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First total synthesis of the anti-inflammatory and pro-resolving lipid mediator 16(*R*),17(*S*)-diHDHA

Dedicated to Professor E. J. Corey on the occasion of his 90th birthday

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ABSTRACT

The first total synthesis of the anti-inflammatory and pro-resolving lipid mediator 16(*R*),17(*S*)-diHDHA , derived from docosahexaenoic acid (DHA), and its 16-epimer have been achieved. Two synthetic approaches are described for the synthesis of 16(*R*),17(*S*)-diHDHA . The first strategy started from DHA and used an enzymatic reaction, a vanadium catalyzed allylic epoxidation and a base-promoted epoxide isomerization. The second approach utilized a chiral pool strategy starting from 2-deoxy-D-ribose to establish the chiral centers; Wittig reactions, mild acetonide cleavage and ester hydrolysis were the key steps in the synthesis.

Inflammation is a response to tissue damage and/ or infection. Acute inflammation that is self-limited and achieves resolution is a protective mechanism,[1,2] but uncontrolled inflammation is the underlining course of chronic diseases including autoimmune diseases, cancer, diabetes, asthma and neurological diseases such as Alzheimer's and Parkinson disease.[3] It is well documented that ω-3 fatty acids mainly found in fish oil have anti-inflammatory properties and help with the resolution of inflammation.[4-6] The pioneering work by Serhan and collaborators revealed that these ω-3 poly-unsaturated fatty acids are converted at the side of inflammation by lipoxygenase enzymes to potent lipid mediators that are responsible for the resolution of inflammation.[7,8]

Several families of pro-resolving lipid mediators have been identified and collectively named specialized pro-resolving mediators (SPMs): lipoxins derived from arachidonic acid, resolvins of the E-type derived from eicosapentaenoic acid (EPA), resolvins of the D-type, maresins, protectins and their sulfido-conjugates derived from docosahexaenoic acid (DHA) and the more recently uncovered metabolites from n-3 docosapentaenoic acid (n-3 DPA).[9-16]

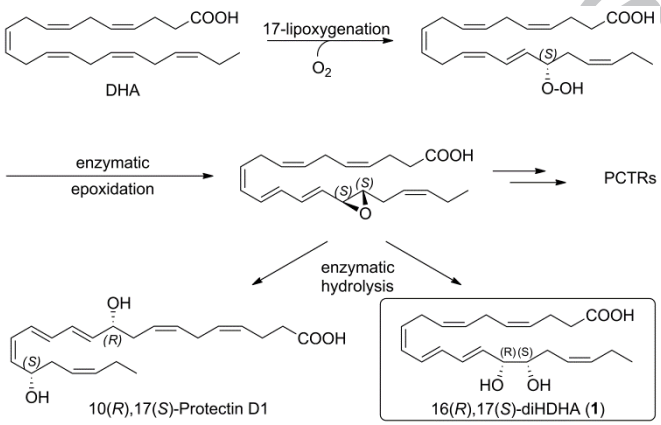


Figure 1. Proposed biosynthesis of 10R,17S-Protectin D1, 16(*R*),17(*S*)-diHDHA and PCTRs.

The proposed biosynthesis of the protectins is outlined in figure 1.[17] DHA is converted by the 15-lipoxidase to 17(*S*)-hydroperoxy-docosahexaenoic acid [17(*S*)-HpDHA] that undergoes enzymatic conversion to the allylic epoxide 16(*S*),17(*S*)-epoxy-docosahexaenoic acid. This intermediate undergoes enzymatic hydrolysis to 10(*R*),17(*S*)-protectin D1 (PD1) whereas a soluble epoxide hydrolase gives the 16(*R*),17(*S*)-diHDHA. The same 16(*S*),17(*S*)-epoxy-docosahexaenoic acid intermediate can be converted by a glutathione S-transferase via a SN2 mechanism to the Protectin conjugate in tissue regeneration (PCTR).[18-20] Due to the growing interest to study the biological and pharmacological properties of these mediators combined with the limited availability from natural sources these products have to be prepared by chemical synthesis. We have recently reported the total synthesis of PD1[21] and the PCTRs.[19] In the current publication we wish to report the total synthesis of 16(*R*),17(*S*)-diHDHA [(4*Z*,7*Z*,10*Z*,12*E*,14*E*,16*R*,17*S*,19*Z*)-16,17-dihydroxy-4,7,10,12,14,19-docosahexaenoic acid (**1**)].

