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Synthesis of Two Stereoisomers of Potentially Bioactive 13,19,20-Trihydroxy Derivative of Docosahexaenoic Acid

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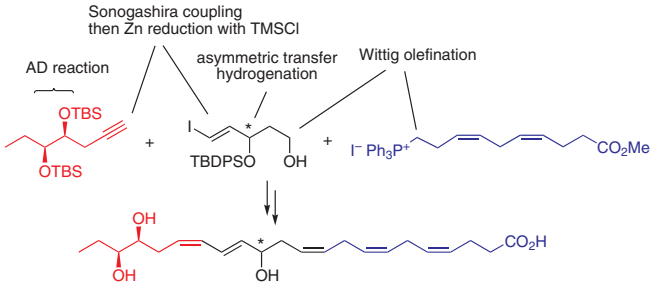

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Abstract The C16–C22 fragment with the acetylene terminus was constructed through the asymmetric dihydroxylation of the corresponding olefin, while the 15-iodo-olefin corresponding to the C11–C15 part was prepared via the asymmetric transfer hydrogenation of the corresponding acetylene ketone followed by hydrozirconation/iodination. Both pieces were joined by a Sonogashira coupling, and the product was further converted into the title compound via a Wittig reaction with the remaining C1–C10 segment and Boland reduction using Zn with TMSCl.

Key words DHA metabolite, trihydroxylated DHA, organic synthesis, enyne, Boland reduction, TMSCl, Hansen protocol

Discovery of new metabolites of docosahexaenoic acid (DHA) formed by lipoxygenases and/or cytochrome P450 enzyme pathways is an active area of study because most of the metabolites isolated to date show properties of resolving and preventing inflammation.[1] Recently, we isolated compound **1**, a dihydroxylated metabolite of DHA[2] (Figure 1). Interestingly, **1** displayed wound-healing activity, a unique property for a DHA metabolite.[3] Subsequently, the compound was synthesized, and the structure was determined.[4] Similar properties were then found in new metabolite **2** ('maresin like'),[5] and the structure of **2** was also determined after organic synthesis as well.[6] We then envisaged that hydroxylated compound **3** would possess similar activities because of the structural similarity in the positions of the hydroxylated carbon atoms relative to those in **1** and **2**. Based on the fact that the ω-epoxide[7] (19,20-epoxide) of DHA is converted into 19,20-dihydroxy-DHA by soluble epoxide hydrolases[7b,8] and that 13-hydroxy-19,20-epoxy derivative of DHA is isolated,[9] compound **3** is likely produced by 13-lipoxygenation[8e,10,11] of the former and/or by epoxide hydrolysis of the latter. It was envisaged that, in a similar way, epoxide hydrolysis of 11-hydroxy-17,18-epoxy-EPA[12] and 11-lipoxygenation[10,13] of 17,18-dihydroxy-EPA would produce **4**, which have high potential to be bioactive.[14]

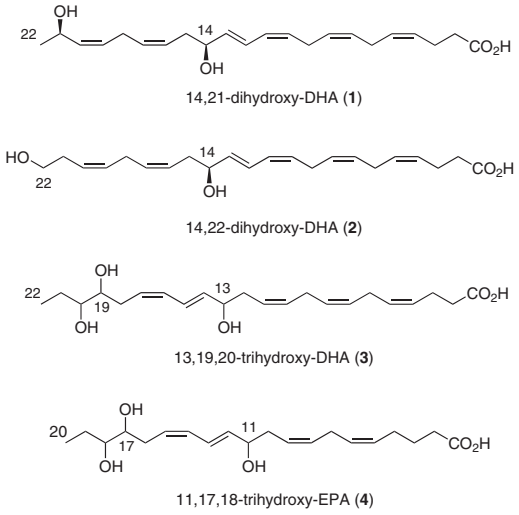

Figure 1 Dihydroxy-DHA metabolites with wound-healing activity and potentially bioactive metabolites of DHA and EPA

Among **3** and **4**, we chose **3** as a synthetic target because it has the same origin (DHA) as **1** and **2**, and we hoped that the method would be applicable to the synthesis of **4**. We established the 19,20-dihydroxy moiety as *syn*, based on

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the same stereochemistry seen in leukotoxin diol and isoleukotoxin diol,[15] in which the diol unit is nonconjugated, as that seen in **3**. Consequently, diastereoisomers **3aa** and **3ab**, shown in Figure 2, represent different relative stereochemistry and would be useful stereoisomers for biological study. We also hoped that, once the method was established, enantiomers of **3aa** and **3ab** could also be synthesized as well.

