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Synthesis of the cis-fused hexahydroxanthene system via cationic cascade cyclization

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ABSTRACT

The cis-fused hexahydroxanthene system can be obtained through a cascade cyclization initiated by Lewis acid-mediated epoxide opening and terminated by reaction with a MOM-protected phenol. Only a single diastereomer of the product was obtained with stereochemistry verified by diffraction analysis. This demonstrates the viability of this approach to natural products containing the cis-fused hexahydroxanthene skeleton, and supports preparation of more complex targets through a similar strategy.

The trans-fused hexahydroxanthene skeleton has been found in natural products isolated from several terrestrial plants, including seven of the eight known schweinfurthins (e.g., schweinfurthin F, **1**, Fig. 1)[1,2] and vedelianin.[3] Still other examples have been found in marine sources, including tribromocacoxanthene,[4] puupehendiol,[5] and taondiol.[6] In contrast, the isomeric cis-fused system is still very rare, but known examples include cymobarbatol (**2**) isolated from a marine source[7] and ugonstilbene B (**3**) isolated from a traditional Chinese medicine.[8] The cis-fused hexahydroxanthene can also be found as a subunit in several larger terpenoids, including kampanol A (**4**), which is a novel inhibitor of farnesyl:protein transferase.[9] Our interest in inhibitors of this enzyme,[10,11] as well as past work on preparation of the trans-fused schweinfurthins and varied analogues,[11] led to an exploration of a new route to cis-fused hexahydroxanthenes that ultimately might be applied to preparation of more complex terpenoids.[12,13]

From a biosynthetic perspective, formation of the trans-fused systems can be envisioned through cyclization of a cationic intermediate generated by addition of an electrophile to the distal olefin of a geranyl arene, or via opening of a terminal epoxide to a parallel cation. In a similar sense, addition of an electrophile could initiate a cationic cascade leading to the cis-fused natural products if Br^+ (for cymobarbatol) or H^+ (for ugonstilbene B) were added to the terminal olefin of a neryl system (i.e., a 2*Z*-olefin). Biomimetic syntheses leading from *E*-olefins to trans-fused hexahydroxanthenes have been reported,[14–16] but there is little information on the synthesis of these cis-fused natural products. During the course of their elegant studies on Lewis acid-assisted chiral Bronsted acids,[17,18] Yamamoto and co-workers have shown that achiral nerylphenol cyclizes in modest yield and low ee when treated with a nonracemic catalyst, but does give only the cis-fused skeleton. In contrast, they found that cyclization of geranylphenol under similar conditions gave mixtures containing predominantly the trans- but also the cis-fused product. Because their studies employed achiral starting materials and thus gave hexahydroxanthenes with stereochemistry only at the two bridgehead positions, their findings may not extend to cyclization of nonracemic systems that include an initial stereocenter, or predict the relationship between the bridgehead positions and the A-ring substituent resulting from such a cyclization.

Recently we reported an efficient synthesis of schweinfurthin F (**1**) through a cascade cyclization initiated by $BF_3{\cdot}OEt_2$-promoted ring opening of geranyl epoxide and terminated through a novel reaction with a phenolic oxygen 'protected' as its MOM ether.[16] Based on these studies, we hypothesized that starting with an aryl epoxide containing the 2*Z*-olefin geometry (e.g., **5**, Fig. 2) would result in a cis ring fusion through the cascade process via one of two reasonable transition states, affording either hexahydroxanthene **6** or **7**. To determine the viability of this approach, as well as the stereochemistry of any product and the stereointegrity of the reaction

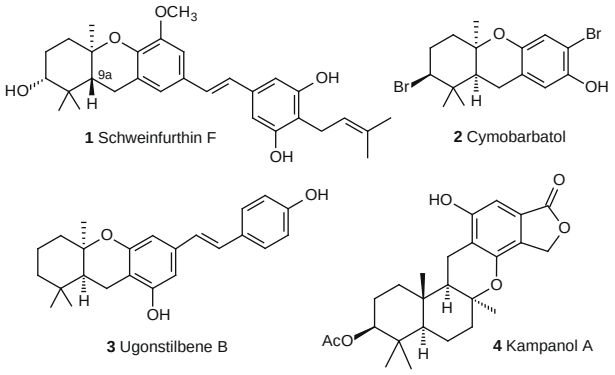

Figure 1. Natural hexahydroxanthenes.

