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An efficient synthesis of the carbocyclic core of zoanthenol

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Dedicated to Professor Larry E. Overman on the occasion of his receipt of the Tetrahedron Prize

ABSTRACT

A concise strategy for the synthesis of the carbocyclic portion of zoanthenol is disclosed. The key step involves a 6-*endo* radical-mediated conjugate addition that constructs the quaternary stereocenter at C(12) and closes the B ring in a stereoselective manner. The synthesis of the C-ring fragment uses an enantioselective desymmetrization to simultaneously establish the absolute stereochemistry of two vicinal quaternary stereocenters. In only 17 steps from known compounds, the route affords an ABC ring system containing all three quaternary stereocenters and appropriate functionality to complete the synthesis of zoanthenol.

1. Introduction

The zoanthamine family of natural products has provided a challenging platform for synthetic innovation since the first member of the family was isolated 25 years ago (Fig. 1).[1,2] This structurally complex and stereochemically dense family of natural products exhibits a range of important biological activities including anti-osteoporotic, anti-inflammatory, antibacterial, and cytotoxic properties.[2] A number of synthetic groups have made important contributions[2] in efforts to access these complex alkaloids, including the total syntheses of norzoanthamine by Miyashita et al. in 2004 and by Kobayashi et al. in 2008.[3] To date no groups have reported the synthesis of zoanthenol (**1**), but Hirama et al. have disclosed an advanced strategy for its completion.[4]

Our synthetic efforts toward the zoanthamine alkaloids initially focused on the assembly of the challenging carbocyclic core (ABC rings) of zoanthenol (**1**). We were drawn to zoanthenol as our initial target due to its oxidized A ring, which allowed for a greater diversity of synthetic approaches because of the range of chemistry available to aromatic systems. The carbocyclic core was of special concern due to the density of stereochemical elements arrayed in the B and C rings. Our retrosynthetic analysis began by unraveling the heterocyclic DEFG rings of zoanthenol, revealing a tricyclic core with a functionalized side-chain (**2**, Scheme 1). The cyclization events[2] required to convert compound **2** to the natural product were well-established as thermodynamically favorable by Kobayashi et al.,[5] Williams and Cortez,[6] and Miyashita et al.[3a] Disconnection of the side-chain from intermediate **2** at the C(8)–C(9) bond revealed tricyclic alkyne **3** and lactam **4**. Tricycle **3** was envisioned to be accessible from tetracycle **5**, which in turn could be formed from aryl bromide **6** by radical-induced intramolecular conjugate addition. This tethered A–C ring system would arise from the addition of benzylic Grignard reagent **7** to enal **8**. Enal **8** would be derived from methyl ketone **9**, which could be obtained from the desymmetrization of *meso* anhydride **10**.

2. Results and discussion

Zoanthenol's C ring is arguably the most complex region of the molecule because it is fused to three other rings and boasts five consecutive stereocenters, of which three are all-carbon quaternary centers. It was our expectation that the C ring would pose the greatest challenges in stereochemical control, as well as in carbon–carbon bond-construction. The vicinal all-carbon quaternary centers (at C(9) and C(22)) posed a particular challenge, thus our strategy was to establish this functionality at an early stage. We targeted the known Diels–Alder cycloadduct **11**[7] (Scheme 2) as a starting material that could be converted to a *meso* anhydride, which could in turn be desymmetrized with a chiral reagent to allow the enantioselective synthesis of zoanthenol. In fact, several reports indicated that the selective methanolysis of a *meso* anhydride was a viable approach.[8] We anticipated that employing a strong acid would induce desilylation of anhydride **11** followed by in situ dehydration. Gratifyingly, the treatment of Diels–Alder adduct **11** with 0.5 equivalents of sulfuric acid in 1,2-dichloroethane produced anhydride **10** in 94% yield. At this point, we were poised to attempt the key desymmetrization. To our delight, treatment of anhydride **10** with quinine and methanol in toluene at 22 °C resulted in the formation of half-ester **12** in >99% yield and 50% ee. Performing the reaction at −50 °C increased the enantiomeric excess to 77% while maintaining a good yield.[9] The enantiomer of