As shown in the retrosynthetic scheme (Figure 2) we have prepared 16(*R*),17(*S*)-diHDHA via two different strategies. In the first approach we used an enzymatic-chemical route starting from DHA (**3**). In the second approach we employed a chiral pool strategy starting from 2-deoxy-D-ribose. The key intermediates **4** and **5** were used to produce the 16(*R*),17(*S*)-diHDHA skeleton.

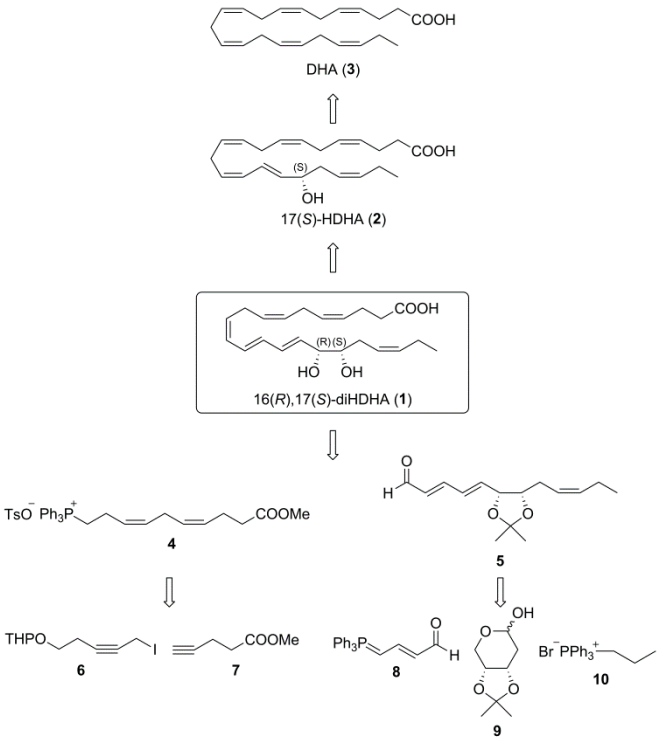
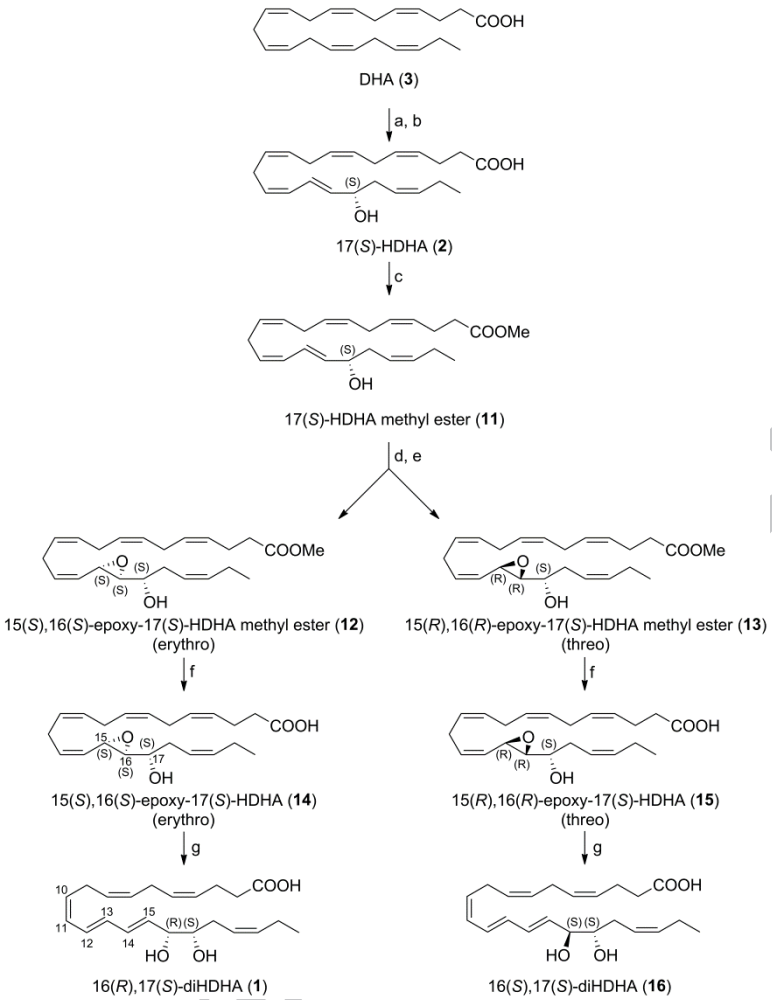


