73, found C 59.11%.

Methyl 3,5-Bis(*O*-methoxymethyl)benzyl Ether. The alcohol, prepared according to the procedure of Townsend[36] (1.387 g, 6.080 mmol) in dry THF (24.3 mL, 0.25 M), was treated with 80% sodium hydride in mineral oil (0.1605 g, 6.688 mmol). After the mixture was stirred for 15 min, methyl iodide (1.035 g, 7.296 mmol) was added. The resulting solution was stirred for 12 h at room temperature. Excess methyl iodide was removed under reduced pressure, and the white residue was purified by silica gel column chromatography (3 × 20 cm, 20−30% EtOAc/hexanes gradient) to provide 1.21 g of the ether as a colorless oil (82.4%), which crystallized: mp 52.0−53.0 °C; TLC R_f 0.39 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, J = 2.4 Hz, 2H), 6.65 (t, J = 2.0 Hz, 1H), 5.16 (s, 4H), 4.39 (s, 2H), 3.48 (s, 6H), 3.39 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.3, 140.8, 108.7, 104.1, 94.4, 74.4, 58.2, 56.1; IR ($CHCl_3$) 3010, 2928, 2827, 1720, 1459, 1293, 1146, 1087, 1041 cm^{-1}; MS *m*/*z* 242 (100), 212 (36), 211 (36), 197 (22), 182 (13), 152 (17); exact mass calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1157. Anal. ($C_{12}H_{18}O_5$) C, H.

Methyl 2-Bromo-3,5-bis(*O*-methoxymethyl)benzyl Ether (68). A procedure comparable to that used in the preparation of **64** furnished bromide **68** as a colorless oil in 94.7% yield, which crystallized: mp 55.0−57.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 5.23 (s, 2H), 5.16 (s, 2H), 4.50 (s, 2H), 3.52 (s, 3H), 3.47 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.2, 154.3, 139.7, 109.3, 104.9, 104.0, 95.2, 94.5, 76.7, 58.7, 56.4, 56.2; IR ($CHCl_3$) 3015, 2932, 2831, 1591, 1453, 1319, 1227, 1149, 1089 cm^{-1}; MS *m*/*z* 323 (12), 322 (86), 321 (13), 320 (91), 292 (23), 291 (100), 290 (21), 289 (99), 211 (6), 165 (8); exact mass calcd for $C_{12}H_{17}BrO_5$ 320.0260, found 320.0267. Anal. ($C_{12}H_{17}BrO_5$) C, H, Br.

[7-(2′-Methoxymethyl-4′,6′-bis(*O*-methoxymethyl)-α-benzyloxy)-2,5-methano-6,8-bis(*O*-methoxymethyl)-1,3-benzodioxepan-4-yloxy]-tris(1-methylethylsilane) (69). The bromide **68** (1.67 g, 5.19 mmol) in dry ether (19.0 mL, 0.2 M) was cooled to −43 °C, and *s*-BuLi (4.42 mL, 5.75 mmol) was added just after cooling began before the solution froze. The mixture was stirred under argon for 5 min at −43 °C, and aldehyde **67** (1.79 g, 3.71 mmol) was transferred by cannula as an ethereal solution (19.0 mL, 0.2 M) and stirring continued at −43 °C for 5 h. The reaction mixture was poured into water and ether, and the aqueous phase was extracted with ether (4×). The extracts were pooled and dried with brine and $MgSO_4$. The concentrated oil was purified by silica gel chomotography (5 × 17 cm, 5−20% EtOAc/hexanes), to furnish 2.42 g of a thick yellow oil consisting of the two diastereomeric benzhydrols **69** (90.0%): TLC R_f 0.19 and 0.14 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.37 (s, 1H), 6.37 (d, J = 7.4 Hz, 1H), 5.77 (d, J = 3.4 Hz, 1H), 5.62 (s, 1H), 5.12 (2H, ABq, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 6.9 Hz), 5.02 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 29.5 Hz), 4.97 (2H, ABq, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 56.7 Hz), 4.89 (d, J = 7.4 Hz, 1H), 4.85 (2H, ABq, J_{AB} = 6.9 Hz, $\Delta\nu_{AB}$ = 50.7 Hz), 4.56 (2H, ABq, J_{AB} = 11.7 Hz, $\Delta\nu_{AB}$ = 71.0 Hz), 3.59 (s, 3H), 3.52 (d, J = 3.7 Hz, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 3.27 (s, 3H), 3.04 (s, 3H), 2.52 (ddd, J = 11.3, 4.3, 3.8 Hz, 1H), 1.85 (d, J = 11.3 Hz, 1H), 1.05−1.15 (m, 21H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.3, 155.9, 155.5, 153.4, 152.0, 138.1, 124.5, 118.8, 112.5, 110.1, 105.2, 103.1, 101.2, 99.9 (1, C-4), 99.2, 94.6, 94.4, 93.7, 73.2, 66.5, 58.3, 57.5, 55.9, 55.9, 55.5, 38.4, 29.2, 17.9, 17.8, 12.1; IR ($CHCl_3$) 3499, 3010, 2945, 2869, 1610, 1588, 1463, 1295, 1035 cm^{-1}; MS *m*/*z* 722 (M^+, 10), 709 (7), 707 (41), 681 (0.3), 647 (13), 631 (92), 601 (29), 429 (12), 384 (11), 285 (16), 270 (90), 238 (14), 225 (100); exact mass calcd for $C_{36}H_{55}O_{12}Si$ 707.3463 for M-OH, found 707.3474. Anal. ($C_{36}H_{56}O_{13}Si$) C, H.

