Synthesis of Nonracemic 3-Deoxyschweinfurthin B (I).

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MARCH 2005

Impact Factor: 4.72 · DOI: 10.1021/jo048444r · Source: PubMed

3 AUTHORS, INCLUDING:

John A Beutler
National Cancer Institute (USA)
181 PUBLICATIONS **3,377** CITATIONS

JOC*Article*

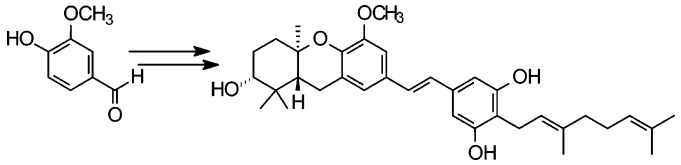
Synthesis of Nonracemic 3-Deoxyschweinfurthin B

Jeffrey D. Neighbors,[†] John A. Beutler,[‡] and David F. Wiemer*,[†]

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294, and Molecular Targets Development Program, Center for Cancer Research, National Cancer Institute, Frederick, Maryland 21702

david-wiemer@uiowa.edu

Received September 3, 2004



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

At this time, the small family of natural products known as the schweinfurthins is composed of four compounds (Figure 1, **1**−**4**) isolated from the African plant *Macaranga schweinfurthii* Pax at the National Cancer Institute.[1,2] Schweinfurthins A (**1**), B (**2**), and D (**4**) display significant activity in the National Cancer Institute's (NCI's) 60 cell line anticancer assay with mean GI_{50} values $<1\ \mu$M. Their biological activity has attracted interest because some central nervous system, renal, and breast cancer cell lines are among the types most sensitive to these compounds. Furthermore, the spectrum of their anticancer activity shows no correlation with any currently used agent and suggests that these compounds may be acting at a previously unrecognized target or through a novel mechanism. Repeated attempts to isolate larger samples of the schweinfurthins from the natural source have met with limited success, and the absolute stereochemistry of these natural products has yet to be determined. For these reasons, as well as their interesting biological activity, we have undertaken an effort directed at total synthesis of the schweinfurthins. An asymmetric synthesis would be particularly attractive because it would allow assignment of the absolute stereochemistry of the natural products and could provide a reliable source of natural schweinfurthins and synthetic analogues for further biological testing.

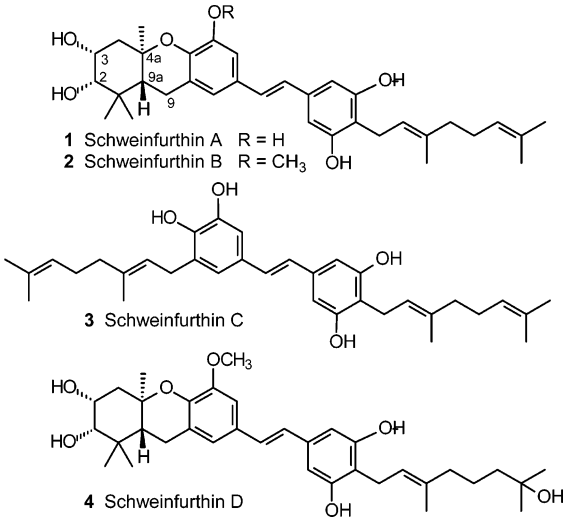


FIGURE 1. Natural schweinfurthins.

Our retrosynthetic analysis of schweinfurthin B (Figure 2) calls for an approach where the central stilbene olefin would be constructed in the penultimate step. This

* To whom correspondence should be addressed. Phone: (319) 335-1365. Fax: (319) 335-1270.
[†] University of Iowa.
[‡] National Cancer Institute.

(1) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998,** *61*, 1509−1512.
(2) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 349−404.

10.1021/jo048444r CCC: $30.25
Published on Web 01/11/2005

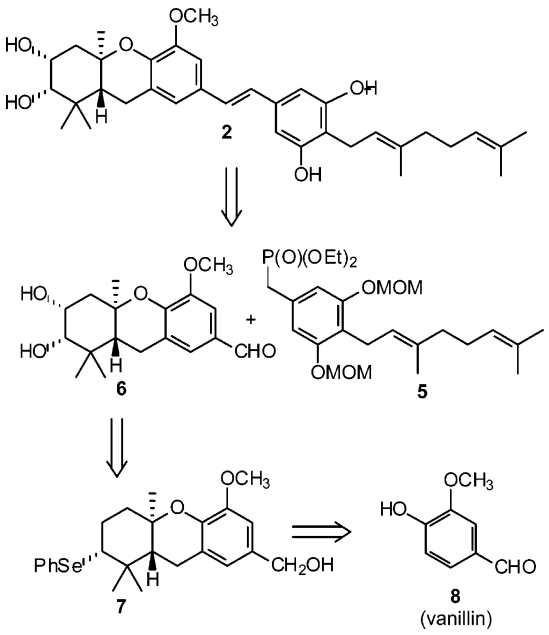
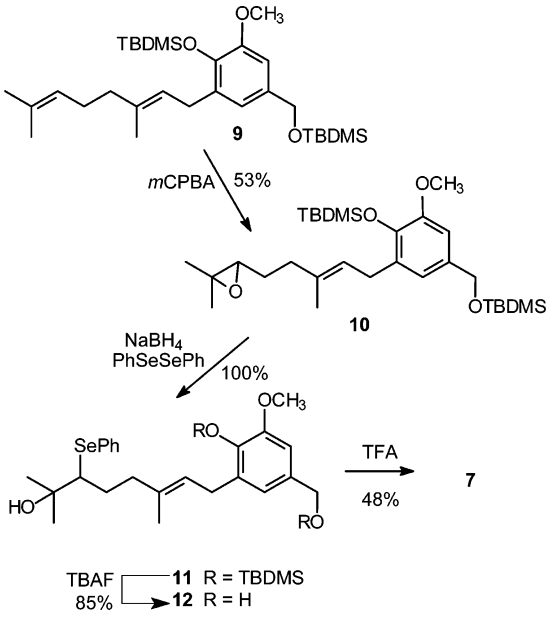