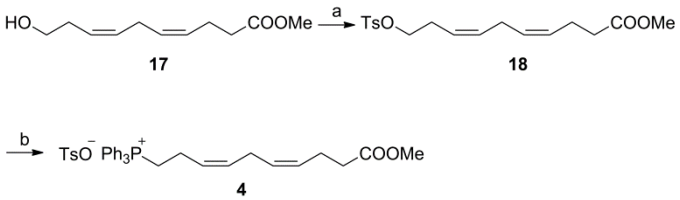
Figure 2. Two retrosynthetic approaches to 16(*R*),17(*S*)-diHDHA.

As shown in Scheme 1 DHA (**3**) was reacted with lipoxidase from soybean in borate buffer pH 9 in the presence of O_2 followed by reduction with Ph_3P to obtain 17(*S*)-hydroxy-docosahexaenoic acid [17(*S*)-HDHA] (**2**) with > 97.2% ee as determined by chiral-HPLC (racemic 17-HDHA was prepared from **2** by Dess-Martin oxidation followed by $NaBH_4$ reduction in ethanol).[22] Esterification of **2** with trimethylsilyldiazomethane in CH_3OH/toluene afforded compound **11** in 85% isolated yield[22] that was submitted to allylic epoxidation with TBHP in the presence of a catalytic amount of vanadyl acetylacetonate to afford a mixture of erythro and threo epoxy-alcohols **12** and **13** in the proportion of 77/23 respectively.[23] It should be mentioned that excess TBHP had to be avoided to minimize diepoxidation. The separation of the epoxides **12** and **13** was easily achieved by flash chromatography in the presence of 1% Et_3N providing a convenient access to 16(*R*),17(*S*)-diHDHA (**1**) and its 16-epi-isomer **16** respectively. Compounds **12** (erythro) and **13** (threo) had the characteristic ^1H-^1H coupling constants between the epoxide and the alcohol ($J_{16,17}$ = 3.0 Hz for **12** and 4.5 Hz for **13**).[23,24] Mild hydrolysis of the methyl ester in compound **12** with 1N LiOH in THF/CH_3OH/H_2O 4/1/1 followed by acidification with sat. NaH_2PO_4 in the presence of ethyl acetate afforded erythro 15(*S*),16(*S*)-epoxy-17(*S*)-HDHA (**14**) that was submitted to a base-promoted epoxide isomerization, modified from the procedures reported by the groups of Falck and Corey.[25-28] The best results were obtained by adding 5 equiv of KHMDS in toluene to **14** in THF at 0 ºC affording 16(*R*),17(*S*)-diHDHA (**1**). The geometry of the 10*Z*,12*E*,14*E*-triene in **1** ($J_{10,11}$ = 11.1, $J_{12,13}$ = 14.4 Hz and $J_{14,15}$ = 15.0 Hz) was confirmed by the ^1H-^1H coupling constants.[24] The ^1H NMR, ^{13}C NMR, UV and HPLC/UV/MS analysis were consistent with the structures of **1**.[24] In a similar manner threo-**13** was converted to 16(*S*),17(*S*)-diHDHA (**16**).[24]



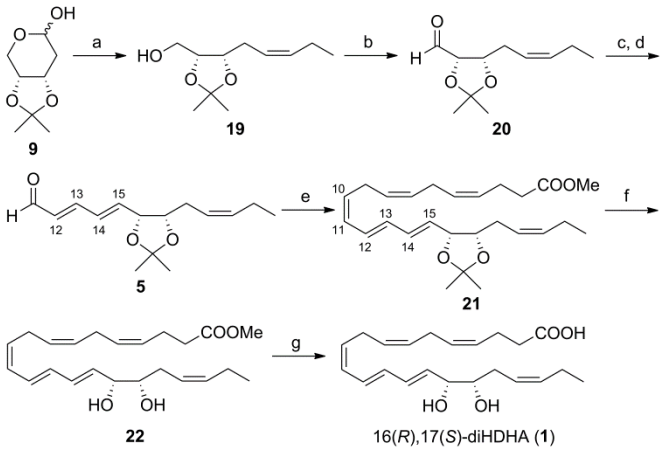
Scheme 1. *Reagents and conditions:* (a) lipoxidase from soybean, O_2, 0.1 M borate buffer pH 9, 0 °C then citric acid, hexane/EtOAc 1/1; (b) Ph_3P, hexane/EtOAc 1/1, 0 °C to 4 °C, > 97.2% ee, 70% (over two steps); (c) $TMSCHN_2$, CH_3OH/Toluene 1/1, 0 °C to rt, 85%; (d) TBHP, cat. $VO(acac)_2$, CH_2Cl_2, –15 °C, 54%; (e) chromatographic separation: 77% erythro, 23% threo; (f) 1 N LiOH, THF/CH_3OH/H_2O 4/1/1, 0 °C to rt, then sat. NaH_2PO_4; (g) KHMDS (toluene), THF, 0 °C, 47% of **1** (over two steps from erythro-**12**) and 48% of **16** (over two steps from threo-**13**).