[7-(2′-Methoxymethyl-3′,5′-bis(*O*-methoxymethyl)-α-benzoyl)-2,5-methano-6,8-bis(*O*-methoxymethyl)-1,3-benzodioxepan-4-yloxy]-tris(1-methylethylsilane). The diastereomeric benzhydrols **69** (2.42 g, 3.34 mmol) and DDQ (0.796 g, 3.51 mmol) were dissolved in reagent-grade *p*-dioxane (50 mL, 0.05 M). The solution was stirred at room temperature overnight and partitioned between water and ether. The aqueous phase was extracted with ether (4×) and the extracts were pooled and dried over brine and $MgSO_4$. The concentrated brown oil was purified by silica gel chromatography (5 × 23 cm, 10% EtOAc/hexanes) to provide the benzophenone as a yellow oil (2.06 g, 85.5%); TLC R_f 0.46 (80:20 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 6.35 (s, 1H), 5.81 (d, J = 3.1 Hz, 1H), 5.60 (s, 1H), 5.18 (s, 2H), 5.00 (2H, ABq, J_{AB} = 6.3 Hz, $\Delta\nu_{AB}$ = 18.2 Hz), 4.85 (s, 2H), 4.80 (s, 2H), 4.58 (s, 2H), 3.59 (d, J = 3.6 Hz, 1H), 3.51 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.15 (s, 3H), 3.10 (s, 3H), 2.54 (ddd, J = 11.6, 3.9, 3.7 Hz, 1H), 1.89 (d, J = 11.6 Hz, 1H), 1.00−1.10 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 194.0, 159.6, 156.8, 156.0, 154.4, 153.9, 142.1, 124.4, 120.5, 113.2, 107.7, 105.2, 101.8, 101.4, 99.4, 99.3, 94.5, 94.2, 72.0, 58.6, 57.4, 56.0, 55.8, 55.7, 38.1 29.2, 17.9, 17.8, 12.2; IR ($CHCl_3$) 3010, 2945, 2871, 1649, 1602, 1579, 1464, 1153, 1042 cm^{-1}; MS *m*/*z* 722 (M^+, 4), 707 (0.2), 677 (13), 661 (16), 585 (13), 459 (14), 437 (11), 383 (17), 268 (100), 253 (26); exact mass calcd for $C_{36}H_{54}O_{13}Si$ 722.3333, found 722.3340. Anal. ($C_{36}H_{54}O_{13}Si$) C, H.

[7-(2′-Methyl formate-3′,5′-bis(*O*-methoxymethyl)-α-benzoyl)-2,5-methano-6,8-bis(*O*-methoxymethyl)-1,3-benzodioxepan-4-yloxy]tris-(1-methylethylsilane) (70). The benzophenone (3.875 g, 5.361 mmol) in dry DCM (21 mL, 0.25 M) was treated with triethylbenzylammonium permanganate (3.505 g, 11.26 mmol) according to the procedure of Schmidt.[58] The reaction mixture was stirred at room temperature for 5 d and purified directly on silica gel (22 × 3 cm, 10−20% EtOAc/hexanes) to provide the methyl ester **70** (2.17 g, 55.4%; 85% based on recovered starting material) as well as 1.32 g of starting benzophenone (34.0%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.36 (s, 1H), 5.82 (d, J = 3.2 Hz, 1H), 5.61 (s, 1H), 5.19 (s, 2H), 5.11 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 19.2 Hz), 4.96 (s, 2H), 4.75 (2H, ABq, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 8.8 Hz), 3.74 (s, 3H), 3.63 (d, J = 3.7 Hz, 1H), 3.54 (s, 3H), 3.46 (s, 3H, 3.25 (s, 3H, 3.12 (s, 3H), 2.56 (ddd, J = 11.4, 3.8, 3.7 Hz, 1H), 1.91 (d, J = 11.3 Hz, 1H), 1.15−1.05 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.8, 167.6, 158.3, 157.1, 155.7, 155.5, 155.5, 132.6, 128.2, 117.7, 113.5, 109.6, 106.3, 105.1, 102.2, 99.5, 99.4, 94.7, 94.5, 94.3, 57.4, 56.2, 56.1, 55.8, 52.4, 38.0, 29.1, 17.9, 17.8, 12.1; IR ($CHCl_3$) 3010, 2954, 2871, 1727, 1654, 1602, 1575, 1464, 1153, 1038 cm^{-1}; MS *m*/*z* 615 (4), 534 (3), 490 (7), 413 (3), 283 (30), 269 (6), 234 (5). Exact mass calcd for $C_{36}H_{52}O_{14}Si$ 736.3126, found 736.3137. Anal. ($C_{36}H_{52}O_{14}Si$) C, H.

