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Concise syntheses of three ω-3 polyunsaturated fatty acids

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ABSTRACT

The synthesis of the three ω-3 polyunsaturated fatty acids, eicosatetraenoic acid (**3**), docosapentaenoic acid (**4**), and stearidonic acid (**5**) has been achieved using eicosapentaenoic acid or docosahexaenoic acid as the starting materials.

The mechanism of action behind the beneficial health effects of ω-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA, **1**) and docosahexaenoic acid (DHA, **2**), remains a topic of interest and discussion. These ω-3 PUFAs exhibit positive effects against cancer,[1] diabetes,[2] cardiovascular diseases,[3,4] and rheumatoid arthritis.[5] The mechanisms behind these effects are still under investigation, but it seems likely that endogenous oxygenated metabolites derived from EPA (**1**) and DHA (**2**) play an important part. Recently, Serhan and co-workers isolated and structurally elucidated several new classes of hydroxylated metabolites of both **1** and **2**, such as the resolvins,[6,7] the protectins,[8,9] and the maresins.[10] These compounds exhibit a plethora of interesting biological activities,[11] and have attracted significant interest as lead compounds toward several maladies.[11] So far, only EPA (**1**) and DHA (**2**) have been employed as enzymatic substrates for the biosynthesis of the aforementioned novel oxygenated metabolites. In this context, multi-milligram quantities were needed of the following three PUFAs; eicosatetraenoic acid, (ETA, **3**), docosapentaenoic acid (DPA, **4**), and stearidonic acid (SDA, **5**), Figure 1.

In the metabolic pathway leading to DHA (**2**), SDA (**5**) is transformed into DPA (**4**) via the sequential conversion into ETA (**3**) and EPA (**1**). Moreover, these three PUFAs exhibit interesting biological activities.[12,13] All three PUFAs are commercially available, but their costs are prohibitively high.[14] Eicosatetraenoic acid (**3**) and docosapentaenoic acid (**4**) are actually dihydroderivatives of EPA (**1**) and DHA (**2**), respectively. We and other research groups have used **1** and **2** as starting materials for the synthesis of several polyunsaturated natural products.[15–20] This approach also seemed attractive for making multi-milligram quantities of **3**–**5**, and these efforts are reported herein.

The synthesis of eicosatetraenoic acid (**3**) started from DHA (**2**), which was converted into epoxy ester **6** according to a slightly modified three-step literature procedure.[21] Subsequently, **6** was transformed into the C-18 aldehyde **7**[21] using the protocol published by Holmeide and Skattebøl.[22] Treatment of **7** with DBU in diethyl ether resulted in the formation of α,β-unsaturated aldehyde **8**,[21] which was reduced immediately to the more stable aldehyde **9**. The aldehyde obtained in this manner was subjected to a Wittig reaction to afford α,β-unsaturated ester **10**, Scheme 1. Flock and Skattebøl have investigated the chemo-selective reduction of several PUFA derived α,β-unsaturated esters with variable results.[15] In our hands, reduction of the α,β-unsaturated bond with DIBAL-H/CuI in the presence of HMPA,[17,18] followed by aqueous hydrolysis with LiOH, yielded the desired PUFA **3** in 22% yield over eleven steps.

The synthesis of docosapentaenoic acid (**4**) commenced with $LiAlH_4$ reduction of the ethyl ester of EPA (**11**) to its corresponding primary alcohol which was then oxidized to the C-20 aldehyde **12**. This aldehyde was converted into the α,β-unsaturated ester **13**, according to Scheme 2. For the regioselective reduction of the α,β-double bond in **13**, the DIBAL-H/CuI method afforded the best yield for this particular compound. Among the methods attempted for the hydrolysis of **14**, aqueous KOH in MeOH gave the highest yield of acid **4**. This concluded our five step synthesis of docosapentaenoic acid (**4**) in 30% overall yield.

