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Stereoselective synthesis of zoanthenol ABC-ring by radical strategy

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Zoanthenol, isolated from *Zoanthus* sp., possesses an extremely complex architecture including congested quaternary carbons. We describe a concise synthesis of the fully functionalized ABC-ring of zoanthenol based on sequential radical reactions.

Zoanthamine alkaloids, which are isolated from marine zoanthid *Zoanthus* sp., exhibit important biological and pharmacological properties.[1] Potent congeners, norzoanthamine,[1e] zoanthamine,[1a] and zoanthenol (**1**, Fig. 1),[1h] consist of heptacyclic rings including a polyfunctionalized phenanthrene carbocycle (ABC) and amino acetal moieties (DEFG). Because of their unique biological activities and complex architectures, the zoanthamine alkaloids have attracted keen interest from the synthetic community. Although many synthetic efforts have been devoted to their total synthesis,[2,3] only two groups have succeeded.[4,5] Most challenging is an efficient and stereocontrolled construction of the congested quaternary carbons at the C9, C12, and C22 positions in the ABC-ring. We describe herein a concise synthesis of the fully functionalized ABC-ring of zoanthenol.

We envisioned the ABC-ring **2** to be accessible from β-ketoester **4** through sequential radical reactions (Fig. 1). The BC-ring would be constructed utilizing an oxidative tandem radical cyclization with concomitant formation of the C12 and C22 quaternary centers (**4**→**3**). Another reductive radical reaction was designed to install the three-carbon unit (C6–C8) at the C9 position (**3**→**2**).

The requisite β-ketoester **4** was synthesized from 7-methylcoumarin by conventional procedures.[6] The key tricyclic system **3** was stereoselectively provided from **4** by a manganese-mediated radical cyclization according to Snider's procedure (Scheme 1).[7] Despite the existence of an electron-rich aromatic ring, the ABC-ring **3** was obtained in good yield (71%).[8] The resulting ketone **3** was converted to olefin **5** by addition of MeLi, dehydration, and subsequent isomerization. LAH reduction followed by epoxidation afforded epoxy alcohol **6** (70%) along with a small amount of the diastereomeric epoxide (12%). One carbon homologation of the primary alcohol **6** was achieved in three steps: TEMPO-catalyzed oxidation of **6**,[9] carbonyl olefination of the resulting aldehyde,[10] and a hydroboration/oxidation sequence to give the elongated primary alcohol **7**. Finally, installation of the ethyl acrylate group by treatment with ethyl propiolate and *N*-methylmorpholine (NMM) afforded β-alkoxy acrylate **8**.

With **8** in hand, we next focused on the construction of the quaternary carbon at C9. After considerable experimentation, we found that the titanium-mediated radical reaction produced the desired compound **9** (Scheme 2). Treatment of **8** with titanocene chloride, which was generated from titanocene dichloride and zinc

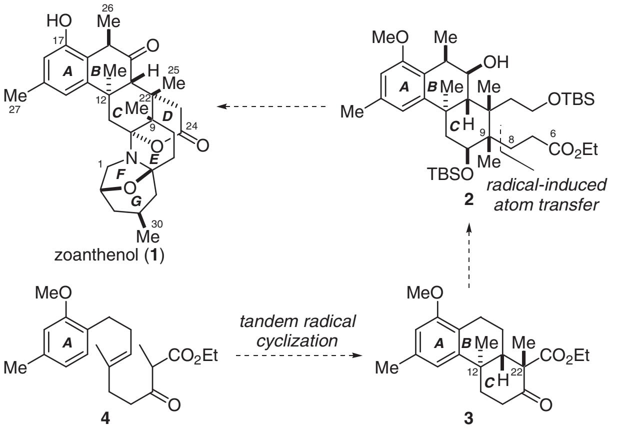

Figure 1. Structure and synthesis plan of zoanthenol.