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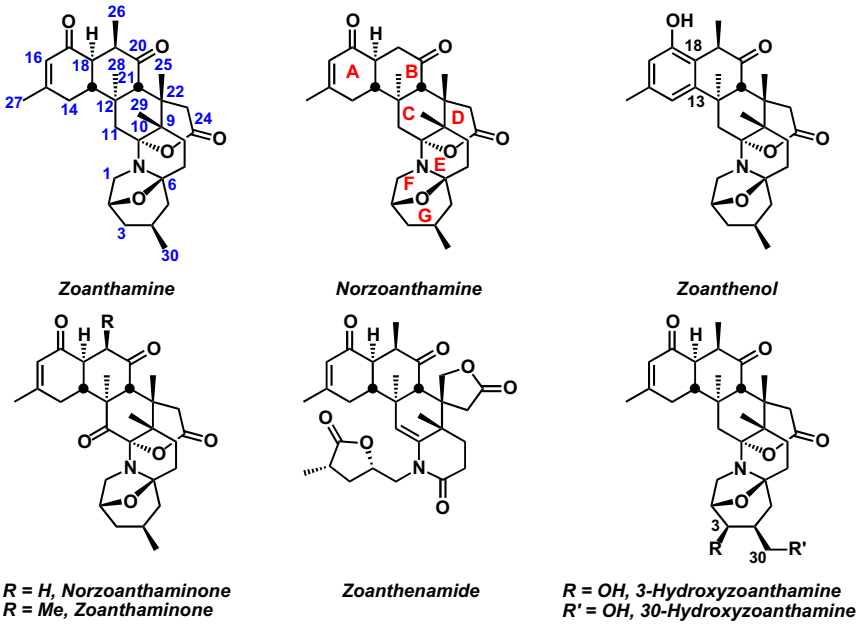
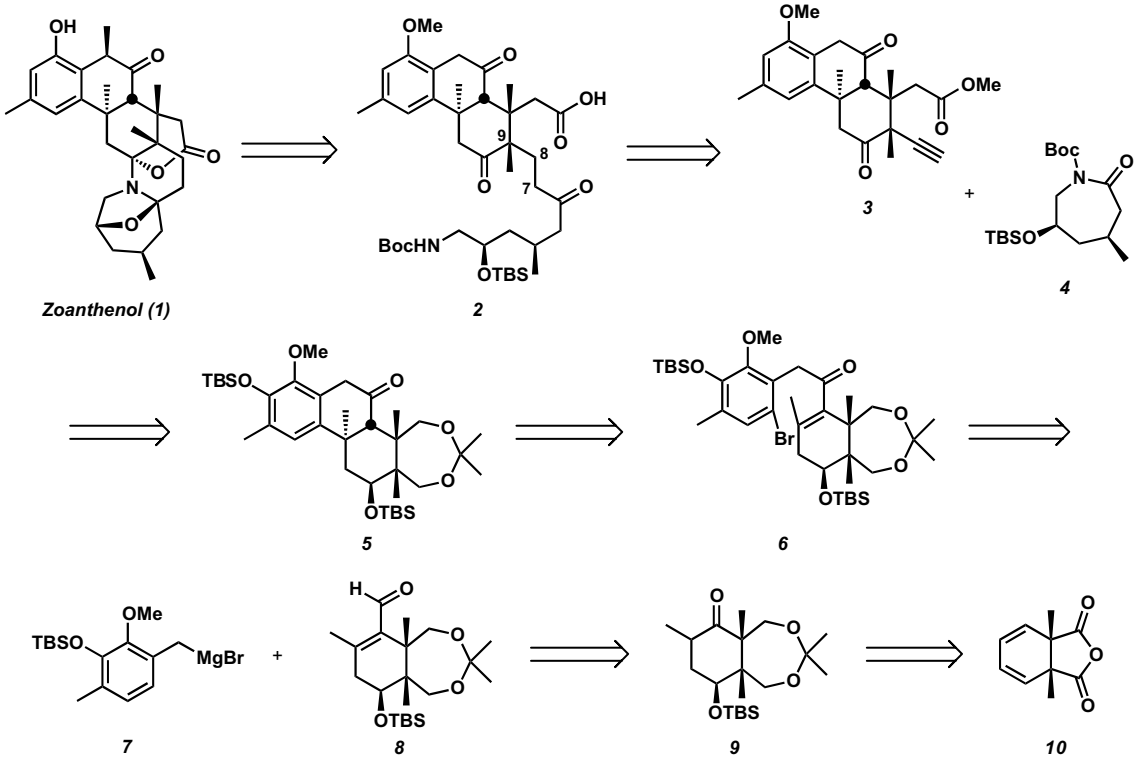