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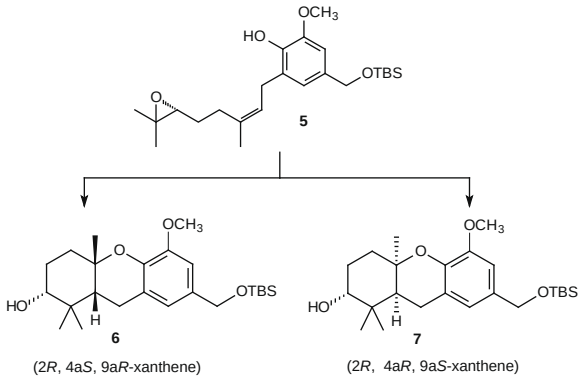


Figure 2. Possible cyclizations of a neryl arene.

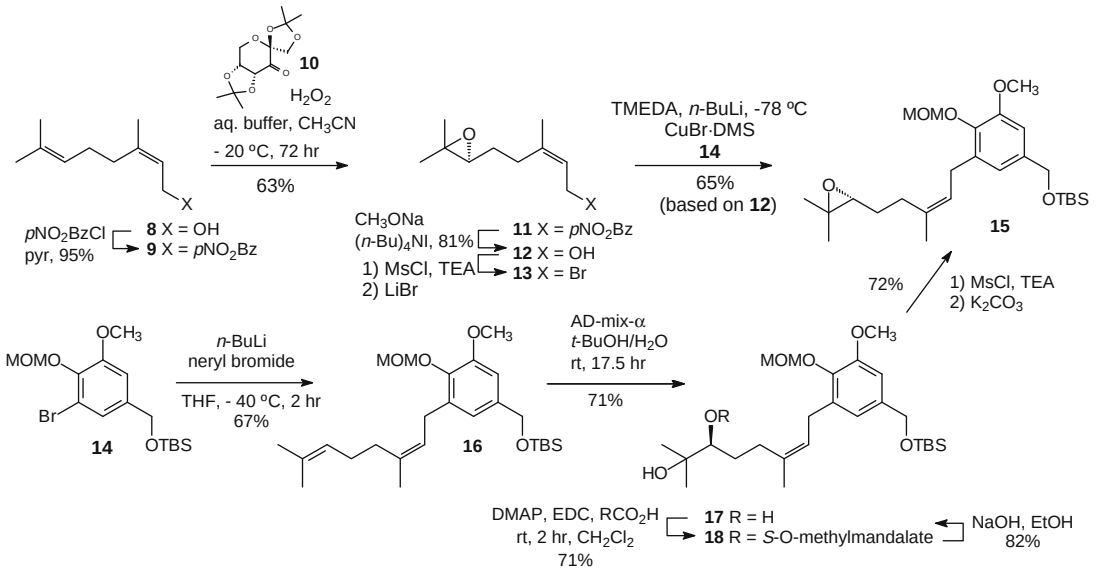
process, we prepared an appropriate substrate containing a *Z*-olefin and attempted cyclization.

The epoxy olefin **15** was chosen as the target compound for this investigation, to parallel extensive studies on cyclization of the isomeric trans olefin.[14–16] Preparation of compound **15** began with the synthesis of (*R*)-6,7-epoxyneryl bromide (**13**, Scheme 1). To this end derivatization of nerol (**8**) through reaction with *p*-nitrobenzoyl chloride (pNO_2BzCl) gave ester **9**[19] and a subsequent Shi epoxidation[20] using the sugar-derived catalyst **10**[21] afforded epoxide **11**.[22] Use of the *p*-nitrobenzoyl ester increased the yield and stereoselectivity of the epoxidation over other potential protecting/directing groups. Saponification of ester **11** afforded (*R*)-6,7-epoxynerol (**12**) which was then converted to the desired allylic bromide **13** via the mesylate. Immediate coupling of this allylic bromide with the presumed cuprate[23] formed from known aryl bromide **14**[16] afforded the desired cyclization precursor, aryl epoxide **15**, in moderate yield.

