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Synthesis of the schweinfurthin hexahydroxanthene core through Shi epoxidation

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Abstract

Use of a Shi epoxidation for introduction of chirality in a key epoxide intermediate, together with revised protecting group tactics, has allowed an efficient synthesis of the hexahydroxanthene subunit common to the natural schweinfurthin F and the synthetic analogue 3-deoxyschweinfurthin B.

The schweinfurthins are a small group of natural products that currently includes eight examples.[1–3] Most of these compounds contain a hexahydroxanthene substructure (e.g., schweinfurthins A, B, E, F, and G, **1**–**5**, Fig. 1) with a hydroxyl group at C-2 that suggests biosynthesis through a cascade cyclization. This family of natural products has attracted some attention due to a unique anticancer profile displayed in the National Cancer Institute's 60 cell line bioassay. In this panel several schweinfurthins, as well as the related compound vedelianin (**6**), display mean cytotoxicity values <1 μM (GI_{50}). More importantly, the pattern of activity they display across the cell lines is not clearly related to any currently used agent.[1,4,5] Indeed some schweinfurthins show 10 nM activity against CNS, renal, and prostate cancer cell lines, while showing up to four orders of magnitude less activity against cell lines of lung or ovarian tissue origin. Potent and unique activity in this assay system could indicate a novel mechanism of action, which would make the schweinfurthins a valuable lead for a new type of chemotherapeutic agent.

For the reasons outlined above, as well as the difficulty of obtaining schweinfurthins from the natural sources, we have undertaken an effort aimed at their total synthesis. This effort has led to the preparation of both enantiomers of schweinfurthin F (**4**), which allowed assignment of the natural absolute configuration, and the synthesis of approximately 20 analogues that have been tested in the 60 cell screen.[6–9] Studies of the natural and synthetic schweinfurthins[10] have illuminated the importance of the right-half resorcinol substructure in the biological activity of this family of compounds, but also confirm the importance of the hexahydroxanthene system.

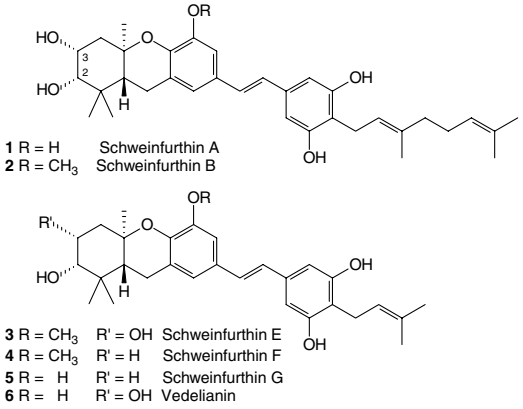

Fig. 1. Hexahydroxanthenes of the schweinfurthin family.

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To date, synthetic efforts have centered on the C-2 hydroxy compounds, including the natural products schweinfurthin F (**4**) and G (**5**), as well as the synthetic analogue 3-deoxyschweinfurthin B (3dSB, **10**). The synthetic plan relies upon a penultimate Horner–Wadsworth–Emmons (HWE) condensation to set the central stilbene olefin and requires two suitable coupling partners as summarized in Figure 2. For example, the coupling of aldehyde **7** representing the left-half of schweinfurthin F and 3dSB with the right-half phosphonates **8** and **9** afforded reasonable access to the stilbenes **4** and **10**. As a part of our ongoing efforts at further development of these agents it became necessary to prepare gram scale quantities of our lead compounds. Here, we report a new synthesis of the hexahydroxanthene **7** that exploits Shi epoxidation to obtain nonracemic intermediates in both improved yield and high ee. This new approach should facilitate the preparation of substantial amounts of the materials of interest.