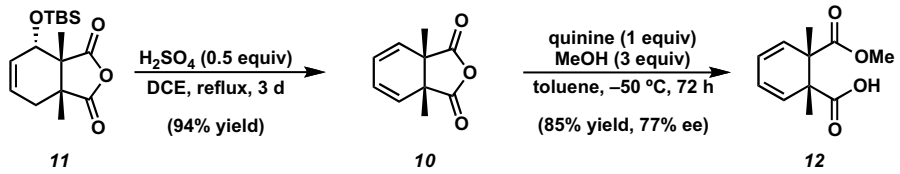
Figure 1.

half-ester **12** could be obtained in similar yield and enantiopurity by substituting quinine for quinidine. Finally, the enantioselectivity could be further increased to 85% by employing *O*-(−)-(menthyl acetate)quinidine in the reaction at −50 °C for 10 days.[10] To the best of our knowledge, this work represents the first example of the desymmetrization of a *meso* anhydride that simultaneously establishes the absolute stereochemistry of two vicinal all-carbon quaternary stereocenters.[11]

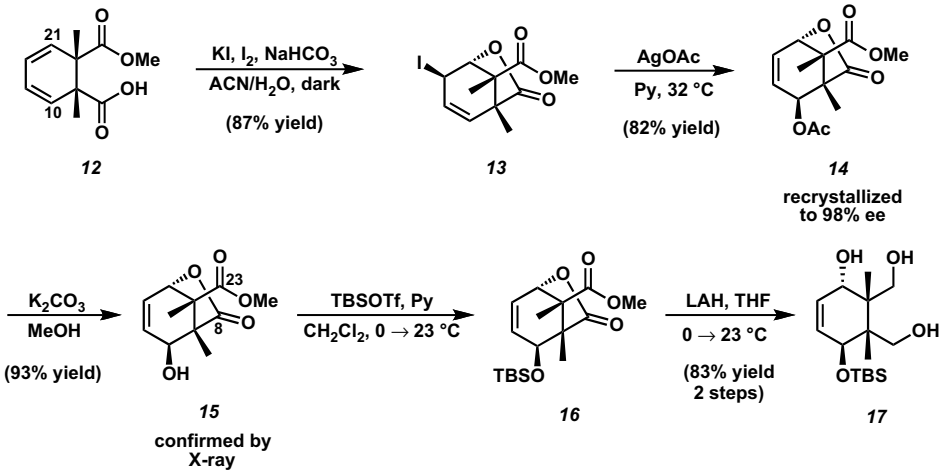
With our desymmetrized C ring in hand, we sought to oxygenate C(10) and C(21) using the carboxylic acid as a relay for the newly established stereochemical information. We were pleased to find that iodolactonization of half-ester **12** could be affected with good positional selectivity and yield (87%) to provide **13** (Scheme 3). Treatment of the iodolactone with silver acetate led to a *syn*-periplanar vinylogous attack by the acetate nucleophile to afford allylic acetate **14**. Recrystallization enhanced the enantiomeric excess of this acetate to 98%. Methanolysis of iodolactone **14** produced allylic alcohol **15**, the connectivity and relative stereochemistry of which were determined unambiguously by X-ray analysis. We sought to convert the ester and lactone functionalities at C(8) and C(23) to the



Scheme 1.



