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A Cascade Cyclization Approach to Schweinfurthin B

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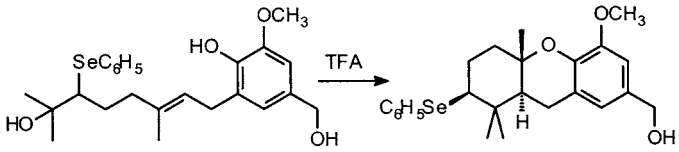
ABSTRACT



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

The schweinfurthins (Figure 1, **1**−**4**) are a small set of doubly prenylated stilbenes isolated from the African plant *Macaranga schweinfurthii* Pax. by Beutler et al. at the National Cancer Institute. Schweinfurthins A (**1**), B (**2**), and D (**4**) display significant activity in the NCI's 60-cell line anticancer assay with GI_{50} values less than 0.5 μM.[1,2] Their profile of activity does not match that of any clinically used anticancer agent, which suggests that these compounds may act either by a novel mechanism or at an unknown site. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis that ultimately should allow assignment of the schweinfurthins' absolute stereochemistry and provide a reliable source for further biological testing.

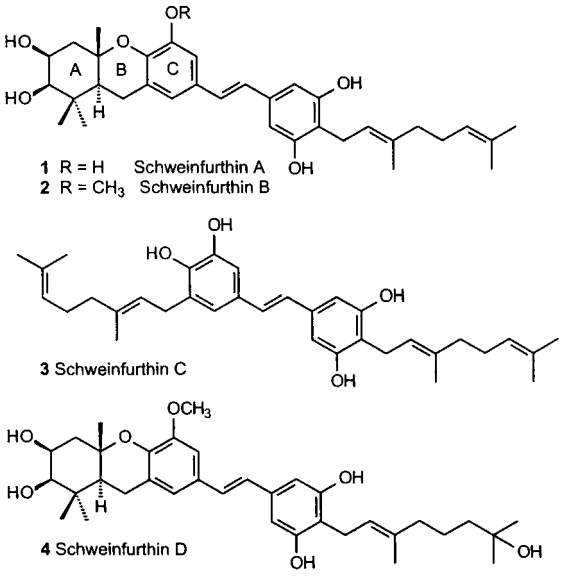


Figure 1. Structures of the schweinfurthins.

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

(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*, 399−404.
(3) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718−8723 and references therein.

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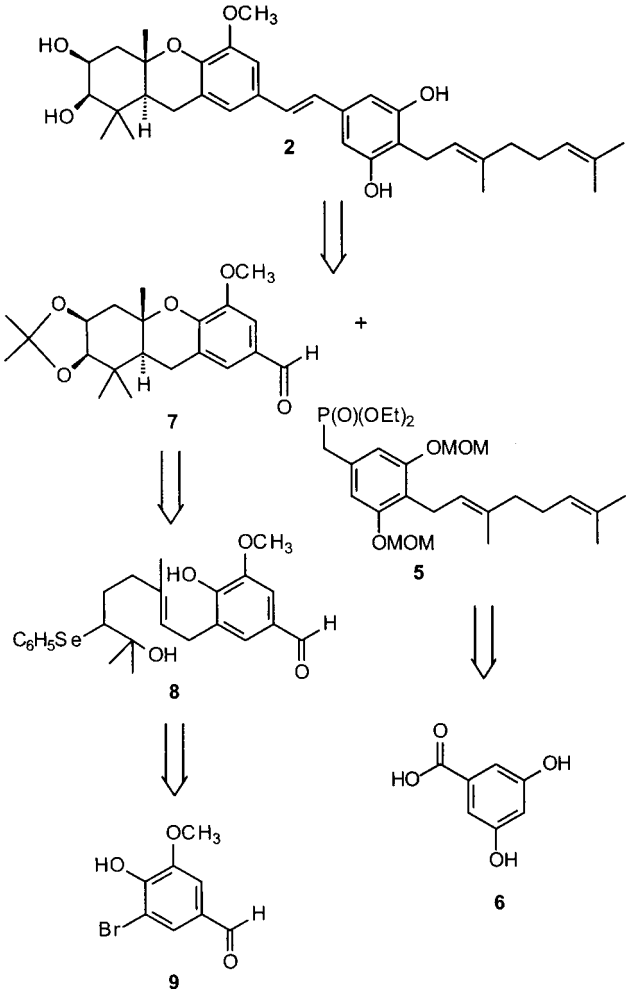
Scheme 1. Retrosynthetic Analysis of Schweinfurthin B