5-[2′-Methyl formate-4′,6′-dihydroxy-α-benzoyl]-2-methoxy-4,6-dihydroxybenzo[furo]furan. The bicyclic TIPS acetal **70** (0.8741 g, 1.185 mmol) and phloroglucinol (0.5975 g, 4.738 mmol) were dissolved in 5:2 dichloromethane/methanol (47 mL, 0.025 M). Next, 49% aqueous HF (236 drops, 200 drops/mmol) was added dropwise, and the solution was stirred for 26 h at room temperature. The solution was neutralized with $NaHCO_3$, filtered, concentrated, and subjected to radial chromatography in 5% MeOH/dichloromethane to furnish the desired methyl acetal (0.1363 g, 28.3%) as a pasty yellow solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 9.35 (s, 1H), 8.70 (s, 1H), 8.6 (br s, 1H), 8.00 (s, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.08 (d, J = 6.4 Hz, 1H), 5.92 (s, 1H), 5.03 (dd, J = 3.0, 2.4 Hz, 1 H), 3.79 (dd, J = 6.4, 4.2, 1H), 3.65 (s, 3H), 2.84 (s, 3H, 2.14 (dd, J = 2.8, 2.8, 2H); ^{13}C NMR (300 MHz, acetone-d_6) δ 198.6, 166.6, 166.1, 162.2, 160.2, 158.8, 156.1, 130.5, 125.1, 114.0, 108.7, 107.8, 107.6, 107.0, 96.2, 54.7, 52.0, 42.7, 38.0; IR ($CHCl_3$) 3690, 3018, 2984, 2929, 1732, 1602, 1446, 1046 cm^{-1}; MS *m*/*z* 418 (21), 400 (19), 389 (12), 386 (11), 372 (31), 357 (16), 339 (87), 325 (43) 312 (19), 297 (12), 280 (18), 221 (29), 195 (47), 189 (18), 168 (58), 163 (22), 154 (16); exact mass calcd for $C_{20}H_{18}O_{10}$ 418.0900, found 418.0896.

5-[2′-Methyl formate-4′,6′-diacetoxy-α-benzoyl]-2-methoxy-4,6-diacetoxybenzo[furo]furan (71). The unprotected methyl acetal (0.0099 g, 0.024 mmol), acetic anhydride (0.061 g, 0.056 mmol), and sodium acetate (0.039 g, 0.47 mmol) were dissolved in reagent-grade toluene (0.95 mL, 0.025 M). The reaction mixture was stirred at room temperature for 2 h. The salts were removed by filtration and washed with dichloromethane. The tetraacetylated methyl acetal **71** was purified by radial chromatography with a 30−50% ethyl acetate/hexanes gradient, to yield 0.0128 g as a yellow solid (92.1%): ^{1}H NMR (300 MHz, $CDCl_3$), as a rotameric pair, δ 7.74 (br d, 2H), 7.26 (br d, 2H), 6.34 (br s, 2H), 6.04 (dd, 2H), 5.06 (br d, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.7 (dd, 2H), 3.01 (s, 6H), 2.33 (s, 12H), 2.29 (s, 12H), 2.12

(m, 4H); ^{13}C NMR (300 MHz, CD_2Cl_2) δ 195.2, 168.9, 168.6, 168.0, 165.1, 164.0, 162.2, 152.8, 151.7, 151.1, 150.9, 132.8, 128.2, 123.7, 119.1, 118.3, 117.5, 114.4, 105.0, 103.5, 51.8, 40.0, 27.2, 21.2, 21.2, 20.7, 18.1.

