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Synthesis of 5-(*S*)-HETE, 5-(*S*)-HEPE and (+)-zooxanthellactone: Three hydroxylated polyunsaturated fatty acid metabolites

Karoline Gangestad Primdahl[a], Yngve Stenstrøm[b], Trond Vidar Hansen[a,b], Anders Vik[a,*]

[a] Department of Pharmaceutical Chemistry, School of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo, Norway
[b] Department of Chemistry, Biology and Food Science, Norwegian University of Life Sciences, P.O. Box 5003, N-1432, Ås, Norway

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ABSTRACT

Short and stereoselective syntheses of the two hydroxylated polyunsaturated fatty acid metabolites, namely 5-(*S*)-HETE and 5-(*S*)-HEPE, are reported in 23% and 30% overall yields, respectively. In addition, synthesis of the polyunsaturated fatty acid natural product (+)-zooxanthellactone has been achieved in 19% overall yield. The three aforementioned compounds have been conveniently prepared in six steps, starting from the corresponding commercially available polyunsaturated fatty acids arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid, respectively. All three hydroxylated polyunsaturated natural products were prepared using a biomimetic synthesis.

1. Introduction

Polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play an important role in the physiology of living organisms. These three PUFAs are excellent substrates for enzymatically mediated oxidation reactions which lead to a diversity of biologically active PUFA derivatives that modulate inflammatory and immune responses.

One such enzyme is 5-lipoxygenase (5-LOX) that transforms AA into 5-(*S*)-HPETE (Fig. 1), which is the precursor in the biosynthesis of the biologically important pro-inflammatory leukotrienes. Reduction of 5-(*S*)-HPETE gives 5-(*S*)-HETE (Borgeat et al., 1976), which is a mediator of neutrophil recruitment during inflammatory processes (O'Flaherty et al., 1981; Potter et al., 1985; Dodge and Thomas, 1985). The enzyme 5-hydroxyeicosanoic dehydrogenase (5-HEDH) oxidizes 5-(*S*)-HETE with high *S*-selectivity (Powell et al., 1992) into 5-oxo ETE, which is an important chemoattractant and stimulant for neutrophils that actively participates in numerous anti-inflammatory processes (Powell and Rokach, 2013).

In the last decades, thorough and continuous efforts by the Serhan group have established that the PUFAs AA, EPA and DHA are substrates for the biosynthesis of several potent anti-inflammatory and pro-resolving lipid mediators, such as the lipoxins, resolvins, maresins and protectins (Serhan and Savill, 2005; Serhan and Petasis, 2011; Serhan, 2014). The biosynthesis of these lipid mediators is orchestrated during an inflammatory response by different lipoxygenases, such as COX-2, 12-LOX or 5-LOX. However, EPA can also act as substrates for 5-LOX, giving the EPA derived homolog of 5-(*S*)-HETE, designated 5-(*S*)-HEPE (Kulkarni and Srinivasan, 1986; Kulkarni et al., 1987), which in turn is oxidized to 5-oxo-EPE. This compound is less potent than 5-oxo-ETE in stimulating neutrophils and eosinohpils (Powell et al., 1995). The inhibition of 5-LOX have been the target of drug development (Young, 2012). Based on the structural similarities between DHA, AA and EPA, one may expect that all three PUFAs participate in the same biosynthetic pathways, although DHA is only a weak inhibitor of leukotriene biosynthesis (Corey et al., 1983). It was recently reported that 4-(*S*)-HDHA is a 5-LOX product of DHA that mediates antiangiogenetic effects (Sapieha et al., 2011). In addition, (+)-zooxanthellactone, a natural product found in several strains of microalgae (Onodera et al., 2004), is most likely formed by an intramolecular lactonization reaction of 4-(*S*)-HDHA. Moreover, several novel 4-hydroxylated derivatives of DHA with interesting biological activities have recently been reported (Serhan et al., 2002; Hong et al., 2003). The biological activities of 5-(*S*)-HEPE and 4-(*S*)-HDHA have not been thoroughly investigated, thus warranting further biological investigations.

Both racemic and stereoselective syntheses of 5-HETE have been reported (Corey et al., 1980; Corey and Hashimoto, 1981; Rokach et al., 1983; Zamboni and Rokach, 1983; Gunn, 1985;

* Corresponding author.
E-mail address: anders.vik@farmasi.uio.no (A. Vik).

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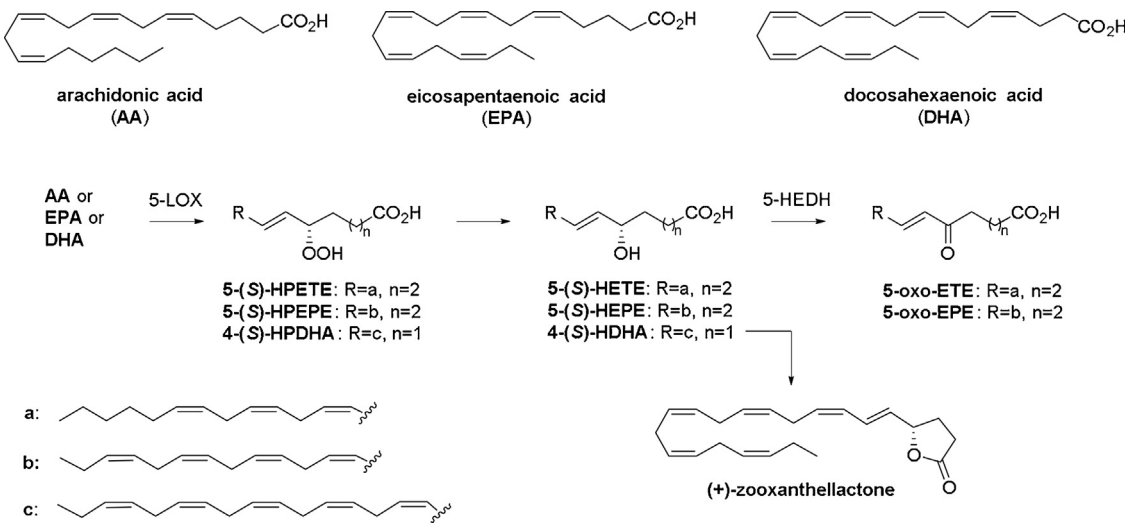