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

One approach to the hexahydroxanthene core could be based on an acid-catalyzed cyclization to assemble both the A- and B-rings on an aromatic C-ring in a single reaction. Previous reports on cyclizations of geranylated phenols are known, but often the cyclizations occurred in low yield with numerous byproducts observed.[4,5] We hypothesized that a substituent α to the incipient carbocation could help stabilize the terminal cation, thereby possibly increasing the yield and providing an opportunity for stereocontrol. There is substantial precedent for stabilization of adjacent cations by phenylthio substituents, and some precedent for stabilization by phenylselenyl groups.[6] As shown in Figure 2, one transition state would place the phenylselenide substituent in an equatorial position with a pseudochair conformation in the incipient B-ring, while the other would require an axial phenylselenide group with a pseudoboat conformation. The use of hydroxyselenides for similar reactions has been described in two seminal papers by Kametani et al., though

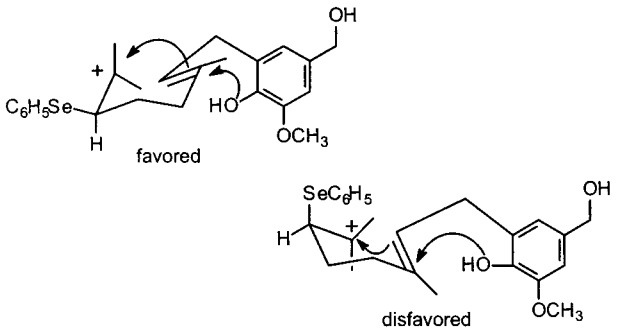
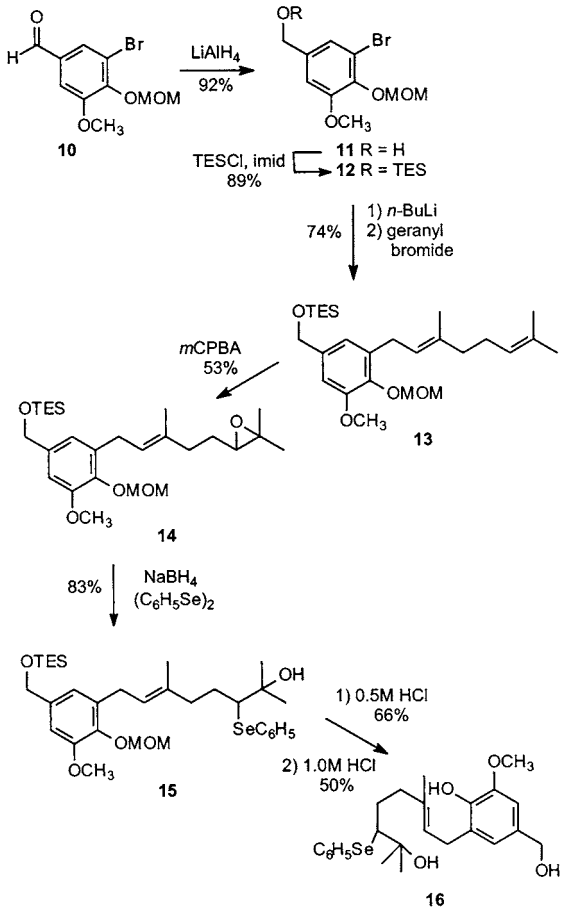


Figure 2. Possible transition states for cyclization of hydroxyselenide **8**.

application to enantiopure material was not attempted.[7] With this aim in mind, racemic β-hydroxyselenide **8** was viewed as a cyclization precursor that would allow evaluation of the viability of such an approach.