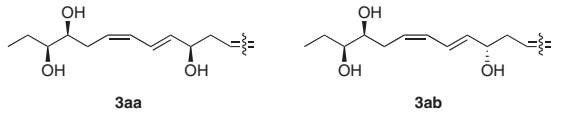
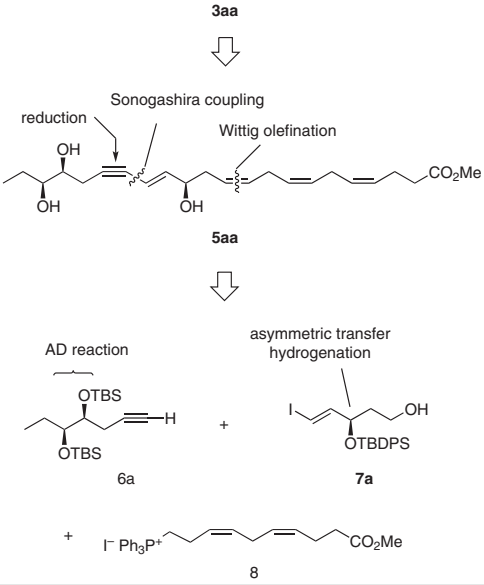


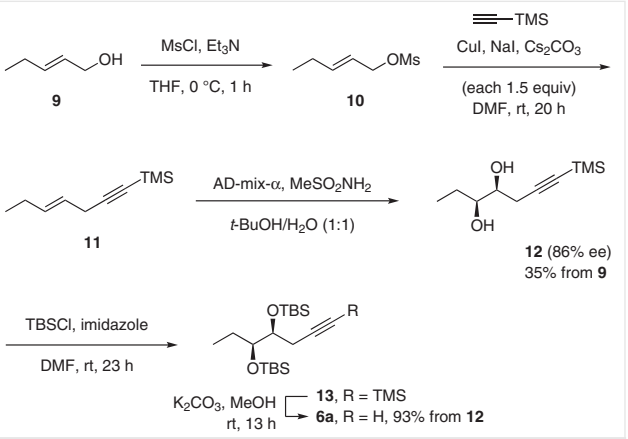
Figure 2 Targeted stereoisomers of **3**

Retrosynthetic analysis of **3aa** indicated acetylene **5aa** to be a key precursor, which could be disconnected to diol derivative **6a**, iodo-olefin **7a**, and Wittig reagent **8** (Scheme 1). We expected the asymmetric dihydroxylation (AD)[16] and the asymmetric transfer hydrogenation[17] to produce the stereogenic centers in **6a** and **7a**, respectively. In practice, the syntheses were successful with high enantioselectivity, as summarized in Schemes 2 and 3. Wittig reagent **8** was prepared by a straightforward method, as delineated in Scheme 4.