Scheme 2.

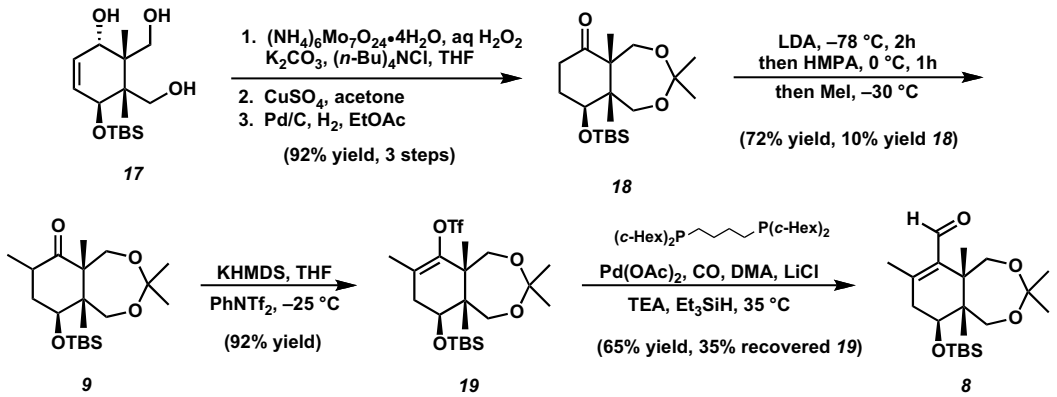


Scheme 3.

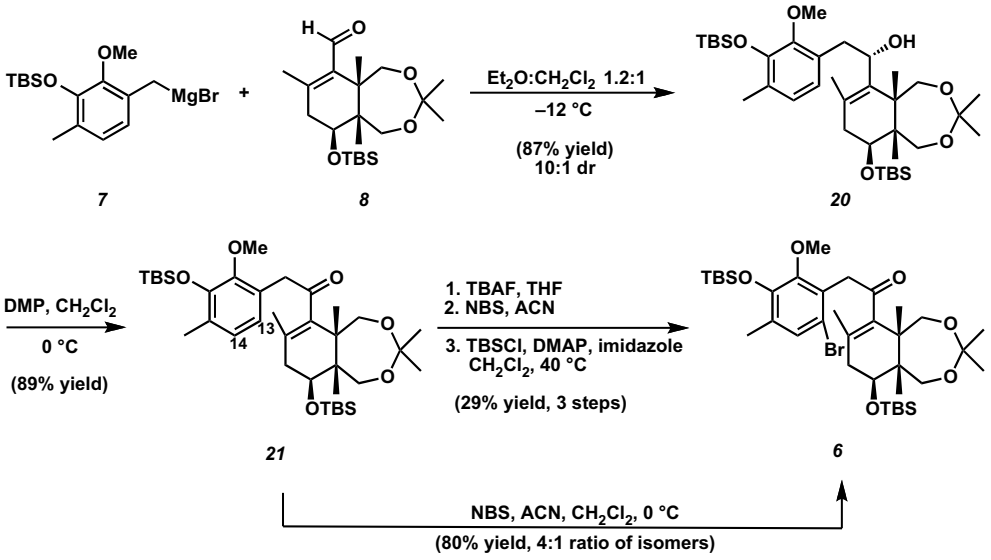
alcohol oxidation state. Thus, allylic alcohol **15** was smoothly silylated upon treatment with TBSOTf and pyridine to provide **16**, which was reduced with lithium aluminum hydride to form triol **17** in 83% yield over the two steps. Triol **17** is a versatile intermediate that has facilitated the exploration of a number of synthetic approaches to zoanthenol.[12]