The synthesis of stearidonic acid (**5**) started with the same chemistry as depicted in Scheme 1, except that EPA (**1**) was used as the starting material. The C-15 aldehyde **16** was obtained in four

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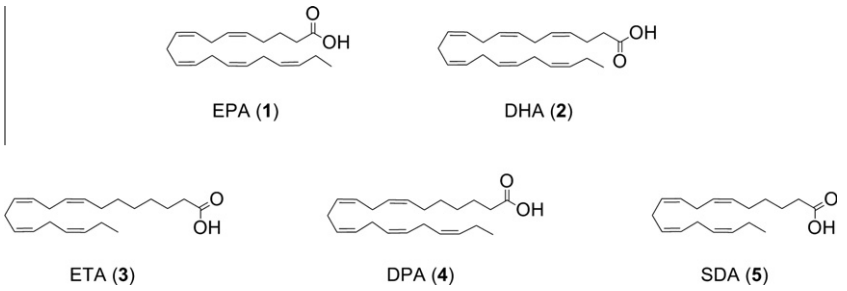
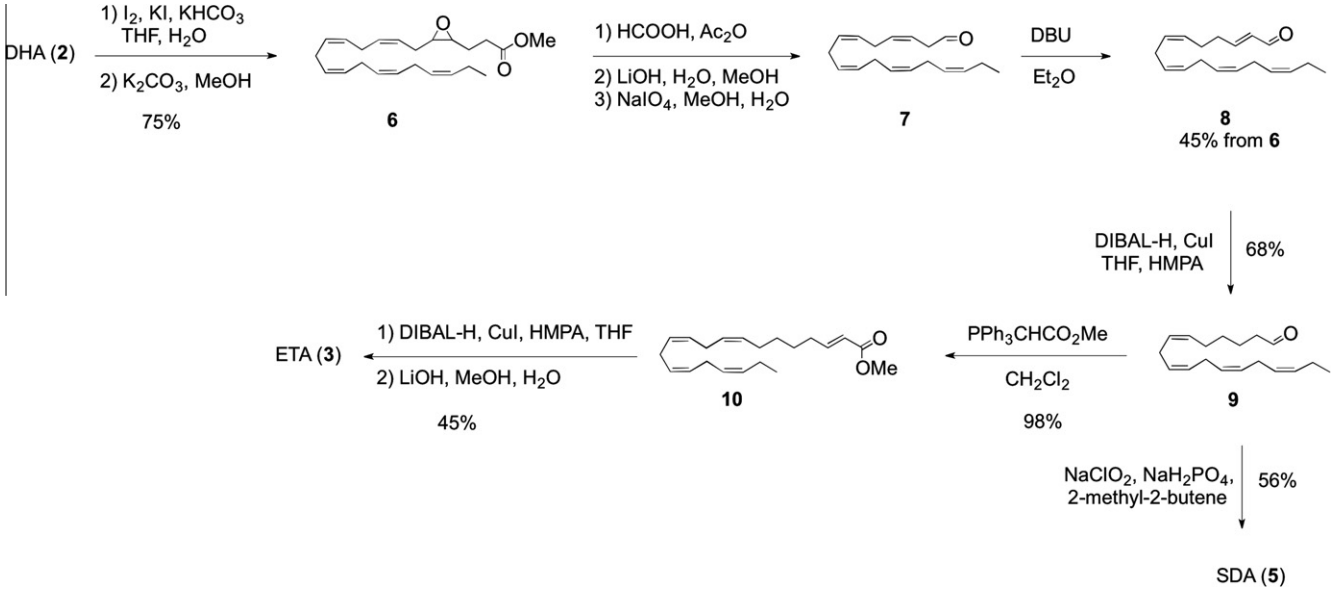


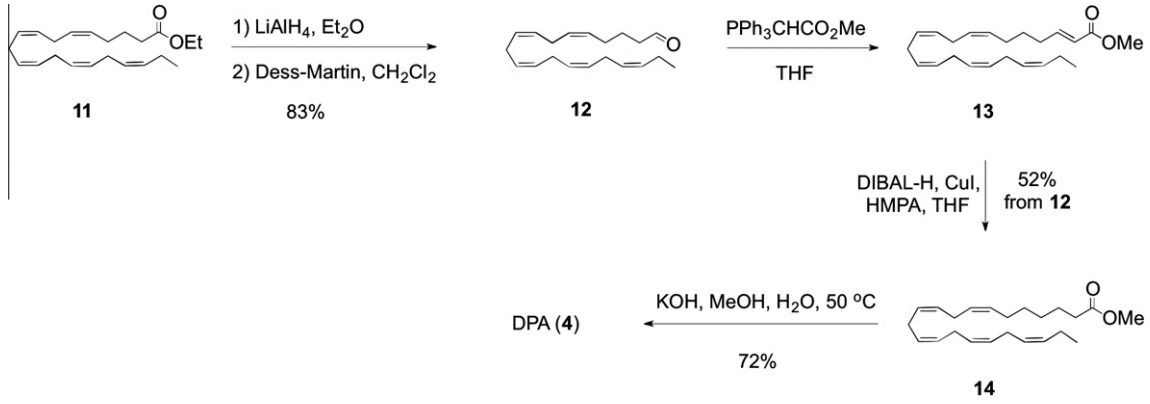
Figure 1.