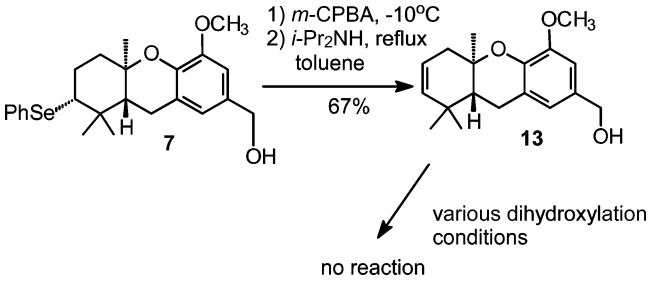
FIGURE 2. Retrosynthetic analysis.

SCHEME 1



approach is highly convergent and should allow facile access to analogues for structure−activity studies. We already have demonstrated that a Horner−Wadsworth−Emmons (HWE) condensation can be used to introduce the stilbene olefin through synthesis of the simplest member of the family, schweinfurthin C (**3**),[3] and the "right-half" phosphonate (**5**) employed in that endeavor can be conserved for synthesis of schweinfurthins A and/or B. All of the tetracyclic schweinfurthins require a dihydroxylated "left-half" core represented in the aldehyde **6**. A synthetic approach to phenyl selenide **7** (Scheme 1), which can be viewed as an advanced precursor to this aldehyde, has been reported in a previous paper.[4] Schweinfurthin B (**2**) was chosen as the initial target so recourse could be made to commercial vanillin as a starting material. This would forego the need for an orthogonal protection of the aryl oxygens because the regiochemistry of the required methyl ether is secured.

SCHEME 2



Our initial route to racemic hexahydroxanthene **7** involved epoxidation of the geranyl arene **9**, available from vanillin in 60% yield over seven steps.[4] The epoxide **10** was opened to phenyl selenide **11**, which, after deprotection and acid-catalyzed cationic cascade cyclization, afforded a single racemic diastereomer of the *trans*-fused tricyle **7**. Completion of the natural product from this point would require selenoxide elimination, dihydroxylation of the resulting olefin, and an HWE condensation of the aldehyde with the phosphonate encompassing schweinfurthin's right half (vide supra). In the event, oxidation of racemic phenyl selenide **7** with *m*-CPBA and thermal elimination of the resulting selenoxide gave the olefin **13** (Scheme 2) in moderate yield.[5] Despite some literature precedent for similar oxidation/elimination reactions under mild reaction conditions, it was necessary to subject this system to a more forceful protocol.[6,7] In this case, the decreased flexibility of the tricyclic system may make it difficult to achieve the *syn* conformation of the selenoxide and the adjacent hydrogen necessary for elimination.

With olefin **13** in hand, introduction of the diol moiety through an osmium-mediated dihydroxylation reaction was examined. Inspection of a molecular model of olefin **13** showed that both faces might be somewhat inaccessible, and that if reaction occurred it would most likely take place from the undesired face of the olefin *trans* to the angular methyl group. Despite this analysis, there is literature precedent for dihydroxylation in similar systems,[8] and both diastereomers of the *cis*-diol would be of use from a structure−activity standpoint. Unfortunately, treatment of olefin **13** with catalytic or stoichiometric osmium tetroxide or potassium osmate failed to give any detectable dihydroxylation products in our hands.[9]

(3) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718−8723.

(4) Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639−3642.

(5) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelburn, D. F. *J. Org. Chem.* **1978**, *43*, 1697−1705.

(6) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434−5447.

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

(8) (a) McMurray, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712−2720. (b) Mori, K.; Komatsu, M. *Liebigs Ann. Chem.* **1988**, 107−119.

(9) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421−433.

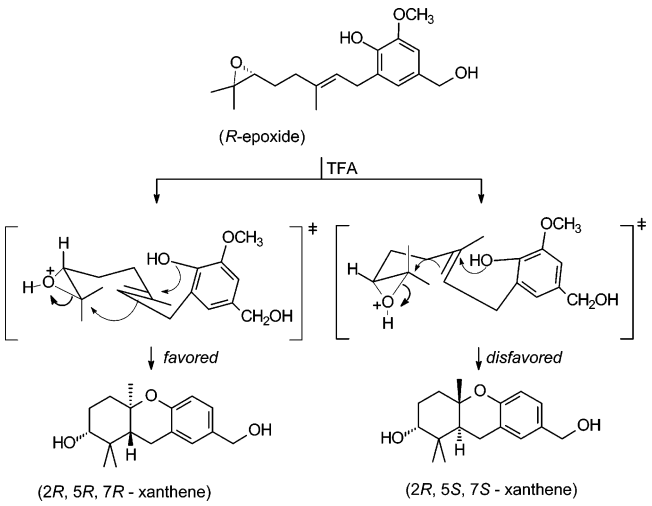
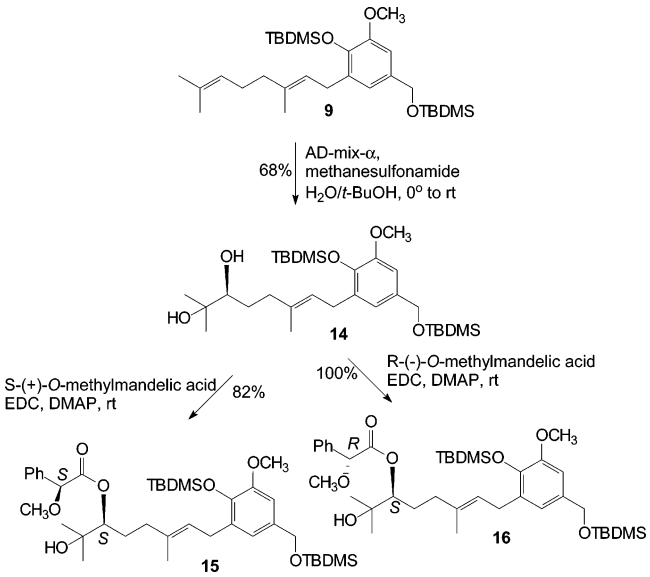