Our original synthesis of aldehyde **7** used a biomimetic cascade cyclization to construct the hexahydroxanthene ring system from an aryl epoxide precursor (Scheme 1).[7] This approach builds upon extensive historical precedent for faithful transmission of stereochemical information through the cationic cascade manifold.[7] After the introduction of the epoxide stereocenter via asymmetric dihydroxylation, the cyclization reaction afforded a single hexahydroxanthene enantiomer. The geranyl precursor was derived from bromovanillin (**11**) that already bears the required methyl ether common to several targets. The first generation route to aldehyde **7** required 16 steps and proceeded in an overall yield of ~10% from vanillin. The goals for this synthesis were to preserve the central strategy while more efficient tactics for the construction of nonracemic cyclization precursors such as epoxide **13** were explored.

As a first effort toward these goals, the use of different protecting groups in the initial stages of the synthetic route was explored. For example, the use of methoxymethyl (MOM) ether protection could save numerous steps if the protecting groups could be carried through the sequence without removal until a very late stage, where the cascade cyclization conditions might be employed for concurrent deprotection.

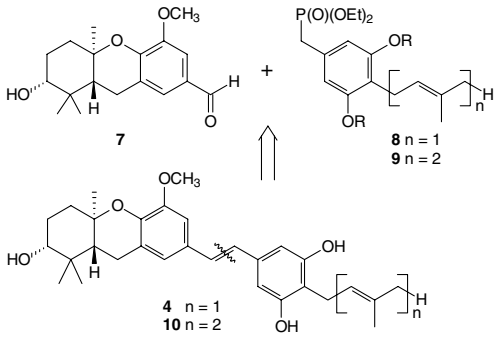
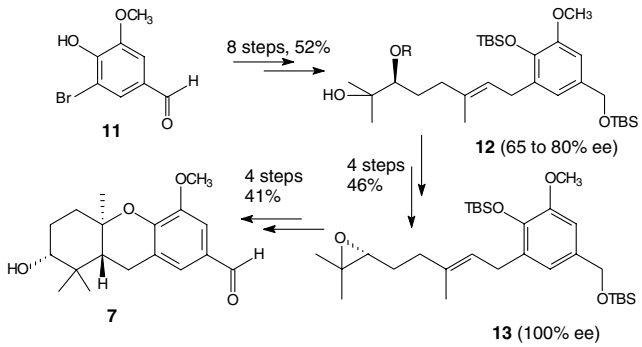


Fig. 2. Retrosynthetic analysis of the schweinfurthins.



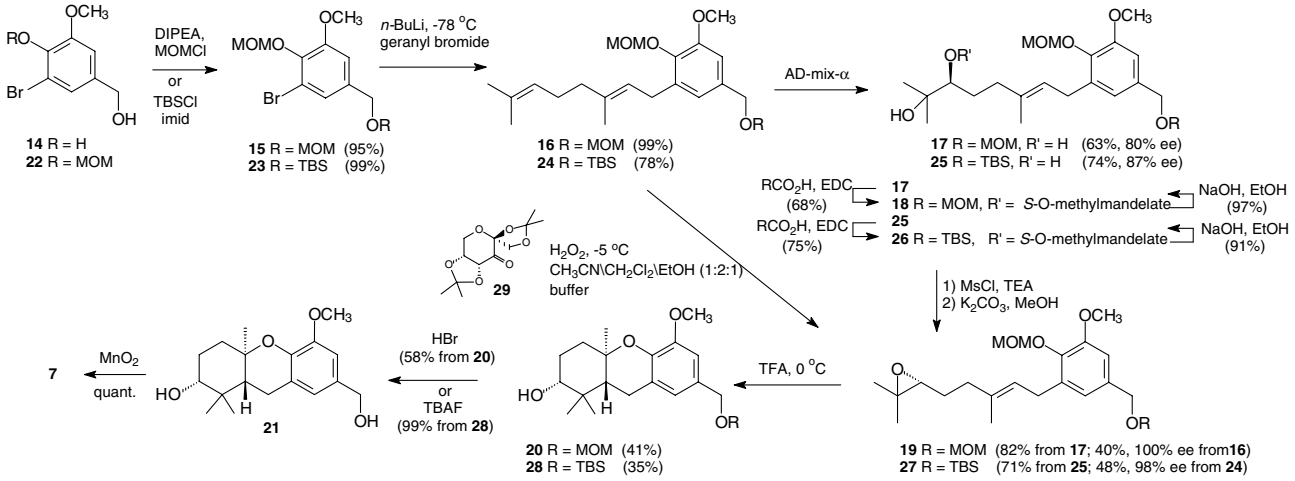
Scheme 1. First generation synthesis of hexahydroxanthene **7**.