In the second strategy the key intermediate **4** was prepared from compound **17** (Scheme 2). We had previously reported the synthesis of **17** from the intermediates **6** and **7**.[19] The free hydroxy group in compound **17** was converted to its tosylate with 3 equiv of tosyl chloride in CH_2Cl_2 in the presence of pyridine to afford **18**, which was then transformed to the phosphonium salt **4** with triphenylphosphine in acetonitrile at reflux in 84% yield.



Scheme 2. *Reagents and conditions:* (a) p-TsCl, pyridine, CH_2Cl_2, 0 °C to rt, 87%; (b) Ph_3P, CH_3CN, reflux, 84%.

The C11–C22 chiral fragment **5** was obtained in 4 steps from 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**9**) (Scheme 3).[29] Wittig reaction of **9** with 2.5 equiv of the ylide generated in situ from *n*-propyltriphenylphosphonium bromide (**10**) with *n*-BuLi (2.5 equiv) in THF in the presence of HMPA at –78 ºC produced **19** in 76% yield.[30] Compound **19** was converted to the aldehyde **20** by oxidation with PCC in CH_2Cl_2.[31] Four-carbon homologation of the aldehyde **20** with recrystallized (2*E*)-4-triphenylphosphoranylidene-2-butenal (**8**)[32,33] in CH_2Cl_2 followed by treatment with catalytic iodine in benzene afforded the *E*,*E*-dienal **5** in 35% yield (2-steps).



Scheme 3. *Reagents and conditions:* (a) **10**, *n*-BuLi, HMPA, THF, –78 °C to 0 °C, 76%; (b) PCC, NaOAc, CH_2Cl_2, rt, 71%; (c) **8**, CH_2Cl_2, rt, 39%; (d) I_2, benzene, rt, 91%; (e) **4**, KHMDS, THF, –78 °C to 0 °C, 52%; (f) PTSA, CH_3OH, 0 °C, 43%; (g) 1 N LiOH, CH_3OH/H_2O 3/1, 0 °C, then sat. NaH_2PO_4, 96%.

Wittig reaction of the phosphorane prepared in situ from the phosphonium tosylate **4** with KHMDS at –78ºC in THF with the dienal **5** gave the isopropylidene protected 16(*R*),17(*S*)-diHDHA methyl ester (**21**) in 52% yield based on recovered aldehyde **5** (Scheme 3). The geometry of the 12*E*,14*E*-diene unit in **5** ($J_{12,13}$ = 15.3 Hz and $J_{14,15}$ = 15.3 Hz) and the 10*Z*,12*E*,14*E*-triene in **21** ($J_{10,11}$ = 10.8 Hz, $J_{12,13}$ = 14.4 Hz and $J_{14,15}$ = 15.0 Hz) were confirmed by the ^{1}H-^{1}H coupling constants.[24] The isopropylidene protective group was cleaved with *p*-toluenesulfonic acid in CH_3OH at 0 ºC to give 16(*R*),17(*S*)-diHDHA methyl ester (**22**). Mild hydrolysis of **22** with 1 N LiOH in CH_3OH/H_2O at 0 ºC under argon followed by acidification with sat. NaH_2PO_4 (pH 3) in the presence of ethyl acetate, afforded 16(*R*),17(*S*)-diHDHA (**1**) in 96% yield. Co-injection of 16(*R*),17(*S*)-diHDHA (**1**) prepared from both routes were analyzed by HPLC/UV/MS and found to be identical.