FIGURE 3. Proposed path of epoxide cyclization.

The risk of an adverse stereochemical outcome of the dihydroxylation and the difficult oxidation observed in practice made it necessary to seek alternative methodology for introduction of functionality in the A ring of the tricycle. The pioneering work of van Tamelen[10] and Corey[11] on biogenic cyclization of oxidosqualene, and subsequently on acid-catalyzed cyclization of synthetic equivalents, suggested that a nonracemic epoxide (Figure 3) could serve as a viable substrate for cyclization. Perusal of the literature shows numerous examples of protic and Lewis acid-catalyzed epoxyolefin cyclizations.[12] In this system, a pseudo-chair−chair-like transition state terminated through capture of the tertiary cation by the phenolic oxygen would afford the desired *trans*-fused xanthene. If a pseudoequatorial disposition of the epoxide moiety were favored, then cyclization of the (*R*)-epoxide could be predicted to favor the (2*R*,5*R*,7*R*)-diastereomer of the resulting tricycle, as shown. This strategy could lead directly to 3-deoxyschweinfurthin B, and in principle further elaboration of the A-ring could lead to the natural product.

There is considerable literature precedent for regioselective dihydroxylation of the terminal olefin in geraniol itself,[13] and it appeared that the steric encumbrance and electronic effects in a geranyl arene would favor parallel regiocontrol. The resulting diol might then be converted to the epoxide via the secondary mesylate,[14] to intersect the route already developed[4] or bring new functionality into the tricyclic system. To our delight, treatment of diene **9** with AD-mix-α in the presence of methanesulfonamide gave the desired diol **14** in 68% yield and 83% ee (Scheme 3). Use of the pictorial device suggested by Sharpless et al.[15] for the facial selectivity of the attack indicated that an (*S*)-alcohol should be expected at the newly created asymmetric center.

SCHEME 3



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

(10) (a) van Tamelen, E. E.; Willet, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752−4754. (b) Willet, J. D.; Sharpless, K. B.; Lord, K. E.; van Tamelen, E. E.; Clayton, R. B. *J. Biol. Chem.* **1967**, *242*, 4181−4191.

(11) Corey, E. J.; Russey, W. E.; Ortiz de Motellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750−4751.

(12) (a) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *92*, 6999−7001. (b) van Tamelen, E. E.; Holton, R. A.; Hopla, R. E.; Kouz, W. E. *J. Am. Chem. Soc.* **1972**, *94*, 8228−8229. (c) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225−8228. (d) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229−8231. (e) Tanis, S. P.; Herrington, P. M. *J. Org. Chem.* **1983**, *48*, 4572−4580. (f) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005−7008. (g) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849−7852. (h) Sen, S. E.; Zhang, Y. Z.; Smith, S. M.; Huffman, J. C. *J. Org. Chem.* **1998**, *63*, 4459−4465. (i) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526−2527. (j) Sen, S. E.; Roach, S. L.; Smith, S. M.; Zhang, Y. Z. *Tetrahedron Lett.* **1998**, *39*, 3969−3972.

(13) (a) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211−3214. (b) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485−6488. (c) Zhang, X.; Archelas, A.; Meou, A.; Furstoss, R. *Tetrahedron: Asymmetry* **1991**, *2*, 247−250.

(14) For examples, see: (a) Rickards, R. W.; Thomas, R. D. *Tetrahedron Lett.* **1993**, *34*, 8369−8372. (b) McMurray, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942−6949. (c) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10003.

(15) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, X.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(16) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374. (c) For application to an extended alicyclic system, see, for example: Gallinis, D. L.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 7804−7807.

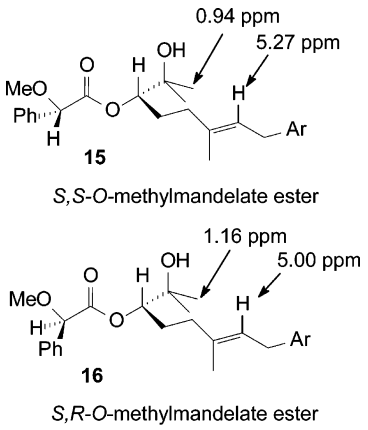
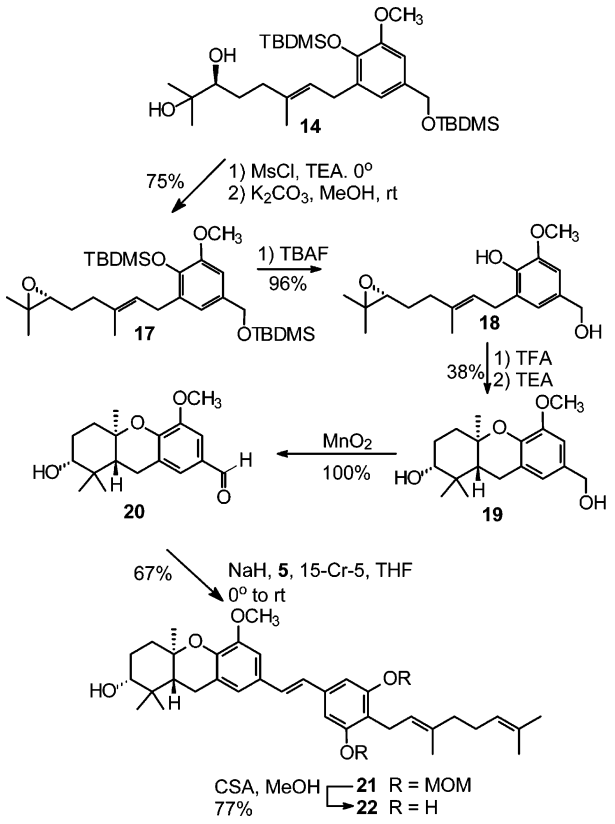