To explore these options (Scheme 2), a straightforward reduction of bromovanillin (**11**) was followed by the treatment of the known benzylic alcohol **14** with MOMCl and Hünig's base to afford the bismethoxymethyl ether **15**. Treatment with *n*-butyl lithium followed by geranyl bromide to trap the intermediate anion gave the geranylated intermediate **16** in excellent yield.

From this intermediate the route is parallel to that previously disclosed. Treatment of the arene **16** with an asymmetric dihydroxylation reagent gave the diol **17** in good ee. The use of the conditions already developed to resolve diol **17** via mandelate ester **18**, followed by formation of epoxide **19** through the mesylate, gave material of high ee and set the stage for the exploration of a cascade cyclization in this system. Treatment of epoxide **19** with TFA under optimized conditions afforded tricycle **20**, with the benzylic MOM protecting group still in place in moderate yields. This result was disappointing because it was anticipated that both protecting groups could be removed by the acid-catalyzed cyclization conditions, thus making a final deprotection unnecessary. The benzylic MOM group proved intransigent to several other deprotection conditions as well.[11] However, after some experimentation we found that treatment with 48% HBr in dichloromethane would afford a modest yield of the desired diol **21**. Oxidation of diol **21** was quantitative.

At this point, examination of silyl ether protection at the benzylic position became attractive, because this group could be removed in high yield. The known arene **22** (available from bromovanillin)[8] was protected as the benzylic *t*-butyldimethylsilyl ether to give bromide **23**, which was subjected to a series of reactions to afford the desired tricycle **28** via intermediates **24**–**27**. While these steps proceeded in yields comparable to those observed with the corresponding MOM compounds, silyl deprotection of compound **28** to afford the diol **21** was virtually quantitative. Thus, after a final oxidation this reaction sequence gave the aldehyde **7** in 13 steps and 9% overall yield from vanillin.

With more efficient protecting group tactics in place a more fundamental series of changes was explored. The linear nature of the sequences used to introduce the epoxide stereocenter of compounds **19** and **27** is cumbersome, and

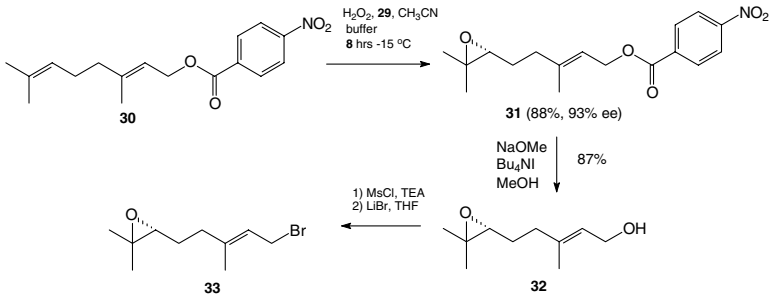


Scheme 2. Protecting group tactics and epoxidations used in synthesis of the hexahydroxanthene intermediate **21**.

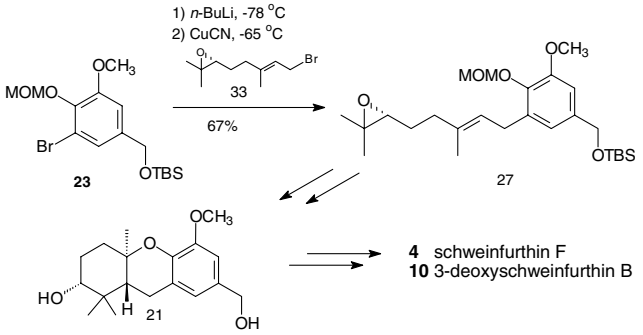
both a traditional resolution and a chromatographic separation of the diastereomers proved necessary to achieve high ee. If direct epoxidation could be accomplished in good yield and high ee, the synthesis would be significantly more efficient. To explore this possibility, the oxidation of compounds **16** and **24** via the nonracemic sugar catalyzed process pioneered by Shi et al.[12] was explored. Because enantioselective epoxidation on aromatic esters of isoprenoids has been successful,[12] it was reasonable to consider epoxidation of these isoprenylated aromatic systems. Oxidation of diene **16** proceeded in just 40% yield, along with significant amounts of recovered starting material (38%) and a trace of the regioisomeric epoxide, but did afford the desired material in high ee (~100% by comparison of rotation with authentic material[7]). Oxidation of diene **24** also proceeded in very good ee (~98%) and somewhat better yield (48%).