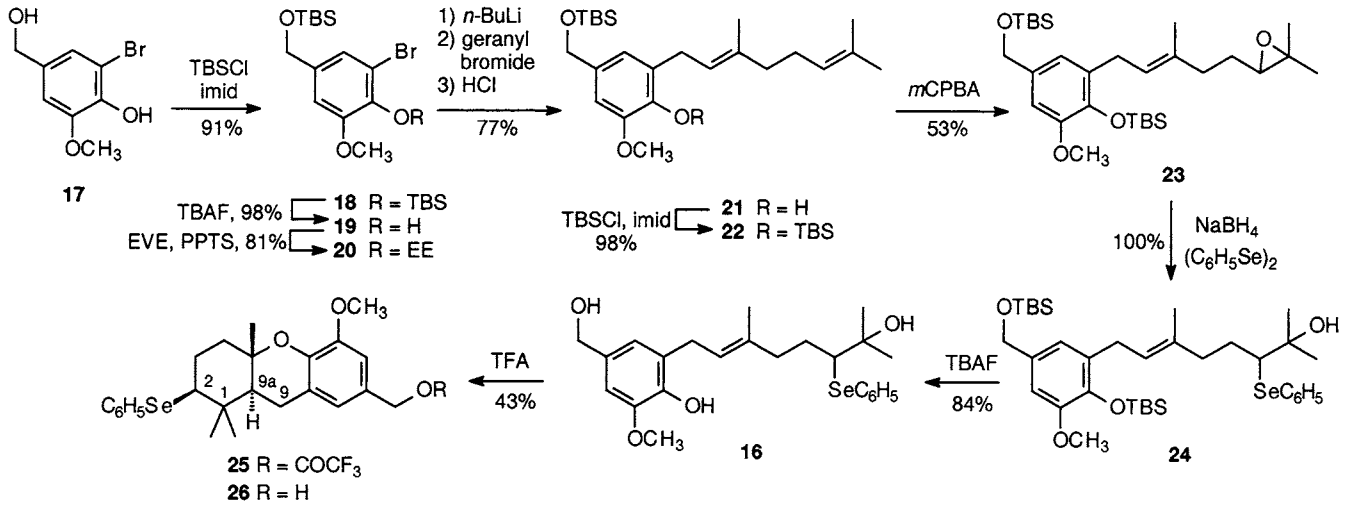
The synthesis began with preparation of the known benzaldehyde derivative **10**[8] (Scheme 2) from commercially

Scheme 2. Initial Synthesis of Hydroxyselenide **16**



available vanillin. Reduction of the aldehyde and subsequent protection of the alcohol as the triethylsilyl ether afforded

Scheme 3. Revised Synthesis of Hydroxyselenide **16**



the fully protected arene **12**, and halogen−metal exchange followed by reaction with geranyl bromide allowed installation of the geranyl chain in 74% yield. An *m*CPBA epoxidation of compound **13** initially afforded a 1:1 mixture of the regioisomeric 6,7- and 2,3-epoxides in 55% yield along with the diepoxide (7%). Even though careful column chromatography could separate the two regioisomers, the low yield of the desired product was unattractive. When the reaction was conducted at lower temperatures with slow addition of the oxidant, the yield of the desired 6,7-epoxide **14** increased to 53% along with only 8% of the 2,3-epoxide and significant recovery of the starting material (32%). Epoxide **14** reacted smoothly with phenylselenide anion generated in situ[9] to give the hydroxyselenide **15** in 83% yield.

The only transformations remaining prior to cyclization were removal of the two protecting groups, but in the best case scenario this was done through a two-step procedure. Initial treatment with 0.5 M HCl hydrolyzed the silyl ether, and subsequent treatment with 1.0 M HCl hydrolyzed the MOM acetal in an overall yield of 33%. Despite numerous attempts, all efforts at removing both protecting groups in a single step gave either incomplete deprotection or lower yields with greater byproduct formation.