FIGURE 4. Mosher−Trost analysis of *O*-methylmandelate esters.

SCHEME 4



Treatment of diol **14** with mesyl chloride and base, followed by in situ nucleophilic displacement of the resulting mesylate by the tertiary alkoxide, did in fact deliver the nonracemic epoxide **17** in good yield (Scheme 4). Deprotection of epoxide **17** to the diol **18** followed by treatment with trifluoroacetic acid to induce cyclization gave the expected tricycle as the trifluoroacetate ester, and subsequent hydrolysis gave the benzyl alcohol **19** as a single diastereomer. That the secondary alcohol of compound **19** is indeed in an equatorial disposition is evidenced by the large coupling constant ($J_{(H2_{ax}-H3_{ax})}$ = 11.9 Hz) observed in the ^{1}H NMR spectrum. Manganese dioxide oxidation cleanly affords aldehyde **20**, and condensation with phosphonate **5** under modified Horner−Wadsworth−Emmons conditions[17] gave the protected stilbene **21** in high yield, all without recourse to protection of the secondary alcohol. Final deprotection of the MOM ethers upon treatment with camphorsulfonic acid gave enantioenriched 3-deoxyschweinfurthin B (**22**) in good yield.[18]

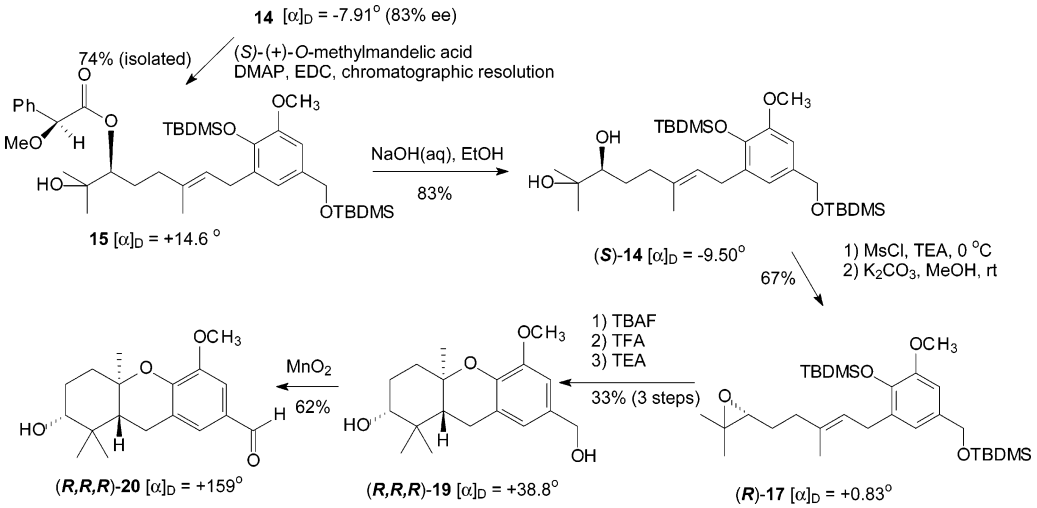
After the viability of this strategy had been demonstrated with enantioenriched epoxide **17**, application of this approach to enantiopure material was pursued. The initial studies with a phenyl selenide cyclization precursor had been made with the assumption that this large substituent could ultimately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

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

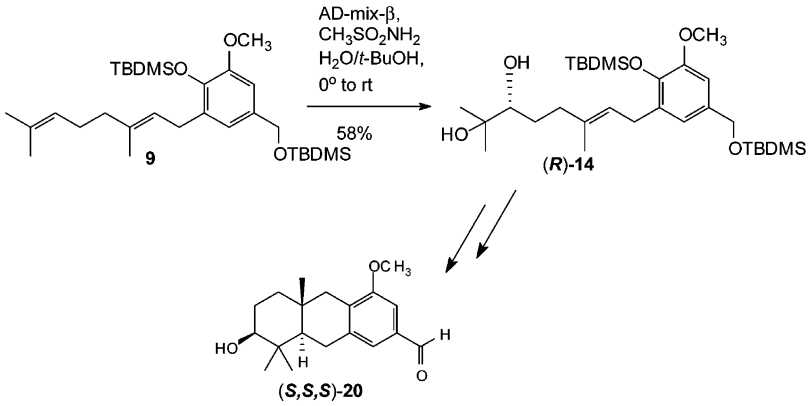
The aldehyde (*R*,*R*,*R*)-**20** displayed a specific rotation of +159°. Two other samples of optically active compound **20** also were available: one with a rotation of +97.8° for material synthesized from diol **14** with an enantiomeric excess of 64% ($[\alpha]_D = -6.1°$), and another with a rotation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

(17) Baker, R.; Sims, R. J. *Synthesis* **1981**, 117.
(18) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, *43*, 291−293.
(19) (a) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43,* 351−353. (b) Toshimitsu, A.; Hirosawa, C., Tamao, K. *Synlett* **1996**, 465−467.
(20) (a) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873−8874. (b) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118,* 8765−8766. (c) Corey, E. J.; Lou, G.; Lin, S. *J. Am. Chem. Soc.* **1997**, *119*, 9927−9928. (d) Corey, E. J.; Lou, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126−1128. (e) Haung, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10003. (f) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215−3216 and references therein.
(21) Schneider, J. P.; Kelly, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 2533−2546.