If epoxidation could be removed from the primary synthetic sequence, a more convergent and efficient approach might result. In particular, the formation of the epoxide prior to the attachment of the terpenoid chain to the arene might improve the regio- and stereoselectivity of the olefin epoxidation. Geraniol (6,7)-epoxide (**32**) has been synthesized as either enantiomer by both a salen Mn(III) catalyst method[13] and via the Shi epoxidation.[12] Similarly, both *R*- and *S*-(6,7)-epoxygeranyl bromide (**33**) have been synthesized.[14,15] With the availability of these reagents, a reaction sequence in which an aryl nucleophile would selectively attack the allylic bromide of epoxygeranyl bromide was of clear interest.

A recent report by Gansaeuer et al.[16] on the copper-mediated displacement of the bromide of epoxy geranyl bromide (**33**) appeared to indicate this should be possible using an organometallic nucleophile derived from the aryl bromide **23**. Toward this end, the known *p*-nitrobenzoate ester **30**[17] (Scheme 3) was treated with hydrogen peroxide in the presence of carbohydrate catalyst **29**, to afford the epoxyester **31** in 80–88% yield and high ee (~93% ee by HPLC analysis).[18] A relatively low reaction temperature (ca. −15 °C) and longer reaction times appeared to be advantageous in this reaction. Under these conditions less than 5% of the starting material was recovered along with a trace of the diepoxide, and the regioisomeric mono epoxide could not be isolated. Hydrolysis of the resulting ester through reaction with base gave *R*-(6,7)-epoxygeraniol (**32**) which was found to have an enantiomeric excess of ~100% based on the comparison of the optical rotation to the literature value[15] ([α] +8.5 (*c* 0.01, CH_3OH) vs



Scheme 3. Synthesis of *R*-(6,7)-epoxygeranyl bromide (**33**).



Scheme 4. Coupling of metallated arene **23** and epoxybromide **33**.

literature +8.5 (*c* 0.01, CH_3OH)). Treatment of alcohol **32** with methanesulfonyl chloride followed by lithium bromide gave the known epoxybromide **33**.

To our great delight subjection of the aryl bromide **23** to halogen metal exchange conditions followed by transmetallation with copper cyanide or copper bromide–dimethyl sulfide complex, gave upon reaction with epoxybromide **33** the desired product **27** in 67% yield (Scheme 4). Epoxide **27** was converted to the aldehyde **7** through the sequence shown in Scheme 2, and then converted to 3-deoxyschweinfurthin B (**10**) via known methods.[7] Analysis of the enantiomeric excess of the final product by HPLC[18] indicated material of 94% ee confirming the stereocontrol of the cascade process. This represents the removal of eight steps from the first generation sequence leading to tricyclic left-half diol **21**, leaving the complete route from vanillin to aldehyde **7** with a total of just eight steps in the longest linear sequence and 23% overall yield.

Use of a Shi epoxidation and new protecting group tactics in this second generation synthesis of the hexahydroxanthene substructure of schweinfurthin F and 3dSB has dramatically improved access to this series of agents. This should allow synthesis of sufficient quantities of 3dSB to initiate in vivo investigations in mice. These efforts will be the subject of future communications in this area.

Acknowledgments

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Supplementary data

Experimental procedures and/or spectral data for compounds **15**–**20**, **23**–**28**, and **31**–**33** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.086.

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