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Chemical synthesis of 12-HHT and related metabolites derived from polyunsaturated fatty acids

Collaboration of organic chemistry and biology has successfully developed a new area of research. Science of metabolites derived from polyunsaturated fatty acids by COX or LOX is one of successful examples. These metabolites are chemical mediators that promote initiation or resolution of inflammation and wound healing. Among the mediators 12-hydroxyheptadecatrienoic acid (12-HHT, **1**) derived from arachidonic acid (ARA) has a somewhat unique history (Fig. 1).

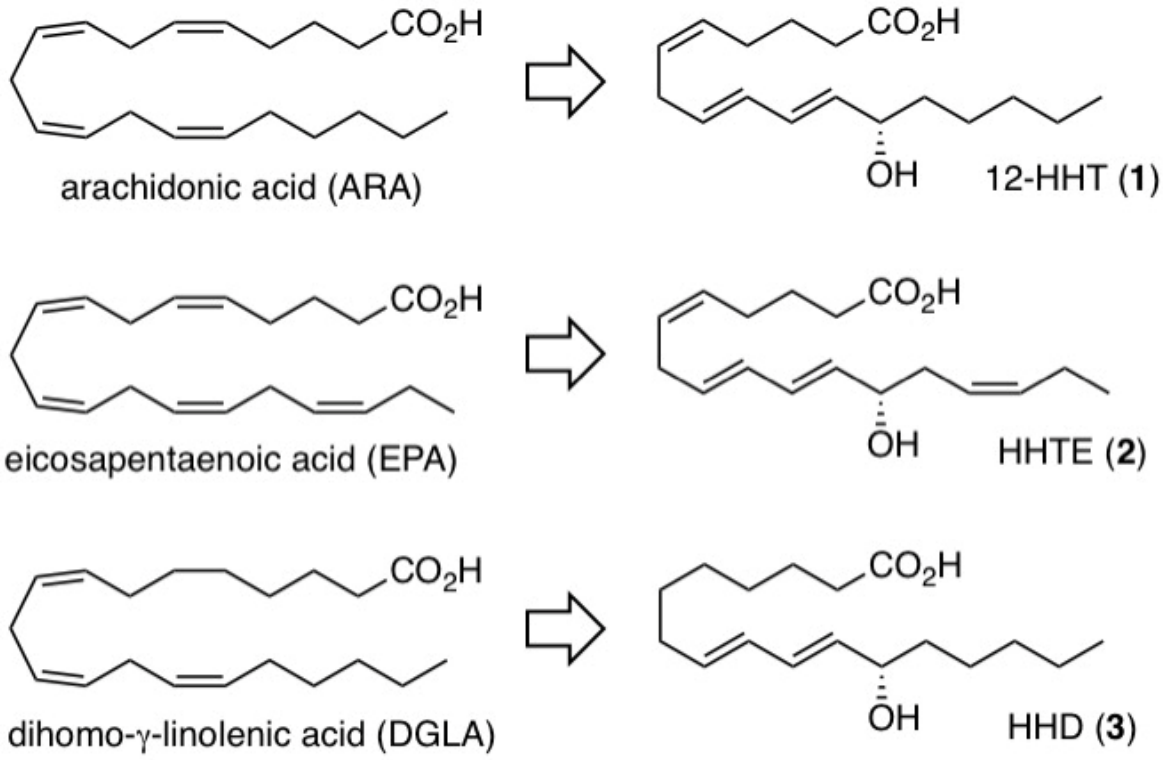

Fig. 1. Polyunsaturated fatty acids and targeted metabolites.

This metabolite has been isolated as a byproduct in the cascade producing thromboxane A_2 in 1970s. Later in 1997 and 2000, Yokomizo and Shimizu have isolated receptors BLT1 and BLT2 for leukotriene B4 (LTB_4), which is an inflammatory mediator derived from ARA. Affinity is high and low, respectively. After a while Yokomizo and Okuno discovered high affinity of 12-HHT for BLT2. BLT2 is ubiquitously distributed in humans. In the colon epithelium, mucosal integrity is maintained by 12-HHT/BLT2, which also responsible for skin wound healing. Similar metabolites HHTE (**2**) and HHD (**3**) originated from eicosapentaenoic acid (EPA) and dihomo-γ-linolenic acid (DGLA) have also been isolated (Fig. 1). However, supply of these metabolites is limited leaving biological study behind.