SCHEME 5

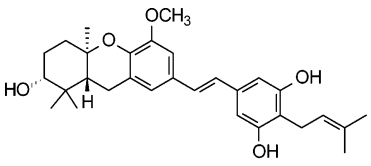


SCHEME 6



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

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



23

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

Experimental Section

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

(22) Yoder, B. J.; Schilling, J. K.; Norris, A.; Miller, J. S.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. International Congress on Natural Products Research, Phoenix, AZ, August 2004; Paper O-16.

(30 μL, 0.22 mmol) in toluene (30 mL) at reflux. After 3 h the mixture was allowed to cool to rt and quenched by addition of 10% aqueous sodium sulfite. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried ($MgSO_4$), and then concentrated in vacuo. The resulting yellow oil was subjected to final purification by column chromatography (10:1, 4:1, and 3:2 hexanes/ethyl acetate) to afford the olefin **13** (13 mg, 62%) as a clear oil: ^{1}H NMR δ 6.75 (s, 1H), 6.71 (s, 1H), 5.55 (dt, *J* = 10.3, 4.0 Hz, 1H), 5.42 (dt, *J* = 10.1, 1.9 Hz, 1H), 4.59 (s, 2H), 3.86 (s, 3H), 2.74 (m, 2H), 2.46 (dd, *J* = 11.9, 6.15 Hz, 1H), 2.01 (dd, *J* = 3.9, 1.9 Hz, 2H), 1.28 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H); ^{13}C NMR δ 148.6, 142.2, 137.7, 131.7, 122.5, 120.6, 120.3, 108.6, 76.6, 65.6, 56.1, 44.5, 39.5, 35.9, 31.3,23.3, 23.1, 20.1; HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1727.

3-(3′,7′-Dimethyl-2-octen-6′(*S*),7′-diol)-4-(*tert*-butyldimethylsiloxy)-5-methoxybenzyloxy]-*tert*-butyldimethylsilane (14). To a solution of AD-mix-α (15.13 g) in water/*t*-BuOH (150 mL, 1:1) was added methanesulfonamide (1.13 g), and the solution was cooled to 6 °C. The geranylated arene **9**[4] (5.29 g, 10.2 mmol) was added via syringe as a neat oil, and the solution was kept at 6 °C for 15 h. Solid Na_2SO_3 was added, and the solution was stirred for 1 h. The solution was extracted with EtOAc, and the resulting organic layer was washed with 2 N NaOH and brine, then dried ($MgSO_4$), and concentrated in vacuo to afford a clear oil. Final purification by column chromatography (1:1 hexanes/ethyl acetate) gave the diol **14** (3.86 g, 68%) as a clear oil: $[\alpha]^{26.4}_D = -7.9$ (*c* 0.10, $CHCl_3$); ^{1}H NMR δ 6.72 (d, *J* = 2.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 5.38 (t, *J* = 7.1 Hz, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.35 (d, *J* = 7.3 Hz, 2H), 3.35 (m, 1H), 2.33−2.23 (m, 2H), 2.17−2.00 (m, 2H), 1.70 (s, 3H), 1.66−1.56 (m, 1H), 1.50−1.36 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 1.00 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H); ^{13}C NMR δ 149.7, 141.3, 135.7, 133.7, 132.1, 123.3, 119.0, 107.3, 78.2, 73.0, 65.0, 54.7, 36.7, 29.7, 28.5, 26.4, 26.1 (3C), 25.9 (3C), 23.2, 21.0, 18.9, 16.2, −3.9 (2C), −5.2 (2C). Anal. Calcd for $C_{30}H_{56}O_5Si_2$: C, 65.17; H, 10.21. Found: C, 65.11, H, 10.22.

(*S*)-*O*-Methylmandelate 15. To a solution of diol **14** (3.65 g, 6.60 mmol), EDC (1.64 g, 8.60 mmol), and DMAP (0.83 g, 6.76 mmol) in CH_2Cl_2 (25 mL) was added (*S*)-(+)-*O*-methylmandelic acid (1.15 g, 6.93 mmol). After 1 h at rt, water was added and the resulting solution was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and concentrated. Further purification by flash chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded the mandelate ester **15** (3.77 g, 82%) as a clear oil, along with a small amount of the diastereomeric ester (not isolated): $[\alpha]^{26.4}_D = +14.6$ (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.40−7.32 (m, 3H), 6.72 (s, 1H), 6.64 (s, 1H), 5.27 (t, *J* = 8.0 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 3.77 (s, 3H), 3.43 (s, 3H), 3.33 (d, *J* = 7.9 Hz, 2H), 1.96 (t, *J* = 8.0 Hz, 2H), 1.78−1.61 (m, 3H), 1.64 (s, 3H), 1.00 (s, 9H), 0.94 (s, 15H), 0.18 (s, 6H), 0.09 (s, 6H); ^{13}C NMR δ 170.4, 149.7, 141.3, 136.5, 135.0, 133.7, 132.1, 129.0, 128.7 (2C), 127.2 (2C), 123.1, 119.0, 107.3, 82.6, 80.7, 72.3, 65.0, 57.3, 54.7, 35.0, 28.5, 28.1, 26.1 (3C), 26.0 (3C), 25.9, 24.6, 18.9, 18.4, 16.3, −3.9 (2C), −5.1 (2C); HRMS (ESI) *m/z* calcd for $C_{39}H_{64}O_7Si_2Na$ $(M + Na)^+$ 723.4088, found 723.4090.