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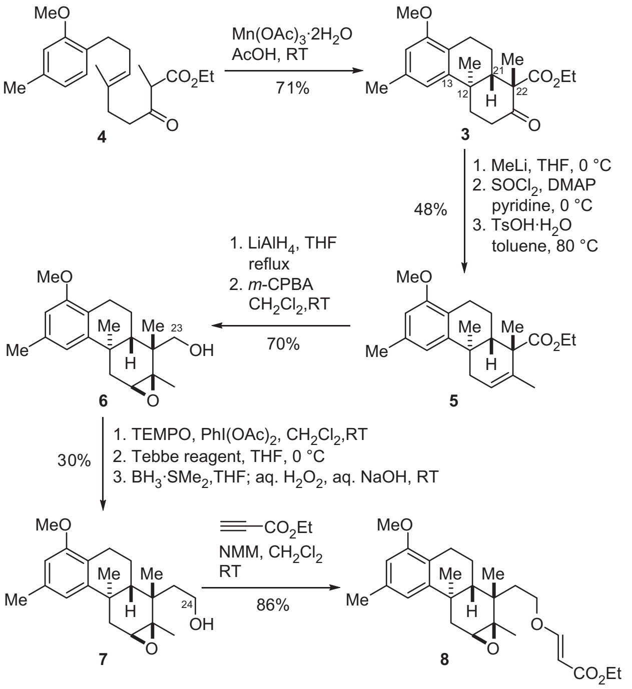
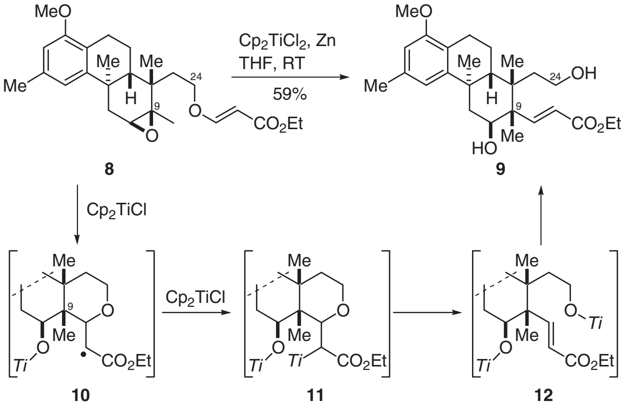
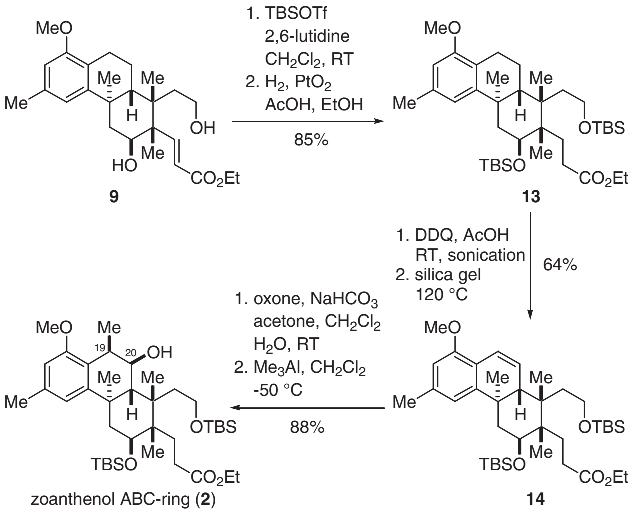


Scheme 1. Synthesis of β-alkoxy acrylate **8**.



Scheme 2. Radical-induced atom transfer.



Scheme 3. Synthesis of zoanthenol ABC-ring.

in THF,[11] afforded diol **9** in 59% yield with complete stereoselectivity. It is noteworthy that the acryl ester moiety of **8** was transferred from the C24 oxygen to the C9 carbon, leading to the efficient construction of the quaternary center and the configurational inversion of C9. We speculated that this manipulation was accelerated by the high oxophilicity of titanium via the successive reaction intermediates **10**, **11**, and finally **12**.

To complete the synthesis of the ABC-ring of zoanthenol, installations of methyl and hydroxy groups in the B-ring were performed (Scheme 3). The diol **9** was protected as its TBS-ether and hydrogenated to give **13** in 85% overall yield. DDQ oxidation followed by heating in the presence of silica gel afforded styrene derivative **14**. Epoxidation of **14** and treatment with Me_3Al realized the regio- and stereoselective installation of the methyl and hydroxy groups at C19 and C20, respectively, to give the fully functionalized ABC-ring **2**.

In conclusion, we have developed a concise route to the zoanthenol ABC-ring. Key features of the synthesis are the oxidative tandem radical cyclization and the radical-induced atom transfer to construct all quaternary carbons. The application of this strategy to the total syntheses of zoanthenol and other zoanthamine alkaloids is being actively investigated in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.104.

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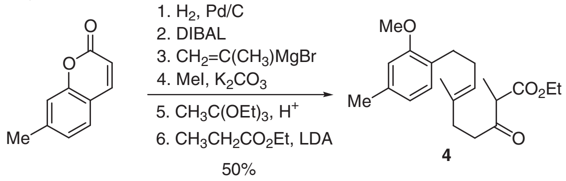
6. The compound **4** was prepared from 7-methylcoumarin as follows (6 steps, 50% overall yield).



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