In summary we have developed two routes for the synthesis of 16(*R*),17(*S*)-diHDHA (**1**),[24] making this anti-inflammatory and pro-resolving lipid mediator from docosahexaenoic acid available for further biological and pharmacological testing. The synthesis of the epimeric 16(*S*),17(*S*)-diHDHA (**16**)[24] has also been accomplished. The synthesis of other specialized pro-resolving mediators (SPMs) will be reported in due course.

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24. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.5 (ddt, *J* = 15.3, 11.1, 1.2 Hz, 1H), 6.0 (br t, *J* = 11.1 Hz, 1H), 5.7 (dd, *J* = 15.3, 6.0 Hz, 1H), 5.6–5.5 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 5.5–5.3 (m, 8H), 4.3–4.2 (m, 1H), 3.0–2.9 (m, 2H), 2.9–2.7 (m, 4H), 2.4–2.2 (m, 6H), 2.1–2.0 (m, 2H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 178.09, 135.44, 135.12, 130.26, 129.44, 128.48, 128.10, 128.06, 128.01, 127.66 (2C), 125.50, 123.63, 72.08, 35.20, 33.92, 26.10, 25.67, 25.61, 22.62, 20.70, 14.09; $[\alpha]_D^{20}$= +13.3 (c 0.3, EtOH) {$[\alpha]_D^{24}$= +13.1 (c 0.55, EtOH)};[22] Chiracel OD, 5 µm, 250 x 4.6 mm, 236 nm, Hexane/i-PrOH (0.05% formic acid) 95:5, 0.6 mL/min, t_R = 15.0 min. Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.4 (ddt, *J* = 15.3, 11.1, 1.2 Hz, 1H), 6.0 (br t, *J* = 11.1 Hz, 1H), 5.7 (dd, *J* = 15.3, 6.0 Hz, 1H), 5.6–5.5 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 5.5–5.2 (m, 8H), 4.3–4.1 (m, 1H), 3.7 (s, 3H), 3.0–2.9 (m, 2H), 2.9–2.7 (m, 4H), 2.4–2.2 (m, 6H), 2.1–2.0 (m, 2H), 1.8-1.7 (d, *J* = 4.2 Hz, 1H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.62, 135.76, 135.27,