(*R*)-*O*-Methylmandelate 16. In a manner identical to that described above for the preparation of ester **15**, the diol **14** (38 mg, 0.07 mmol), EDC (20 mg, 0.1 mmol), and DMAP (10 mg, 0.08 mmol) were allowed to react with (*R*)-(−)-*O*-methyl mandelic acid (12 mg, 0.07 mmol). Standard workup and final purification by column chromatography (5:1 hexanes/ethyl acetate) afforded the target ester **16** (41.5 mg, 82%) as a clear oil along with the (*R*,*R*)-diastereomer (total yield of 100%). A diastereomeric ratio of 84:16, corresponding to an initial ee of 68% for compound **14**, was determined by integration of signals at 5.00 and 5.27 ppm in the ^{1}H NMR spectrum of the initial mixture. Data for diastereomer **16**: ^{1}H NMR δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.36−7.28 (m, 3H), 6.73 (s, 1H), 6.57 (s, 1H), 5.00 (t, *J* = 6.6 Hz, 1H), 4.80 (m, 2H), 4.65 (s, 2H), 3.78 (s, 3H), 3.43 (s, 3H), 3.24 (d, *J* = 6.9 Hz, 2H), 1.60 (m, 5H, 1H exchanges with D_2O), 1.45 (s, 3H), 1.16 (s, 6H), 0.99 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.09 (s, 6H); ^{13}C NMR δ 170.9, 149.7, 141.3, 136.3, 134.9, 133.6, 132.1, 128.8, 128.6 (2C), 127.1 (2C), 123.0, 119.0, 107.3, 82.7, 80.7, 72.4, 65.1, 57.3, 54.7, 35.4, 28.3, 28.2, 26.6, 26.1 (3C), 26.0 (3C), 24.7, 18.9, 18.4, 16.1, −3.9 (2C), −5.1 (2C); HRFABMS *m/z* calcd for $C_{39}H_{64}O_7NaSi_2$ $(M + Na)^+$ 723.4088, found 723.4101.

[4-(*tert*-Butyldimethylsilyloxy)-5-methoxy-3-(3′,7′-dimethyl-6′-epoxy-2′-octenyl)benzyloxy-*tert*-butyldimethylsilane (17). To a solution of diol **14** (2.03 g, 3.7 mmol), in CH_2Cl_2 (20 mL) at 0 °C, was added TEA (1.35 mL, 9.69 mmol) followed 30 min later by MsCl (0.43 mL, 5.58 mmol). After 35 min, the reaction was allowed to warm to rt, and after a total of 2 h, a second aliquot of TEA (0.80 mL, 5.74 mmol) was added and the reaction was stirred for 30 min. A solution of K_2CO_3 (2.31 g, 16.7 mmol) in MeOH (70 mL) was poured into the vessel, and the solution was allowed to react for 20 h. After filtration and extraction of the resulting filtrate with ethyl acetate, the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under vacuum to afford a white oil. Final purification by flash chromatography (12:1 hexanes/ethyl acetate) yielded the target epoxide **17** as a viscous clear oil (1.48 g, 75%): ^{1}H NMR δ 6.72 (d, *J* = 1.7 Hz, 1H), 6.65 (d, *J* = 1.6 Hz, 1H), 5.36 (tm, *J* = 7.2 Hz, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.72 (t, *J* = 6.3 Hz, 1H), 2.30−2.10 (m, 2H), 1.70 (s, 3H), 1.75−1.60 (m, 2H), 1.28 (s, 3H), 1.25 (s, 3H), 0.99 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H); ^{13}C NMR δ 149.7, 141.3, 135.0, 133.7, 132.1, 123.3, 119.0, 107.3, 65.0, 64.2, 58.3, 54.7, 36.3, 28.5, 27.4, 26.1 (3C), 26.0 (3C), 24.9, 18.9, 18.7, 18.4, 16.2, −3.9 (2C), −5.2 (2C). Anal. Calcd for $C_{30}H_{54}O_4Si_2$: C, 67.36; H, 10.17. Found: C, 67.12; H, 10.28.

(6′*R*)-4-Hydroxy-3-methoxy-5-(3′,7′-dimethyl-6′-epoxy-2′-octenyl)benzyl Alcohol (18). Silyl ether **17** (840 mg, 1.57 mmol) was dissolved in THF (70 mL), and the solution was cooled to 0 °C. To this solution was added TBAF (4.6 mL, 1.00 M in THF), and the reaction was allowed to warm to rt and after 1.5 h was quenched with satd NH_4Cl. After extraction with ethyl acetate, the combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. Final purification by flash chromatography (4:1 hexanes/ethyl acetate) gave the diol **18** (352 mg, 96%): ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 1H), 6.74 (s, 1H), 5.70 (s, 1H), 5.37 (t, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 5.5 Hz, 2H), 3.89, (s, 3H), 3.36 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.24−2.12 (m, 2H), 1.74 (s, 3H), 1.68−1.62 (m, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.3, 142.8, 135.3, 132.1, 127.0, 122.7, 120.7, 107.5, 65.6, 64.3, 58.4, 56.0, 36.4, 27.8, 27.3, 24.8, 18.7, 16.1. Anal. Calcd for $C_{18}H_{26}O_4 \cdot 0.5H_2O$: C, 68.55; H, 8.63. Found: C, 68.23; H, 8.53.