We turned our attention to the conversion of triol **17** to the proposed C-ring synthon **8**. Thus, allylic alcohol **17** was selectively oxidized,[13] the primary alcohols were constrained with an acetal functionality, and the resulting enone was hydrogenated to afford ketone **18** in excellent yield over three steps (Scheme 4). The ketone was then α-methylated under standard conditions to provide methyl ketone **9** as a mixture of diastereomers. The mixture was enolized with KHMDS and trapped by *N*-phenyl bis(trifluoromethanesulfonimide) to afford enol triflate **19** in 92% yield. Treatment of enol triflate **19** under the reductive carbonylation conditions developed during our earlier studies[14] led to the formation of enal **8** in 65% yield with complete recovery of the unreacted enol triflate **19**.

The A and C rings were smoothly coupled by treatment of enal **8** with benzylic Grignard **7**,[12,14] affording alcohol **20** in 87% yield as a 10:1 mixture of diastereomers (Scheme 5). Subsequent oxidation of this alcohol with Dess–Martin periodinane[15] provided the corresponding enone (**21**) in 89% yield. To explore the possibility of a radical-induced cyclization of the A ring into the C-ring enone, the C(13) aryl bromide derivative of enone **21** was synthesized. *N*-Bromosuccinimide is known to brominate positions *para* to electron releasing groups.[16] While there was little precedent to suggest the superior directing ability of silyl ethers relative to methyl ethers in this reaction, there was significant evidence that hydroxyls were superior to methyl ethers.[17] As a result, we carried out a three-step protocol to regioselectively produce aryl bromide **6**. The yield for the sequence was disappointingly low, owing to competitive desilylation and general decomposition during the silylation and



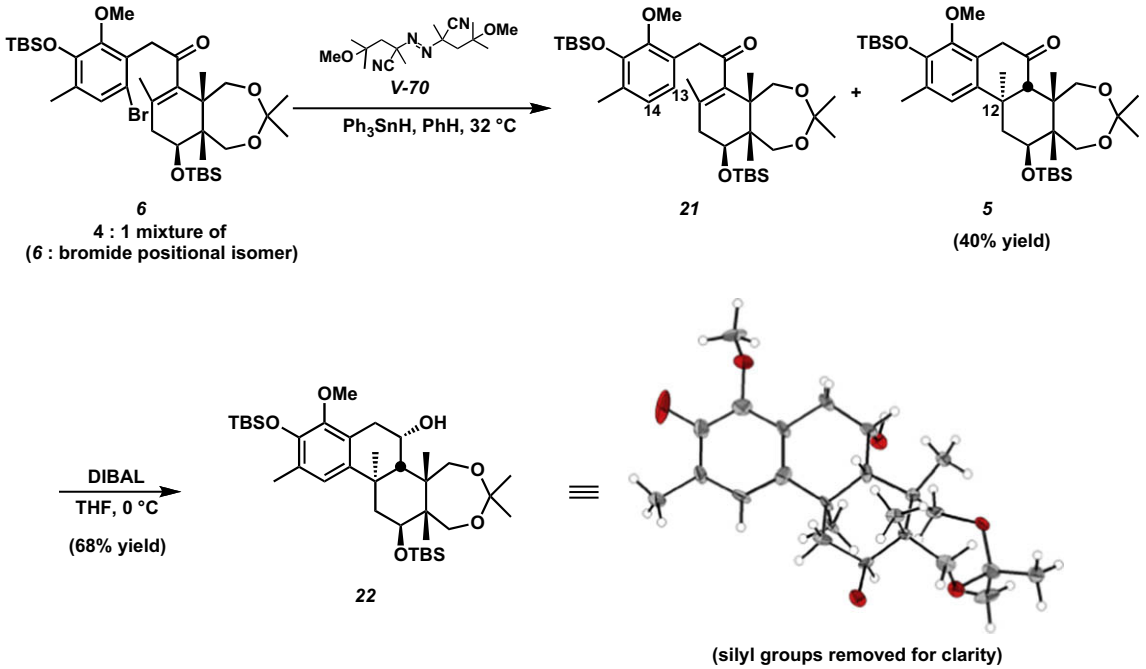
Scheme 4.