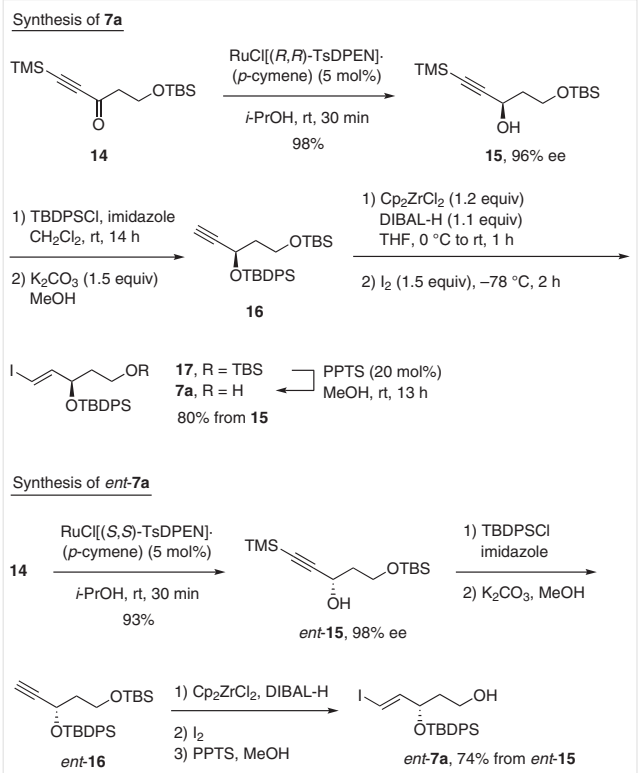
Scheme 1 Retrosynthesis of **3aa**

Synthesis of **6a** was started with mesylation of alcohol **9**, which was followed by the CuI-assisted coupling[18] with TMS-acetylene to afford **11** and the S_N2' regioisomer (structure not shown) in a 72:28 ratio, as determined with ^1H NMR spectroscopy (Scheme 2). Although the mixture was difficult to separate by chromatography on silica gel, the diols after the AD reaction were separated by chromatography on silica gel to afford **12** in 35% yield with 86% ee, as determined by ^1H NMR spectroscopy of the derived MTPA ester. Diol **12**[19] was protected as TBS ether **13**, which produced **6a** in 93% yield after TMS-desilylation with K_2CO_3.

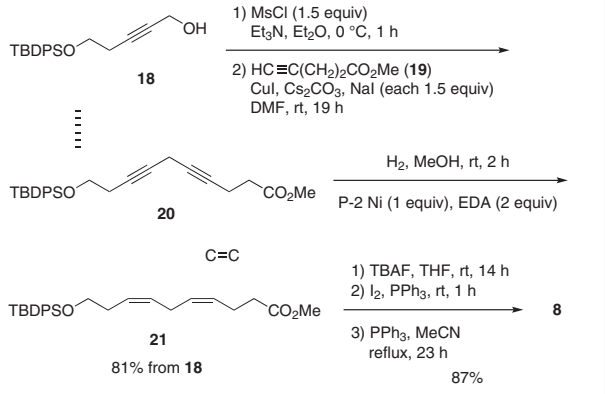


Scheme 2 Synthesis of diol intermediate **6a**

Synthesis of **7a** was carried out according to our previous method.[20] In brief, 1,3-propanediol was converted into alcohol **15** with 96% ee, as determined by HPLC analysis, via the asymmetric transfer hydrogenation[17] of ketone **14**[21] (Scheme 3). TBDPS protection of the hydroxy group in **15**