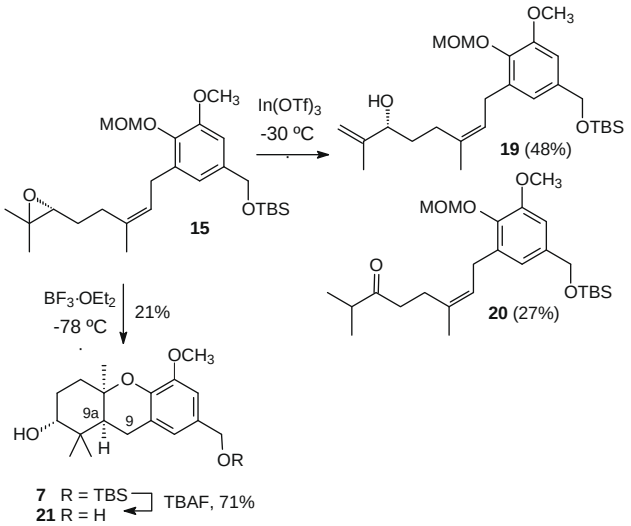
The stereochemistry (6*R*) and ee (92%) of alcohol **12** were determined by comparison to the known optical rotation,[24] and later verified by HPLC analysis of a subsequent intermediate. It was assumed that the epoxide stereochemistry would be preserved through the copper-mediated nucleophilic substitution to give the aryl epoxide **15**.[16,23] This degree of enantiomeric purity is acceptable, but it appeared prudent to explore an alternative route to epoxide **15** that would afford this crucial intermediate as a single enantiomer. To this end, aryl bromide **14** was subjected to halogen metal exchange conditions and treated with neryl bromide to afford arene **16**. Unlike the reaction of compound **14** with bromide **13**, the latter reaction gave the desired alkylated arene **16** without use of TMEDA or transmetalation to an organocopper intermediate. Subjection of arene **16** to asymmetric dihydroxylation conditions with AD-mix-α generated the enantioenriched diol **17**. Esterification of diol **17** with (*S*)-*O*-methylmandelic acid followed by chromatographic resolution of the resulting diastereomeric esters (**18**) led to isolation of the individual esters as enantiopure materials. Saponification of the major diastereomer followed by formation of the secondary mesylate and base-promoted epoxidation gave aryl epoxide **15** as a single enantiomer. This independent synthesis allowed confirmation of the assignment of the absolute configuration of epoxide **15** through a Mosher–Trost analysis,[25,26] as well as verification of the enantiomeric excess of the Shi epoxidation.

With epoxide **15** in hand as a single enantiomer, attention was turned to the cationic cascade cyclization. After experimentation with different protic and Lewis acids, it was found that treatment of epoxide **15** with the mild Lewis acid $In(OTf)_3$ resulted in opening of the epoxide but only afforded the allylic alcohol **19** and ketone **20**. Other acids gave larger amounts of polymer and lower amounts of monomeric products. Finally, treatment of compound **15** with $BF_3{\cdot}OEt_2$ at −78 °C gave the tricyclic alcohol **7** (Scheme 2) as a single diastereomer along with a considerable amount of polymeric material. The cis-fused nature of the ring system initially was assigned based on comparison of the ^1H NMR data of this compound with that for the corresponding trans-fused isomer[9,14] as well as literature data for cymobarbatol (**2**) and the trans-fused isocymobarbatol.[7] The most notable difference was seen in the spin system encompassing the benzylic hydrogens at C-9 and the bridgehead hydrogen at C-9a. In the cis-fused compounds the C-9 hydrogens are well resolved and the large geminal coupling constant (18 Hz) can be easily recognized, whereas in the trans-fused systems the C-9 hydrogens are not resolved and appear as a complex multiplet. The patterns for the methyl resonances are also clearly different for the cis- and trans-fused compounds.