A second synthetic strategy was developed to address this problematic deprotection issue. Because the silyl ether could be readily removed, it appeared attractive to protect the phenolic functionality as a silyl ether as well. However, introduction of the phenolic silyl ether would have to follow the alkylation step in the synthetic sequence, because migration of the silyl group from the oxygen to the adjacent ortho carbon has been observed in similar reactions.[10] Therefore, an ethoxyethyl-protected phenol was envisioned for the sequence up to and including the alkylation step, at which point it would be removed and a silyl ether installed in its place.[11]

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

(4) (a) Barua, A. K.; Banerjee, S. K.; Basak, A.; Bose, P. K. *J. Indian Chem. Soc.* **1976**, *53*, 638−639. (b) Manners, G.; Jurd, L.; Stevens, K. *Tetrahedron* **1972**, *28*, 2949−2959. (c) Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525−1528.

(5) Mechoulam and Yagen have reported cyclization of geranylolivetol in 88% yield, but this required heating with concentrated H_2SO_4 in nitromethane. Mechoulam, R.; Yagen, B. *Tetrahedron Lett.* **1969**, 5349−5352.

(6) (a) For a review, cf.: Harring, S. R.; Edstrom, E. D.; Livinghouse, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, H. W., Ed.; Jai Press: Greenwich, CT, 1992; Vol 2., pp 299−376. For more recent examples, cf.: (b) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351−353. (c) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett* **1996**, 465−467 and references therein.

(7) (a) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128−1129. (b) Kametani, T.; Kurobe, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1085−87.

(8) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115−2122.

(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699.

(10) When treated with *n*-butyllithium, both compound **18** and the TIPS analogue show a 1,3 O−C silyl migration in the only isolable products.

(11) The EE group was not carried throughout the sequence to avoid introduction of diastereomers and because the phenolic EE group was readily cleaved upon silica gel column chromatography.

(12) (a) Brink, M. *Acta Chem. Scand.* **1965**, *19*, 255−256. (b) Claus, P.; Schilling, P.; Gratzl, J. S.; Kratzl, K. *Monatsh. Chem.* **1972**, *103*, 1178−1193.

(13) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681−684.

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

The relative stereochemistry of the hexahydroxanthene was assigned after extensive NMR spectroscopy on the trifluoroacetate **25**. Analysis of the coupling constants observed for the C-2 hydrogen (schweinfurthin numbering) suggested an axial disposition and hence an equatorial orientation for the phenylselenide group. The bridgehead methine hydrogen (C-9a) also appeared to be in an axial orientation on the basis of analysis of the coupling constants with the benzylic hydrogens at C-9. In this case, a COSY spectrum nicely displayed the H-9_{ax}, H-9_{eq}, H-9a spin system, indicative of a *trans*-decalin skeleton. Furthermore, the chemical shifts of the methyl groups compared favorably to those reported for a related trans-fused system but did not agree with those of a related cis-fused structure.[14] Finally, a NOESY spectrum revealed correlations (Figure 3) of the bridgehead methyl group with axial hydrogens at C-3 and C-9 and to the axial methyl group at C-1. On the other face of the molecule, complementary correlations were observed between the equatorial methyl group at C-1 and the axial hydrogen at C-9a, as well as from the axial hydrogen at C-2 to both the C-1 equatorial methyl group and the C-9 equatorial hydrogen.

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

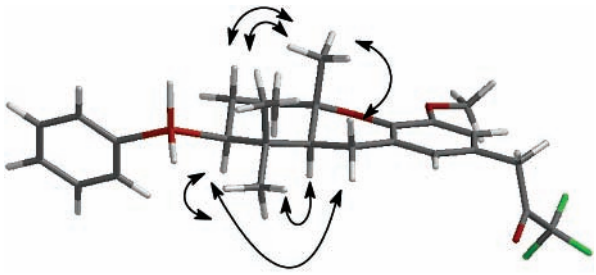


Figure 3. Selected NOESY correlations for compound **25** shown on a SPARTAN minimized structure (PM3 level).

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

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

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

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(14) Rouessac, A.; Rouessac, F. *Tetrahedron* **1987**, *37*, 4165−4170.