Scheme 3 Synthesis of **7a** and *ent*-**7a**

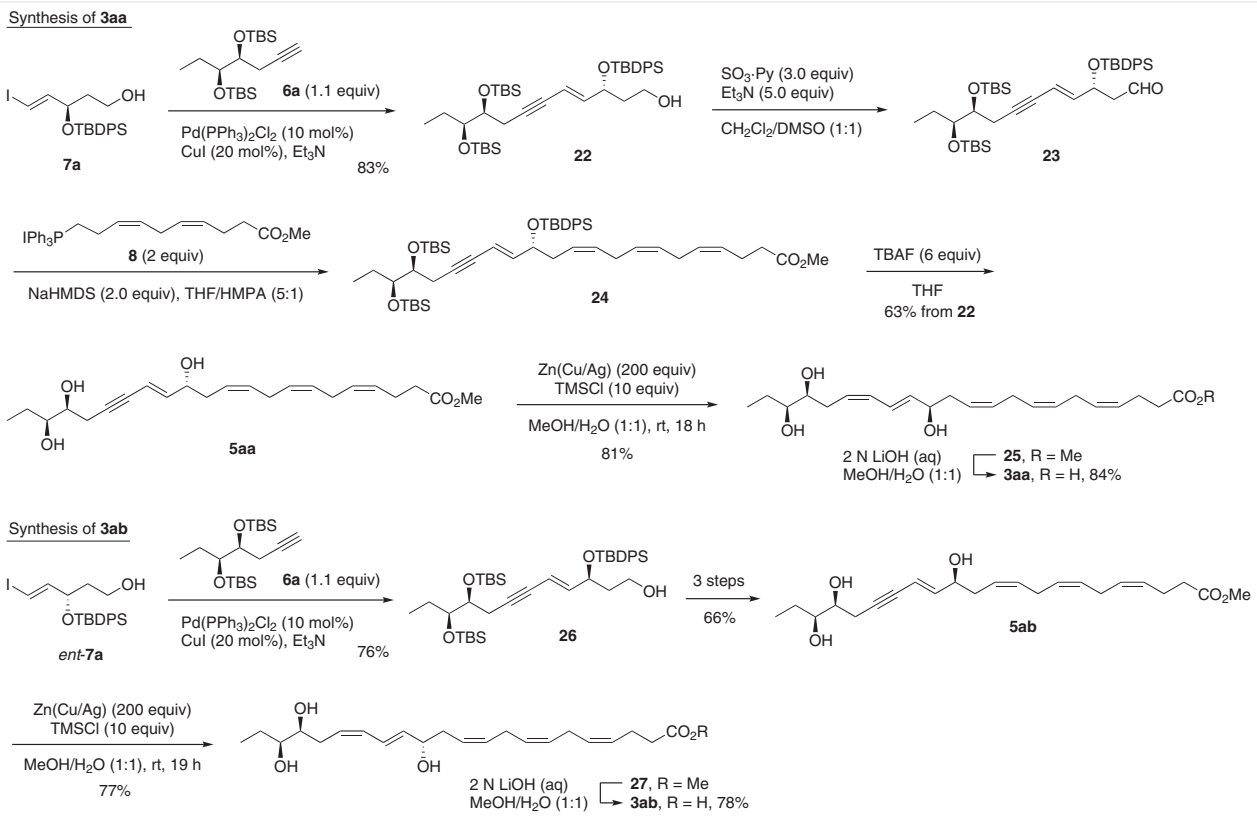


Scheme 4 Synthesis of the Wittig reagent **8**

and subsequent deprotection of the TMS group afforded **16**, which was subjected to hydrozirconation with in situ generated $Cp_2Zr(H)Cl$,[22] iodination, and TBS desilylation to give *trans*-iodide **17** stereo- and regioselectively in 80% yield. In a similar manner, ketone **14** was converted into *ent*-**15** with 98% ee, and the subsequent transformations furnished *ent*-**7a**.

Wittig reagent **8** was synthesized from alcohol **18**[23] by the method delineated in Scheme 4. Thus, mesylation of **18** followed by CuI-assisted coupling[18] with acetylene **19** afforded **20**, which gave olefin **21** in 81% yield upon reduction with P-2 Ni[24] under hydrogen. Desilylation, iodination, and the reaction of the resulting iodide with PPh_3 proceeded cleanly to furnish Wittig reagent **8** in a good yield.

Construction of the target compound **3aa** began with the Sonogashira coupling of **7a** with **6a** (1.1 equiv) to afford **22** in 83% yield (Scheme 5). Oxidation with SO_3·pyridine(Py)/Et_3N afforded the somewhat unstable aldehyde **23**, which was then subjected to a Wittig reaction with the ylide generated from **8** and NaHMDS in the presence of HMPA (11 equiv, THF/HMPA = 5:1).[25] Olefin **24** was produced stereoselectively and cleanly, and subsequently, treated with TBAF to furnish the key intermediate **5aa** in 63% yield from alcohol **22**. Next, **5aa** was subjected to the Boland reduction of the triple bond under the modified conditions reported by Hansen,[26] who added TMSCl to Zn(Cu/Ag) in aqueous MeOH. In practice, the reduction was successful in cleanly affording **25** in 81% yield. By contrast, an attempted reduction under the standard conditions[27] (without TMSCl) caused elimination of the hydroxy group at C13 and afforded a mixture of **25** and the elimination byproducts in a 73:27 weight ratio.[28] A similar elimination reaction has been reported previously.[29] Finally, hydrolysis of **25** produced **3aa** in 84% yield.