Diol 19. To a solution of epoxyphenol **18** (352 mg, 1.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added trifluoroacetic acid (0.26 mL, 3.4 mmol). The resulting solution was allowed to stir for 2 h, and Et_3N (1.4 mL, 10.0 mmol) was added. After an additional 30 min, water (75 mL) was added, the phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water and brine, then dried ($MgSO_4$), and concentrated. Final purification by flash chromatography (2:1 to 1:1 hexanes/ethyl acetate) afforded the tricyclic diol **19** (135 mg, 38%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 6.70 (s, 1H), 4.57 (s, 2H), 3.86 (s, 3H), 3.39 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.69 (d, *J* = 8.9 Hz, 2H), 2.15−2.04 (m, 2H), 1.88−1.59 (m, 6H, 2H exchange with D_2O), 1.23 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 142.1, 132.0, 122.5, 120.4, 108.5, 78.0, 76.8, 65.5, 56.0, 46.7, 38.3, 37.6, 28.3, 27.3, 23.1, 19.7, 14.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1823.

Aldehyde 20. To a solution of benzylic alcohol **19** (251 mg, 0.82 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (1.71 g, 19.6

mmol) as a single aliquot. The resulting suspension was allowed to stir for 26 h and then filtered through Celite, and the residue was concentrated in vacuo to afford the aldehyde **20** as a white solid (249 mg, 100%): mp 160.5−162.0 °C; $[\alpha]^{25.0}_D$ = +97.8 (*c* 0.126, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.80 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 3.90 (s, 3H), 3.45 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.80−2.77 (m, 2H), 2.22−2.15 (m, 1H), 1.94−1.82 (m, 2H), 1.74−1.61 (m, 2H), 1.28 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 191.1, 149.5, 148.7, 128.7, 127.3, 122.5, 107.3, 78.4, 77.8, 56.0, 46.5, 38.4, 37.5, 28.2, 27.3, 23.0, 20.0, 14.3. HRMS *m/z* calcd for $C_{18}H_{25}O_4$ $(M + H)^+$ 305.1753, found 305.1743. Anal. Calcd for $C_{18}H_{24}O_4 \cdot H_2O$: C, 67.06; H, 8.13. Found: C, 66.98; H, 8.17.

3-Deoxydimethoxymethylschweinfurthin B (21). A suspension of NaH (29 mg, 1.2 mmol) and 15-crown-5 (4 μL, 0.02 mmol) in THF (1.5 mL) was cooled to 5 °C. To this were added aldehyde **20** (10 mg, 0.03 mmol) and phosphonate **5** (22 mg, 0.05 mmol) in THF (2 mL). The mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was extracted with ether. The resulting organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Final purification by column chromatography (3.5:1 to 1:1 hexanes/ethyl acetate) gave the stilbene **21** (15.2 mg, 80%) as a straw-colored oil: ^1H NMR ($CDCl_3$) δ 6.95−6.85 (m, 6H), 5.24 (s, 4H), 5.24 (t, 1H,), 5.07 (t, *J* = 11.7 Hz, 1H), 3.89 (s, 3H), 3.50 (s, 6H), 3.40 (m, 3H), 2.72 (d, *J* = 8.7 Hz, 2H), 2.16−1.85 (m, 7H), 1.79 (s, 3H), 1.70−1.65 (m, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9 (2C), 148.9, 142.5, 136.7, 134.6, 131.2, 128.9, 128.2, 126.4, 124.3, 122.6, 122.5, 120.5, 119.5, 106.8, 105.9 (2C), 94.5 (2C), 78.1, 77.0, 55.9 (2C), 55.9, 46.7, 39.8, 38.4, 37.7, 28.3, 27.3, 26.7, 25.6, 23.1, 22.7, 19.8, 17.6, 16.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{39}H_{54}O_7$ (M^+) 634.3870, found 634.3871.

3-Deoxyschweinfurthin B (22). To a solution of stilbene **21** (24 mg, 0.04 mmol) in MeOH (2 mL) was added camphorsulfonic acid (10 mg, 0.04 mmol). The resulting solution was stirred at rt for 20 h and then heated to 60 °C for an additional 5 h. The reaction was quenched by addition of satd $NaHCO_3$ and extracted with ethyl acetate, and the organic phase was washed with brine and dried over $MgSO_4$. Concentration in vacuo, followed by final purification by column chromatography (1:1 hexanes/ethyl acetate), afforded **22** (16 mg, 79%) as a clear oil: ^1H NMR ($CDCl_3$) δ 6.83 (m, 4H), 6.55 (s, 2H), 5.31 (s, 1H), 5.28 (t, *J* = 6.9 Hz, 1H), 5.06 (m, 1H), 3.88 (s, 3H), 3.43 (m, 3H), 2.72 (d, *J* = 9.1 Hz, 2H), 2.15−2.06 (m, 5H), 1.90−1.82 (m, 3H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H),0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2 (2C), 148.9, 142.7, 139.2, 137.1, 132.1, 128.8, 128.6, 125.7, 124.2, 122.6, 121.4, 120.6, 112.8, 107.0, 106.2 (2C), 78.0, 77.1, 55.0, 46.8, 39.7, 38.4, 37.6, 28.3, 27.3, 26.4, 25.7, 23.1, 22.5, 19.8, 17.7, 16.2, 14.3; HRMS (ESI) *m/z* calcd for $C_{35}H_{46}O_5$ (M^+) 546.3345, found 546.3342.

