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Stereoselective synthesis of zooxanthellactone

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ABSTRACT

The marine polyunsaturated natural product zooxanthellactone was synthesized in six steps and in 11% overall yield from eicosapentaenoic acid. The key synthetic steps were a Sonogashira cross-coupling reaction and a stereoselective semi-reduction. These efforts, together with NMR and optical rotation data, confirmed the reported structure of zooxanthellactone.

Polyunsaturated fatty acids (PUFAs), and in particular their oxygenated derivatives, display a wide variety of interesting biological activities.[1] Several marine natural products derived from eicosapentaenoic (EPA, **1**) and docosahexaenoic acid (DHA, **2**) have been reported (Fig. 1).[2,3] One such example is zooxanthellactone (**3**), that was reported isolated from several strains of microalgae of the genus *Symbiodinium*.[4] The biosynthesis mostly likely involves DHA (**2**) as the substrate for a lipoxygenase-catalyzed formation of the 4*S*-hydroxyl functional group, via the corresponding hydroperoxide, followed by the formation of the γ-lactone in **3**. This natural compound exhibits mild cytotoxic activity toward several human cancer cell lines.[4]

Two groups have reported the synthesis of racemic **3**.[5] In connection with the preparation of polyunsaturated fatty acids[6] and their derivatives,[7] all-Z skipped PUFAs such as EPA (**1**) and DHA (**2**), have been used as starting materials. Hence, we decided on a synthetic strategy where alkyne **5** was to be prepared from EPA (**1**). The vinylic halide **9** should be accessible from commercially available acid **6**. A Sonogashira reaction between these two fragments, followed by a *Z*-stereoselective reduction of the triple bond, would yield the natural product **3** (Fig. 1 and Scheme 1).

The alkyne **5** was prepared in 56% yield from the aldehyde **4** as outlined in Scheme 1 following a literature protocol.[8] The Ohira–Bestmann[9] and the Colvin reactions[10] were also attempted for the conversion of aldehyde **4** into alkyne **5**, but the Corey–Fuchs reaction[11] provided the best result producing alkyne **5** (56% yield from aldehyde **4**).

(*S*)-Vinylic iodide **9** was then prepared in a three-step sequence as depicted in Scheme 1. The acid chloride **7**, obtained from **6**, was directly converted via a Rosenmund reduction into aldehyde **8**.[12] This unstable aldehyde was immediately submitted to a Takai olefination reaction.[13] After purification by column chromatography, the vinylic iodide **9** was obtained in 20% yield in three steps. In addition, the *Z*-isomer of **9** was also isolated in 5% yield.

The Sonogashira cross-coupling reaction[14] between **5** and iodide **9** was conducted at ambient temperature using $Pd(PPh_3)_2Cl_2$, CuI, and Et_3N in THF. This afforded a 71% yield of alkyne **10**. The final step of the synthesis of zooxanthellactone (**3**) was the *Z*-selective semi-reduction of the internal triple bond in **10**. The first experiments were conducted with Lindlar's catalyst.[15] In all our attempts, no conversion of alkyne **10** was observed. A modification of the Lindlar protocol, adding pyridine and 1-octene, was also unsuccessful.[16] Next, an effort to use pure 10% $Pd/CaCO_3$ was made.[17] ^1H NMR analysis of the crude reaction product showed a significant amount of over-reduced products. When 10% of $Pd/CaCO_3$ in EtOAc/pyridine/1-octene (10:1:1) was tried, only a minor amount of the desired natural product **3** was isolated. In addition, experiments with the Zn(Cu/Ag) protocol reported by Boland et al.[18] were unsuccessful. Finally, $Pd/BaSO_4$[19] with pyridine as the solvent gave the desired natural product **3**, albeit in 29% yield due to problems with over-reduction of the product (Scheme 1).[20]

The MS and NMR data of **3** were in agreement with the literature.[4] However, the specific optical rotation value was lower ($[\alpha]_D^{25}$ +40.3 (*c* 0.30, CH_3Cl)) than that reported by Ojika and coworkers ($[\alpha]_D^{25}$ +64.6, (*c* 0.24, CH_3Cl)). HPLC analysis of the final product with a chiral stationary phase column revealed the presence of 12% of impurity (see Supporting information). Synthesis