Scheme 5 Synthesis of **3aa** and **3ab**

In a similar way, the coupling reaction of *ent*-**7a** with **6a** gave **26**, which was converted into **5ab** in 66% yield. Reduction of **5ab** with Zn/TMSCl proceeded cleanly, and the resulting ester **27** was hydrolyzed to acid **3ab**. The ^{1}H NMR spectra of **3aa** and **3ab** were completely superimposed, whereas some of the olefinic carbons in the ^{13}C NMR spectrum were observed at different positions (see the Supporting Information).

In summary, we developed a method to produce the title triol and successfully performed the syntheses of **3aa** and **3ab** through the Boland reduction of enyne **5aa** and **5ab** with Zn(Cu/Ag), which proceeded cleanly in the presence of TMSCl.[30] The ^{13}C NMR spectra of these products were found to be useful for determining the relative stereochemistry between the carbon atoms at C13 and *syn* C19,C20. Synthesis of the enantiomers of **6a** and **7a** is undoubtedly possible by changing the chirality of the catalysts and would furnish the enantiomers of **3aa** and **3ab**. The asymmetric dihydroxylation reaction of the *cis* olefin corresponding to **11** produces the *anti* diol, which is the key intermediate for the synthesis of another set of targets with *anti* stereochemistry at C19 and C20.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706415.

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(30) To an argon-bubbled suspension of Zn powder (4.30 g, 65.8 mmol) in H_2O (20 mL) were added $Cu(OAc)_2$ (436 mg, 2.40 mmol) and, after 20 min, $AgNO_3$ (442 mg, 2.60 mmol). The suspension was stirred for 45 min and filtered by suction, and the remaining solids were washed with H_2O, MeOH, acetone, and Et_2O, sequentially. A solution of triol **5aa** (129 mg, 0.330 mmol) in H_2O/MeOH (1:1, 20 mL) was added to the above solids. Subsequently, TMSCl (0.410 mL, 3.28 mmol) was added. The mixture was stirred at rt for 18 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified first by chromatography on silica gel (hexane/EtOAc) and second by recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, ø 20 × 250 mm, hexane/EtOAc 30:70, 25 mL/min) to afford methyl ester **25** (104 mg, 81%) as a colorless liquid: R_f = 0.22 (hexane/EtOAc = 1:2); $[\alpha]_D^{21}$ –2.3 (*c* 1.0, $CHCl_3$). IR (neat): 3480, 1733, 1652, 759 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H), 1.44–1.66 (m, 2 H), 1.77 (br s, 1 H), 2.22–2.52 (m, 10 H), 2.77–2.90 (m, 4 H), 3.40 (dt, *J* = 8.4, 4.2 Hz, 1 H), 3.53 (q, *J* = 5.8 Hz, 1 H), 3.68 (s, 3 H), 4.25 (q, *J* = 6.0 Hz, 1 H), 5.31–5.60 (m, 7 H), 5.77 (dd, *J* = 15.2, 6.0 Hz, 1 H), 6.16 (t, *J* = 11.2 Hz, 1 H), 6.55 (dd, *J* = 15.2, 11.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 22.9, 25.7, 25.9, 26.6, 32.3, 34.1, 35.4, 51.7, 71.9, 73.5, 75.1, 125.0, 125.3, 127.5, 127.9, 128.0, 128.3, 129.4, 130.8, 131.2, 136.5, 173.8. HRMS (FD): *m/z* calcd for $C_{23}H_{36}O_5$ [M]$^+$: 392.25627; found: 392.25781.