130.22, 129.30, 128.49, 128.12 (2C), 128.02, 127.88, 127.69, 125.38, 123.71, 72.00, 51.59, 35.27, 33.99, 26.11, 25.66, 25.59, 22.79, 20.74, 14.19; $[\alpha]_D^{20}$= +10.9 (c 1.5, benzene); Chiracel OD, 5 µm, 250 x 4.6 mm, 236 nm, Hexane/i-PrOH 95:5, 0.6 mL/min, t_R = 13.8 min. Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.8–5.6 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.6–5.5 (ddt, *J* = 10.8, 7.2, 1.2 Hz, 1H), 5.5–5.3 (m, 7H), 5.2–5.0 (ddt, *J* = 10.8, 9.0, 1.5 Hz, 1H), 3.9–3.8 (m, 1H), 3.7 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.7–3.6 (s, 3H), 3.1–2.9 (m, 2H), 3.0–2.9 (dd, *J* = 3.0, 2.1 Hz, 1H), 2.9–2.7 (m, 4H), 2.4–2.3 (m, 6H), 2.1–2.0 (m, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.64, 135.15, 134.86, 129.24, 128.98, 128.30, 127.91 (2C), 127.19, 126.50, 123.07, 68.41, 61.79, 51.59, 50.74, 33.98, 31.39, 26.10, 25.66, 25.59, 22.79, 20.66, 14.14; $[\alpha]_D^{20}$= +18.3 (c 0.48, benzene). Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.8–5.6 (dt, *J* = 11.1, 7.5 Hz, 1H), 5.6–5.5 (ddt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 5.5–5.3 (m, 7H), 5.2–5.0 (ddt, *J* = 11.1, 9.0, 1.5 Hz, 1H), 3.8–3.6 (s and m, 5H), 3.1–2.9 (m, 2H), 3.0–2.9 (dd, *J* = 4.5, 2.4 Hz, 1H), 2.9–2.7 (m, 4H), 2.4–2.3 (m, 6H), 2.2–2.0 (m, 2H), 2.0–1.9 (d, *J* = 6.6 Hz, 1H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.61, 135.33, 134.93, 129.21, 128.98, 128.30, 127.95, 127.89, 127.19, 126.38, 122.99, 70.28, 62.23, 52.02, 51.59, 33.98, 32.59, 26.09, 25.66, 25.59, 22.79, 20.66, 14.15; $[\alpha]_D^{20}$= +5.6 (c 0.29, benzene). 16(*R*),17(*S*)-diHDHA (**1**): ^{1}H NMR (CD_3OD, 300 MHz): δ 6.7–6.5 (dd, *J* = 14.4, 11.1 Hz, 1H), 6.4–6.2 (m, 2H), 6.1–6.0 (br t, *J* = 11.1 Hz, 1H), 5.9–5.7 (dd, *J* = 15.0, 7.2 Hz, 1H), 5.5–5.3 (m, 7H), 4.1–3.9 (m, 1H), 3.6–3.5 (dt, *J* = 8.1, 4.8 Hz, 1H), 3.0–2.9 (m, 2H), 2.9–2.8 (m, 2H), 2.5–2.2 (m, 5H), 2.2–2.0 (m, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 176.57, 134.38, 133.85, 133.81, 133.67, 131.20, 129.89, 129.82, 129.59 (2C), 129.09, 128.64, 126.31, 76.29, 75.98, 35.36, 31.84, 27.08, 26.51, 24.49, 21.68, 14.58. UV (EtOH) λ_{max} 264, 274, 285 nm; HPLC-UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 274 nm, H_2O/CH_3OH (0.1% formic acid) 50:50–30:70, 0.2 mL/min, t_R = 18.4 min; HPLC/MS (m/z): 359.3 [M-H]$^-$. 16(*S*),17(*S*)-diHDHA (**16**): ^{1}H NMR (CD_3OD, 300 MHz): δ 6.7–6.5 (dd, *J* = 14.4, 11.1 Hz, 1H), 6.4–6.2 (m, 2H), 6.1–6.0 (br t, *J* = 11.1 Hz, 1H), 5.8–5.7 (dd, *J* = 15.0, 6.9 Hz, 1H), 5.5–5.3 (m, 7H), 4.1–3.9 (m, 1H), 3.5–3.4 (dt, *J* = 7.8, 5.0 Hz, 1H), 3.0–2.9 (m, 2H), 2.9–2.8 (m, 2H), 2.5–2.2 (m, 5H), 2.2–2.0 (m, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 176.25, 134.36, 134.30, 133.72, 133.48, 131.27, 129.86, 129.80, 129.60, 129.56, 129.22, 128.63, 126.26, 76.14, 75.88, 35.82, 31.71, 27.09, 26.52, 24.25, 21.64, 14.57. UV (EtOH) λ_{max} 264, 274, 285 nm; HPLC-UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 274 nm, H_2O/CH_3OH (0.1% formic acid) 50:50–30:70, 0.2 mL/min, t_R = 19.9 min; HPLC/MS (m/z): 359.2 [M-H]$^-$. Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8–7.7 (d, *J* = 8.5 Hz, 2H), 7.4–7.3 (d, *J* = 8.5 Hz, 2H), 5.5–5.3 (ddt, *J* = 10.5, 7.3, 1.5 Hz, 1H), 5.4–5.2 (m, 3H), 4.0 (t, *J* = 6.9 Hz, 2H), 3.7–3.6 (s, 3H), 2.8–2.7 (m, 2H), 2.5–2.3 (m, 6H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.46, 144.69, 133.11, 131.49, 129.79 (2C), 128.66, 128.21, 127.88 (2C), 123.37, 69.56, 51.55, 33.87, 27.06, 25.58, 22.73, 21.61. Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.9–7.6 (m, 17H), 7.1–7.0 (d, *J* = 7.8 Hz, 2H), 5.6–5.4 (m, 1H), 5.4–5.1 (m, 3H), 3.8–3.6 (m, 2H), 3.6 (s, 3H), 2.5 (br t, *J* = 6.7 Hz, 2H), 2.5–2.3 (m, 2H), 2.3 (s, 3H), 2.3–2.1 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.44, 144.60, 138.26, 134.88 (d, *J* = 2.9 Hz, 3C), 133.64 (d, *J* = 9.8 Hz, 6C), 130.40 (d, *J* = 12.1 Hz, 6C), 129.82, 128.52, 128.18 (2C), 128.13, 126.81 (d, *J* = 14.9 Hz, 1C), 126.17 (2C), 118.35 (d, *J* = 85.8 Hz, 3C), 51.52, 33.71, 25.40, 22.66, 21.95 (d, *J* = 48.9 Hz, 1C), 21.23, 20.33 (d, *J* = 3.5 Hz, 1C). Compound **20**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.7–9.6 (d, *J* = 3.0 Hz, 1H), 5.6–5.4 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 5.4–5.2 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 4.4–4.3 (m, 1H), 4.3–4.2 (dd, *J* = 7.2, 3.0 Hz, 1H), 2.4–2.2 (m, 2H), 2.1–1.9 (m, 2H), 1.6 (s, 3H), 1.4 (s, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.64, 135.02, 122.89, 110.55, 81.91, 78.41, 27.76, 27.43, 25.19, 20.78, 13.90. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6–9.5 (d, *J* = 8.1 Hz, 1H), 7.2–7.0 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.6–6.4 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.3–6.1 (m, 2H), 5.6–5.4 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 5.4–5.2 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 4.7–4.6 (m, 1H), 4.3–4.2 (dt, *J* = 7.5, 6.3 Hz, 1H), 2.4–2.1 (m, 2H), 2.1–1.9 (m, 2H), 1.5 (s, 3H), 1.4 (s, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.63, 150.54, 140.13, 134.43, 132.27, 130.16, 123.44, 108.85, 78.33, 78.04, 28.69, 28.01, 25.43, 20.84, 14.05. Compound **21**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.4 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.4–6.3 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.3–6.1 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.1–6.0 (br t, *J* = 10.8 Hz, 1H), 5.9–5.8 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.5–5.2 (m, 7H), 4.6–4.5 (m, 1H), 4.2–4.1 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.7–3.6 (s, 3H), 3.0–2.9 (m, 2H), 2.9–2.7 (m, 2H), 2.4–2.3 (m, 4H), 2.3–2.1 (m, 2H), 2.1–1.9 (m, 2H), 1.5 (s, 3H), 1.4 (s, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.54, 134.01, 133.71, 131.94, 130.89, 129.18, 128.88, 128.68, 128.60, 128.50, 127.98, 127.64, 124.11, 108.21, 79.11, 78.52, 51.56, 33.98, 28.75, 28.19, 26.21, 25.59, 25.57, 22.80, 20.79, 14.12. 16(*R*),17(*S*)-diHDHA methyl ester (**22**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.5 (dd, *J* = 14.7, 11.1 Hz, 1H), 6.5–6.3 (dd, *J* = 14.7, 10.8 Hz, 1H), 6.3–6.1 (dd, *J* = 14.7, 10.8 Hz, 1H), 6.1–6.0 (br t, *J* = 11.1 Hz, 1H), 5.8–5.7 (dd, *J* = 14.7, 7.2 Hz, 1H), 5.6–5.5 (dtt, *J* = 10.5, 7.2, 1.5 Hz, 1H), 5.5–5.3 (m, 6H), 4.3–4.1 (m, 1H), 3.8–3.6 (m, 1H), 3.6 (s, 3H), 3.0–2.9 (m, 2H), 2.9–2.7 (m, 2H), 2.4–2.3 (m, 4H), 2.3–2.1 (m, 2H), 2.1–1.9 (m, 2H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.63, 135.27, 133.26, 131.95, 130.88, 130.68, 129.18, 128.68, 128.53, 128.49, 127.94, 127.60, 124.06, 74.93, 73.95, 51.60, 33.98, 29.99, 26.24, 25.60, 22.81, 20.72, 14.21.

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Highlights

- First total synthesis of 16(*R*),17(*S*)-diHDHA and its 16-epimer have been achieved
- Two synthetic approaches described: enzymatic-chemical and a chiral pool strategy
- Key steps: lipoxidase, allylic epoxidation and base-promoted epoxide isomerization
- Chiral centers were stablished from 2-deoxy-D-ribose in the second approach

Graphical Abstract

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First total synthesis of the anti-inflammatory and pro-resolving lipid mediator 16(*R*),17(*S*)-diHDHA

Ana R. Rodriguez, Bernd W. Spur

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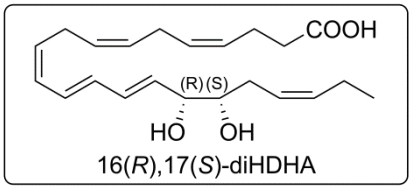

16(*R*),17(*S*)-diHDHA