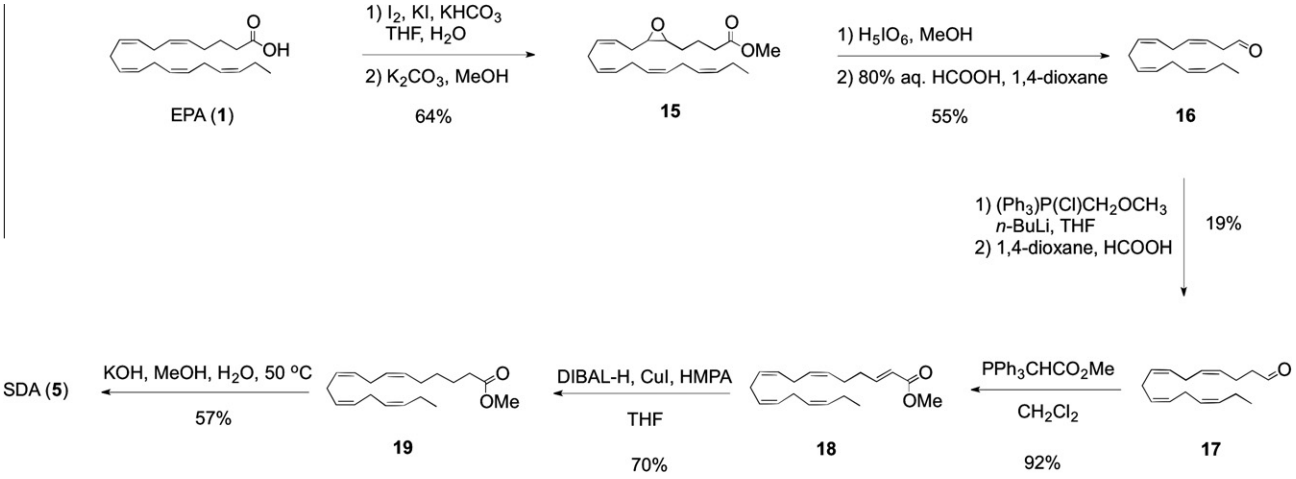
Scheme 1.

steps and in 35% yield as previously reported.[22] Aldehyde **16** was subjected to a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride and *n*-butyl-lithium as base which afforded the C-16 aldehyde **17** in 19% yield after hydrolysis.[15] This aldehyde was then converted into the α,β-unsaturated ester **18**. Again, regioselective reduction (CuI/DIBAL-H) and hydrolysis (KOH in aqueous MeOH) afforded stearidonic acid (**5**) in 3% overall yield over the nine steps (Scheme 3). Stearidonic acid (SDA, **5**) was also obtained in 56% yield from aldehyde **9** using Pinnick oxidation[23] (Scheme 1). This protocol afforded the acid **5** in 13% yield over eight steps.

In conclusion, the three ω-3 polyunsaturated fatty acids eicosatetraenoic acid (**3**), docosapentaenoic acid (**4**), and stearidonic acid (**5**) have been prepared using well established chemistry from eicosapentaenoic acid (**1**) and docosahexaenoic acid (**2**). All spectral data were in accord with the structures and no significant isomerization of the sensitive skipped Z-olefins was observed. Our synthesis of **4** compares favorably with that reported in the literature,[24] and the two PUFAs **3** and **5** are now available by simple operational procedures. Enzymatic studies of the three ω-3 polyunsaturated fatty acids **3**–**5** will be reported in due time elsewhere.



Scheme 2.



Scheme 3.

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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.2012.08.009.

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