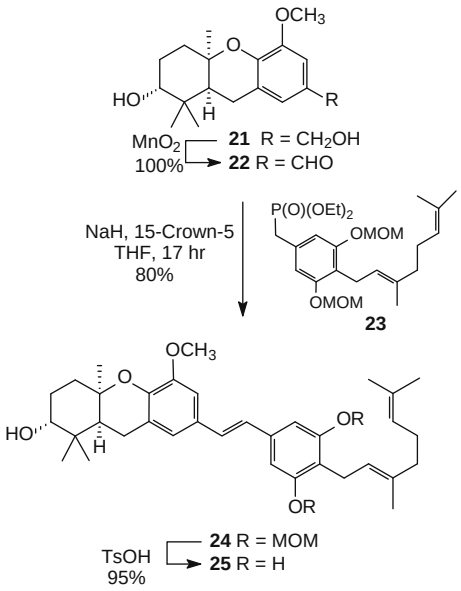
While analysis of the ^1H NMR data provided good evidence for a cis-fused product, and supported one where the –OH group was cis to the bridgehead methyl group, the exact diastereomer was unproven. In the case of cymobarbatol (**2**) the natural product dis-



Scheme 1. Syntheses of the neryl arene **15**.



Scheme 2. Lewis acid-catalyzed reactions of epoxide **15**.



Scheme 3. Synthesis of schweinfurthin analogue **25**.

plays a trans relationship between the A-ring bromide and the bridgehead methyl group, and that structure was secured by a single crystal diffraction analysis.[7] To address any potential ambiguity, compound **7** was treated with TBAF to afford the benzylic alcohol **21** (Scheme 2) and, when this compound proved to be crystalline, a single crystal diffraction analysis was conducted. This information, together with the known configuration of the starting epoxide **15**, established the absolute stereochemistry as 2*R*, 4a*R*, and 9a*S*. The crystal structure (Fig. 3) also identified that an orthogonal orientation of the A-ring relative to the rest of the ring system places the axial methyl group of the geminal pair in the shielding region of the aromatic group.

Once the absolute stereochemistry of diol **21** was established, the material was used to prepare a new schweinfurthin analogue (Scheme 3). Treatment with manganese dioxide afforded aldehyde **22** which was coupled to the known phosphonate **23** in high yield to give stilbene **24**. Removal of the methoxymethyl acetals upon treatment of stilbene **24** with *p*-toluenesulfonic acid gave the desired 9a-epi-3-deoxyschweinfurthin B (**25**).[14] While this isomer did not show significant bioactivity in preliminary assays, it may be useful as a standard during further investigations of *Macaranga* species.

In conclusion, these studies have shown that cyclization of the neryl derivative **15** takes place upon treatment of this epoxide with $BF_3{\cdot}OEt_2$ to afford the cis-fused hexahydroxanthene **7**, and thus they extend the scope of cascade cyclizations terminated by reaction with a MOM acetal. The modest yield, increased polymer formation, and longer reaction time would appear to indicate that the transition state leading to the cis system is harder to attain than that leading from the geranyl analogue to the trans-fused hexahydroxanthene. Nevertheless, because they have demonstrated the viability of *Z*-olefin cyclizations to MOM-protected phenols, these findings encourage studies that would employ still larger isoprenoids to access systems that contain cis-fused rings such as the kampanols[9] and memnobotrins.[27]

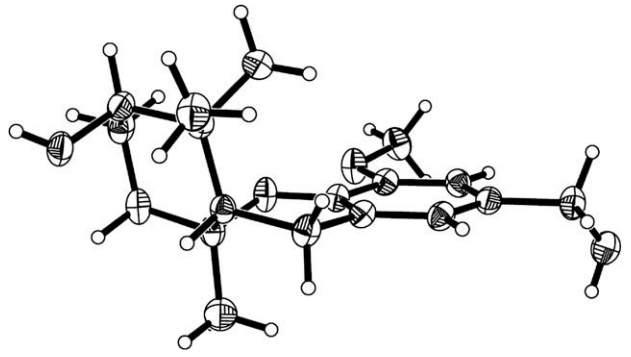


Figure 3. ORTEP of the single crystal analysis of diol **21**.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and/or spectral data for compounds **9**, **11–13, 15–18**, and **21**, **22**, **24**, and **25** are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.052.

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