5-[2′-Methyl formate-4′,6′-diacetoxy-α-benzoyl]-2-thiophenyl-4,6-diacetoxy-benzo[furo]furan. *exo*-Tetraacetoxybenzophenone-Thiophenyl Acetal (72). The methyl acetal **71** (0.0986 g, 0.168 mmol) and thiophenol (0.0204 g, 0.184 mmol) were dissolved in dry dichloromethane (3.4 mL, 0.05 M) followed by BF_3-etherate (0.0477 g, 0.336 mmol). The solution was stirred at room temperature for 4 h and then directly separated by radial chromatography in 30% ethyl acetate/hexanes to afford the upper R_f *exo* isomer (0.0475 g, 42.6%) and the lower R_f *endo* isomer (0.0779, 34.3%; 76.9% total of **72**). Another 0.192 g of starting material **71** was recovered (19.1%): ^{1}H NMR (300 MHz, $CDCl_3$), as a rotameric pair, δ 7.74 (s, 2H), 7.42 (m, 4H), 7.30 (m, 8H), 6.37 (s, 2H), 6.11 (d, J = 5.8 Hz, 1H), 6.06 (d, J = 5.8 Hz, 1H), 5.18 (dd, J = 11.0, 4.3 Hz, 1H), 5.07 (dd, J = 11.1, 4.4 Hz, 1H), 3.80 (m, 8H), 2.34 (s, 12H), 2.31 (s, 6H), 2.07 (m, 8H; IR ($CDCl_3$) 3050, 2957, 2929, 1773, 1726, 1637, 1614, 1441, 1235, 1198, 1039 cm^{-1}. *endo*-Thiophenyl Acetal: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.64 (s, 1H), 7.31 (m, 5H), 7.24 (m, 6H), 7.02 (s, 1H, 6.43 (s, 1H), 6.41 (s, 1H), 6.11 (d, J = 6.2 Hz, 2H), 5.61 (d, J = 7.7 Hz, 1H), 5.56 (d, J = 7.7 Hz, 1H), 3.85 (m, 2H), 3.79 (s, 6H), 2.62 (m, 2H), 2.35 (s, 12H), 2.32 (s, 12H).

5-[2′-Methyl formate-4′,6′-diacetoxy-α-benzoyl]dihydro-4,6-diacetoxyfuro[2,3-*b*]benzofuran. The *exo*-furothiophenyl acetal **72** (0.011 g, 0.016 mmol) was dissolved in dry dichloromethane (0.33 mL, 0.05 M) and cooled to −78 °C before addition of recrystallized *m*-CPBA (0.0031 g, 0.018 mol). The solution was stirred at −78 °C for 30 min, warmed to −43 °C, and stirred 1 h. The resulting solution was shaken with 5% Na_2SO_3, and the organic layer was then washed with 5% $NaHCO_3$ and dried with brine and $MgSO_4$. The solvent was removed, leaving 0.0060 g of crude sulfoxides as a pasty white residue, which was pyrolyzed in reagent-grade toluene (2.9 mL, 0.003 M) in a preheated 120 °C oil bath and stirred for 50 min. After workup, the mixture was purified by Chromatotron in 20% ethyl acetate/hexanes to provide 0.0054 g of the desired olefin as a white solid (59.7%): ^{1}H NMR (300 MHz, acetone-d_6) δ 12.22 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 6.47 (dd, J = 2.7, 2.5 Hz, 1H), 6.43 (d, J = 7.1 Hz, 1H), 6.40 (s, 1H), 5.23 (dd, J = 2.7, 2.5 Hz, 1H), 4.47 (dt, J = 7.2, 2.2 Hz, 1H), 3.74 (s, 3H), 2.33 (s, 6H, 2.32 (s, 6H).

5-[2′-Methyl formate-4′,6′-dihydroxy-α-benzoyl]dihydro-4,6-dihydroxyfuro[2,3-*b*]benzofuran (73). The protected olefin was dissolved in reagent-grade dioxane (0.065 mL). A pD 8.45 phosphate buffer was added to give a white slurry (0.213 mL). Porcine Liver Esterase was then added as a 8.0 pH, 1.0 M NH_4SO_4 buffer slurry (0.370 mL, 0.025 M total). The solution was suspended for 24 h at 25 °C and resubjected to the identical reaction conditions for a second 24-h period. The solid obtained by lypohilization was stirred in acetone for 12 h and centrifuged to remove insoluble material. The supernatant was concentrated to provide a yellow oily residue. Purification by preparative TLC afforded the olefin **73** as a white solid: ^{1}H NMR (300 MHz, acetone-d_6) δ 6.96 (d, J = 1.7 Hz, 1H), 6.68 (br s, 1H), 6.40 (d, J = 7.3 Hz, 1H), 6.39 (d, J = 2.6 Hz, 1H), 6.03 (s, 1H), 5.26 (dd, J = 2.6, 2.4 Hz, 1H), 4.43 (dt, J = 7.4, 2.0 Hz, 1H).

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