Scheme 5.

bromination steps. We were pleased to find that direct bromination of enone **21** afforded bromoarene **6** in 80% yield as a 4:1 mixture of isomers resulting from bromination at C(13) and C(14), respectively. Gratifyingly, the desired isomer was the major product, and the mixture was adequate for the investigation of the radical cyclization.

With aryl bromide **6** in hand, we began to explore radical cyclization reactions to close the B ring of zoanthenol. Although *endo* radical conjugate addition cyclization reactions are much less common than *exo* reactions,[18] good precedent for arene radical conjugate addition to make a quaternary center and a six-membered ring did exist.[19] To our delight, we found that in the presence of azo radical initiators (e.g., AIBN) and a hydrogen atom donor (e.g., Bu_3SnH), significant amounts of ketone **5** were formed from **6** (Scheme 6). In addition to the desired product, debrominated material (**21**) was obtained. Fortunately, the reduced material is readily separated from tetracycle **5** and can be rebrominated to allow for sufficient material throughput. The most effective conditions for the cyclization employed the azo initiator V-70 with slow addition of Ph_3SnH at 32 °C. The use of V-70, which decomposes more readily ($t_{1/2} \approx 10$ h at 30 °C) than AIBN ($t_{1/2} \approx 10$ h at 80 °C), allows us to initiate the radical reaction at lower temperatures and reduces the amount of debrominated enone recovered, resulting in improved yields of **5**. In the event, cyclization occurs to provide tetracycle **5** in 40% yield as a single diastereomer possessing the desired stereochemistry at both the newly formed all-carbon quaternary center and the tertiary center at the B–C ring junction. The stereochemical outcome of the key radical cyclization was unambiguously confirmed by X-ray structure analysis of alcohol **22**, which was obtained by DIBAL reduction of ketone **5**.[20]



Scheme 6.

Importantly, this result completes the synthesis of the carbocyclic core of zoanthenol, requiring just 17 steps from known Diels–Alder adduct **11**.

3. Conclusions

In summary, we have described an efficient synthetic approach to the carbocyclic core of zoanthenol that addresses the demanding combination of a fused polycyclic framework and multiple contiguous stereocenters. The synthetic approach is highlighted by a versatile desymmetrization of a bis-quaternary *meso* anhydride that enables access to either enantiomer of zoanthenol by selecting the appropriate cinchona alkaloid. The resulting stereochemical information is then relayed around the C ring by a series of diastereoselective reactions. Additionally, good selectivity is observed during the Grignard addition to couple the A and C rings, and the superior directing ability of a silyl ether in the presence of a methyl ether was established in arene bromination reactions. Finally, the key radical cyclization occurs with excellent diastereoselectivity to construct the third all-carbon quaternary center within a single six-membered ring and establishes the correct relative stereochemistry for the tertiary center at the B–C ring junction. Overall, the approach allows access to the challenging carbocyclic core of zoanthenol in 17 steps.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.023.

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10. In practice, high ee material was most readily accessible by advancing the 77% ee material and recrystallizing at a later step. For the purpose of synthetic explorations, racemic material was employed and could be accessed by use of catalytic quinine (10 mol %) at ambient temperature with 1.1 equiv of DBU, 3–5 equivalents MeOH, and 0.1 M toluene.
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20. TBS groups removed from the figure for clarity.