With the above background in mind, organic synthesis of 12-HHT and the metabolites derived from EPA and DGLA in optically active forms was undertaken using the two key transformations based on Sharpless asymmetric epoxidation and the Suzuki-Miyaura coupling reaction. Thus, the former reaction of trimethylsilyl (TMS)-substituted allylic alcohol in racemic form (*rac*–**4**) afforded epoxide **5** and allylic alcohol (*R*)-**4** (Fig. 2, eq 1) The TMS group was responsible for attaining high enantiomeric excesses for both (98% ee). Furthermore, the TMS group in epoxide **5** directed reaction with Bu_3SnLi and the resulting vinylstannane was converted to iodide **6** with trans iodo-olefin selectively. Allylic alcohol (*R*)-**4** was also converted to **6** via epoxidation and the Mitsunobu inversion. The borane reagent **7** for the Suzuki-Miyaura coupling was derived from the corresponding acetylene by hydroboration with $HB(Sia)_2$ (eq 2). This reagent was mixed with iodoalcohol **6** in the presence of $Pd(PPh_3)_4$ as a catalyst and aqueous NaOH to furnish methyl ester of **2**, which upon hydrolysis afforded **2**. Similarly, racemic (*E*)-1-iodooct-1-en-3-ol was converted to optically active 12-HHT (**1**) and HHD (**3**). The synthesis was scaled up to more than 100 mg of **1**. With 12-HHT in hand, the authors found that 12-HHT was decomposed to some extent in a halogenated solvent such as CH_2Cl_2 and $CHCl_3$ at room temperature overnight, whereas EtOH was a safe solvent.

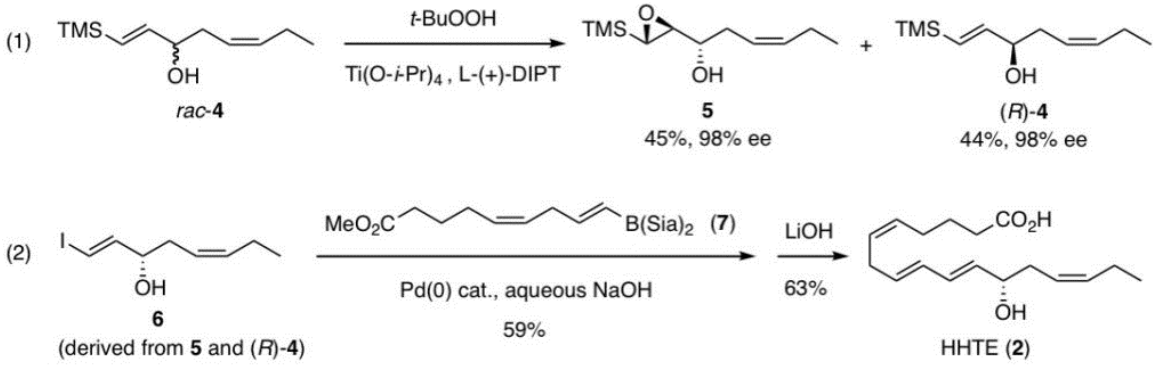

Fig. 2. Synthesis of HHTE and the two key transformation. Sia: -$CHMeCHMe_2$

In addition, Suzuke-Miyaura coupling is a strong and convenient method for construction of conjugated olefins and compatible with hydroxyl and ester groups. We have utilized this coupling for synthesis of 12-HHT analogues, resolvin E1, protectin D1, and maresin 1.

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Publication

Asymmetric synthesis of 12-hydroxyheptadecatrienoic acid and its 5,6-dihydro- and 14,15-dehydro-derivatives.
Kobayashi Y, Morita M, Ogawa N, Kondo D, Tojo T
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