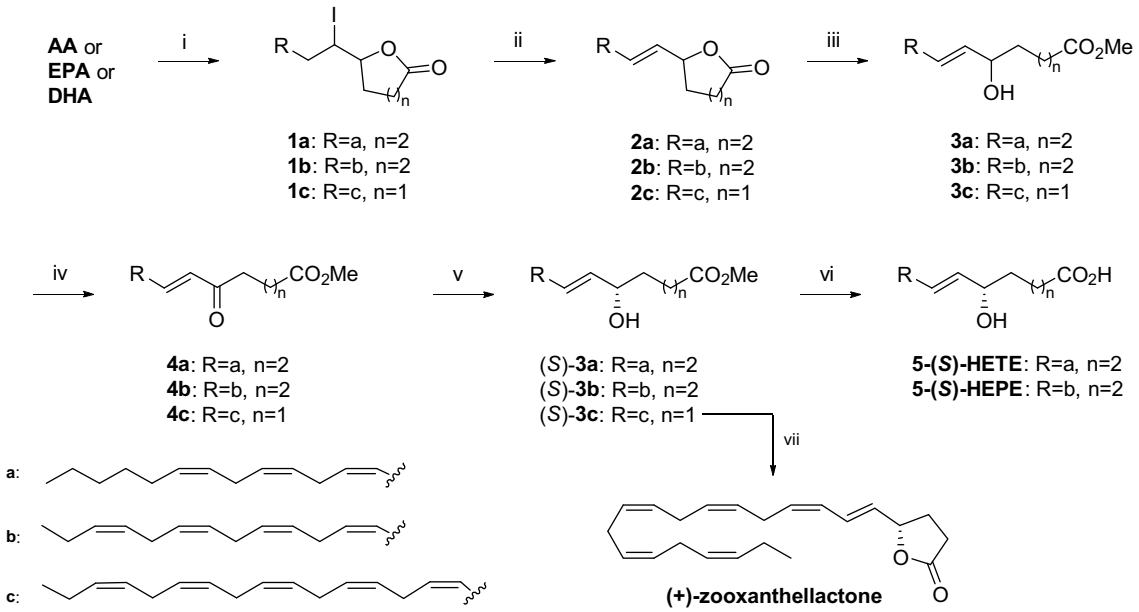
Fig. 1. Outline of the biosynthesis of 5-(*S*)-HETE, 5-(*S*)-HEPE, 5-(*S*)-HDHA and (+)-zooxanthellactone.

Nicolaou et al., 1986; Shimazaki et al., 1988; Gueugnot et al., 1996; Tyagi et al., 2012). In addition, 5-HETE has also been prepared by biocatalysis (Easton et al., 2001). So far, only racemic syntheses of 5-HEPE and 4-HDHA have been demonstrated on a preparative scale (Kuklev and Smith, 2004; Yamamoto et al., 2005; Itoh et al., 2006; Itoh et al., 2010). Thus, stereoselective methods to prepare these compounds are of interest. In connection with our interest in the biosynthesis, total synthesis and biological studies of hydroxylated PUFA-derived natural products (Hansen and Stenstrøm, 2000, 2001; Jakobsen et al., 2014; Aursnes et al., 2014a,b; Tungen et al., 2014a,b; Primdahl et al., 2015), we aimed to develop a short and simple stereoselective synthesis of the interesting hydroxy-derived natural products mentioned above from their corresponding commercially available PUFAs, namely AA, EPA and DHA.

2. Results and discussion

The compounds were prepared as outlined in Scheme 1. The free fatty acids were converted into the iodolactones **1** by utilizing a protocol reported by Ulven and co-workers (Tyagi et al., 2012). Then, an elimination reaction using DBU provided the lactones **2**, which were treated with trimethylamine in methanol to yield the hydroxy esters **3** following protocols of Skattebøl and co-workers (Holmeide et al., 2001). The alcohols were then oxidized to the corresponding oxo-compounds **4** using either the Dess–Martin periodinane reagent or the Swern oxidation conditions.

Next, various methods and protocols for the stereoselective reduction of the oxo-compounds **4a**–**c** were investigated. In general, asymmetric transfer hydrogenation of ketones delivers high stereoselectivity only on aryl alkyl ketones (Foubelo et al.,



Scheme 1. Reagents: (i) I_2, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) DBU, toluene; (iii) Et_3N, MeOH; (iv) Dess–Martin periodinane in CH_2Cl_2, or $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (v) **8** (15 mol%), catecholborane (1.5 eqiv.), CH_2Cl_2, −78 °C; (vi) LiOH, H_2O, *i*PrOH; (vii) TFA, CH_2Cl_2.