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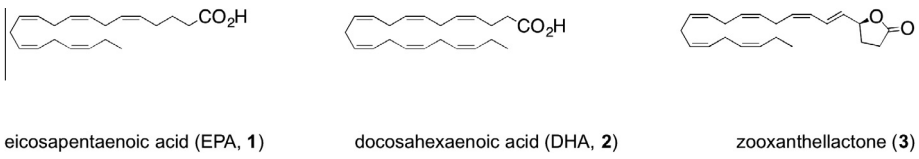
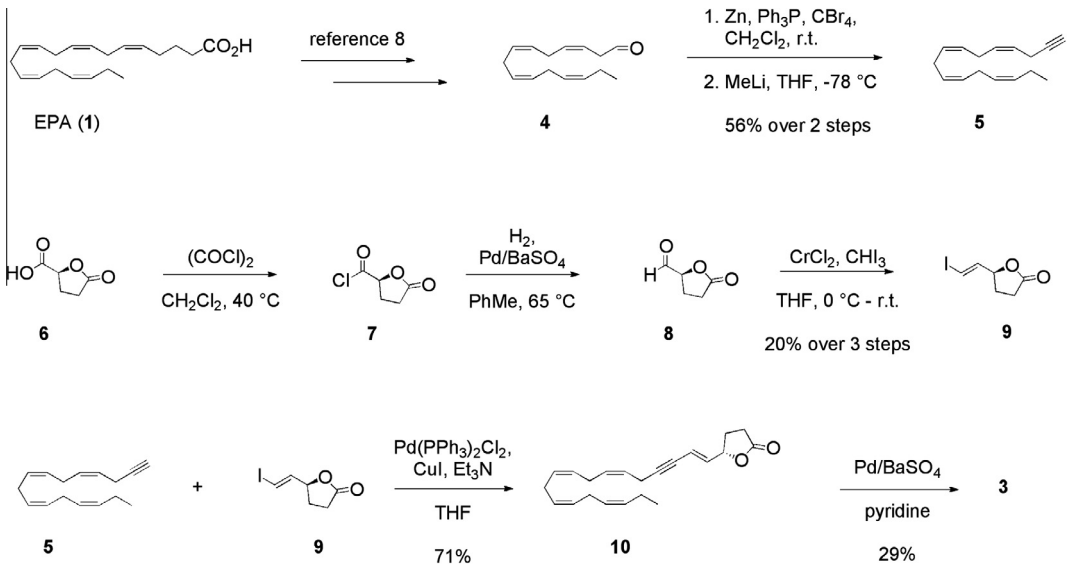


Figure 1. Structures of EPA (**1**), DHA (**2**), and zooxanthellactone (**3**).



Scheme 1. Synthesis of zooxanthellactone (**3**).

of the *R*-enantiomer of zooxanthellactone (**3**) using the same synthetic sequence as outlined in Scheme 1, followed by HPLC analysis, confirmed that this impurity was the undesired *R*-enantiomer. Most likely, a racemization process occurred during the Sonogashira reaction due to the formation of a π–allyl intermediate. Such an intermediate has been reported to form in the Tsuji–Trost reaction,[21] where palladium expels an allylic leaving group when forming the π–allyl palladium-complex. The lactone ring may be opened through a similar mechanism. When the lactone ring is reformed, this results in either retention or inversion of the stereogenic center. Granberg and Bäckvall reported that such a reaction leads to inversion of stereogenic centers by rear side attack on π–allyl complexes.[22] One example of such an inversion process of the stereogenic center in a γ-lactone ring has been reported under Sonogashira cross-coupling conditions.[23] All efforts to suppress the racemization process were unsuccessful,[24] resulting in the formation of the natural product **3** with 75–83% enantiomeric excess.

In summary, a short, effective, and stereoselective synthesis of zooxanthellactone (**3**) in 11% overall yield starting from EPA (**1**) has been presented. The advantage of employing EPA (**1**) as the starting material is the conservation of the double bond configuration in the all-*Z* skipped tetraene moiety. These efforts confirmed the reported structure and provided mg quantities for biological evaluations.

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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.2014.03.085.

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