(−)-3-(3′,7′-Dimethyl-2-octen-6′(*S*),7′-diol)-4-(*tert*-butyl-dimethylsiloxy)-5-methoxybenzyloxy]-*tert*-butyldimethylsilane ((*S*)-14). To a solution of mandelate ester 15 (203 mg, 0.29 mmol) in EtOH (10 mL) was added NaOH (0.63 mL, 0.63 mmol, aq, 1 M). After 5 h at rt, HCl (0.63 mL, 0.063 mmol, aq, 1 M) was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with water and brine, then dried ($MgSO_4$), and concentrated in vacuo to give a slightly yellow oil. Purification by column chromatography (1:1 hexanes/EtOAc) afforded the diol (*S*)-**14** (132 mg, 83%) as a colorless oil: $[\alpha]^{26.4}_D = -9.6$ (*c* 0.03, $CHCl_3$); spectral data were identical to those of the enantioenriched diol **14**.

(+)-[4-(*tert*-Butyldimethylsilyloxy)-5-methoxy-3-(3′,7′-dimethyl-6(*R*′)-epoxy-2′-octenyl)benzyloxy-*tert*-butyldimethylsilane ((*R*)-17). To a solution of diol (*S*)-**14** (1.41 g, 2.56 mmol), in CH_2Cl_2 (20 mL) at 0 °C, was added TEA (1.05 mL, 7.64 mmol) followed 50 min later by MsCl (0.27 mL, 3.50 mmol). After 45 min, the reaction was allowed to warm to rt, a second aliquot of TEA (0.60 mL, 4.36 mmol) was added, and the reaction was stirred for 4 h. This solution was transferred via cannula into a suspension of K_2CO_3 (2.35 g, 17.0 mmol) in MeOH (40 mL), and the resulting suspension was allowed to react for 20 h. After filtration and extraction of the resulting filtrate with ethyl acetate, the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under vacuum to afford a colorless oil. Final purification by flash chromatography (12:1 hexanes/EtOAc) yielded the target epoxide (*R*)-**17** as a single enantiomer (0.91 g, 67%) as a viscous colorless oil: $[\alpha]^{26.4}_D = +0.83$ (*c* 0.18, $CHCl_3$); both ^1H and ^{13}C spectra were identical to those of racemate **10** and enantioenriched compound **17**.

Tricyclic Diol (*R,R,R*)-19. Silyl ether (*R*)-**17** (936 mg, 1.75 mmol) was dissolved in THF (15 mL), and the solution was cooled to 0 °C. To this solution was added TBAF (5.4 mL, 1.0 M in THF), and the reaction was allowed to warm to rt and after 2.5 h was quenched with satd NH_4Cl. After extraction with ethyl acetate, the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. This oil (430 mg, 1.4 mmol) was dissolved in CH_2Cl_2 (60 mL) at 0 °C, and trifluoroacetic acid (0.3 mL, 3.89 mmol) was added. The resulting solution was allowed to stir 5 h, and then Et_3N (0.7 mL, 5.09 mmol) was added. After an additional 1 h, water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, then dried ($MgSO_4$), and concentrated. Final purification by flash chromatography (2:1 to 1:1 hexanes/EtOAc) afforded the tricyclic diol (*R,R,R*)-**19** (177 mg, 33% from epoxide (*R*)-**17**) as a light yellow oil: $[\alpha]^{26.4}_D = +38.8$ (*c* 0.03, $CHCl_3$); spectral data were identical to those of the enantioenriched diol **19**.

Aldehyde (*R,R,R*)-20. To a solution of benzylic alcohol (*R,R,R*)-**19** (118 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (954 mg, 11.0 mmol) as a single aliquot. The resulting suspension was allowed to stir for 19 h and then filtered through Celite, and the residue was concentrated in vacuo to give a yellow solid. Final purification by flash chromatography (3:1 hexane/EtOAc) gave the aldehyde (*R,R,R*)-**20** as a white solid (74 mg, 62%): $[\alpha]_D = +159$ (*c* 0.012, $CHCl_3$); the spectral data were identical to those of the enantioenriched aldehyde **20**.

3-(3′,7′-Dimethyl-2-octen-6′(*R*),7′-diol)-4-(*tert*-butyldimethylsiloxy)-5-methoxybenzyloxy]-*tert*-butyldimethylsilane ((*R*)-14). To a solution of AD-mix-β (8.57 g) in water/*t*-BuOH (100 mL, 1:1) was added methanesulfonamide (0.62 g), and the solution was cooled to 0 °C. The geranylated arene 9 (3.19 g, 6.15 mmol) was added via syringe as a neat oil, and the solution was kept at 0 °C for 20 h. Solid Na_2SO_3 was added, and the solution was stirred for 1 h. The solution was extracted with EtOAc, and the resulting organic layer was washed with 2 N NaOH and brine, then dried ($MgSO_4$), and concentrated in vacuo to afford a clear oil. Final purification by column chromatography (1:1 hexanes/EtOAc) gave the diol (*R*)-**14** (1.97 g, 58%) as a clear oil: $[\alpha]^{25.0}_D = +8.5$ (86% ee) (*c* 0.223, $CHCl_3$); both ^1H and ^{13}C NMR spectra were identical to those of diol (*S*)-**14**.

Acknowledgment. Financial support from the Breast Cancer Research Program (Grants DAMD17-01-1-0276 and DAMD17-02-1-0423) and the University of Iowa Graduate College is gratefully acknowledged.

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

JO048444R