Asymmetric Total Synthesis of 19,20-Epoxydocosapentaenoic Acid, a Bioactive Metabolite of Docosahexaenoic Acid

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ABSTRACT

In this study, we report the first asymmetric total synthesis of 19,20-epoxydocosapentaenoic acid (19,20-EDP), a naturally occurring bioactive cytochrome P450 metabolite of docosahexaenoic acid, a major constituent of fish oil. Our strategy involves direct asymmetric epoxidation to produce an enantiopure *beta*-epoxyaldehyde that can be appended to the rest of the skipped polyene core by Wittig condensation. Our route is step-economical and late-divergent, and could be an appealing method by which to synthesize EDP analogues for biological studies.

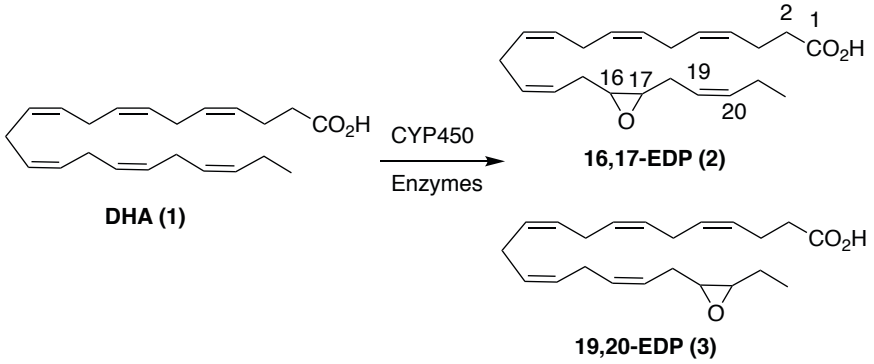
INTRODUCTION

Long-chain polyunsaturated fatty acid (lcPUFA) epoxides, produced from dietary lipids by cytochrome P450 monooxygenase enzymes, are an important class of endogenous lipid signaling molecules. These epoxides play an important role in inflammation, blood pressure, pain perception, tissue fibrosis, angiogenesis and tumorigenesis.[1-3] Among all the lcPUFA epoxides, those derived from DHA (**1**, Structures shown in Scheme 1) are generally quite potent.[1,3] *In vivo*, 16,17-epoxydocosapentaenoic acid (16,17-EDP, **2**) and 19,20-EDP (**3**) are two of the most abundant EDPs[4] Therefore, both are suggested to be important lipid mediators and could be crucial drug leads for cancer, fibrotic disorders, inflammatory diseases or hypertension.[5-7]

The challenge in studying EDPs is obtaining significant quantities of pure materials. Chemical epoxidation of **1** (using *m*-CPBA, for example) is neither chemoselective nor enantioselective, and purification of pure positional isomers and enantiomers is a laborious process. Enzymatic epoxidation can be used to prepare single enantiomers of **2** and **3**,[8] but chemical inversion must then be used to access the corresponding enantiomers, and this method is non-diversifiable and cannot be used to synthesize analogues. A synthetic route that allows one to synthesize large quantities of specific positional isomers and stereoisomers and amenable to the synthesis of potential analogues is, thus, very attractive. Several lcPUFA epoxides have yielded to total synthesis over the years (Scheme 2). E.J. Corey and co-workers[9] reported the enantioselective synthesis of the arachidonic acid metabolite 11,12-epoxyeicosatrienoic acid

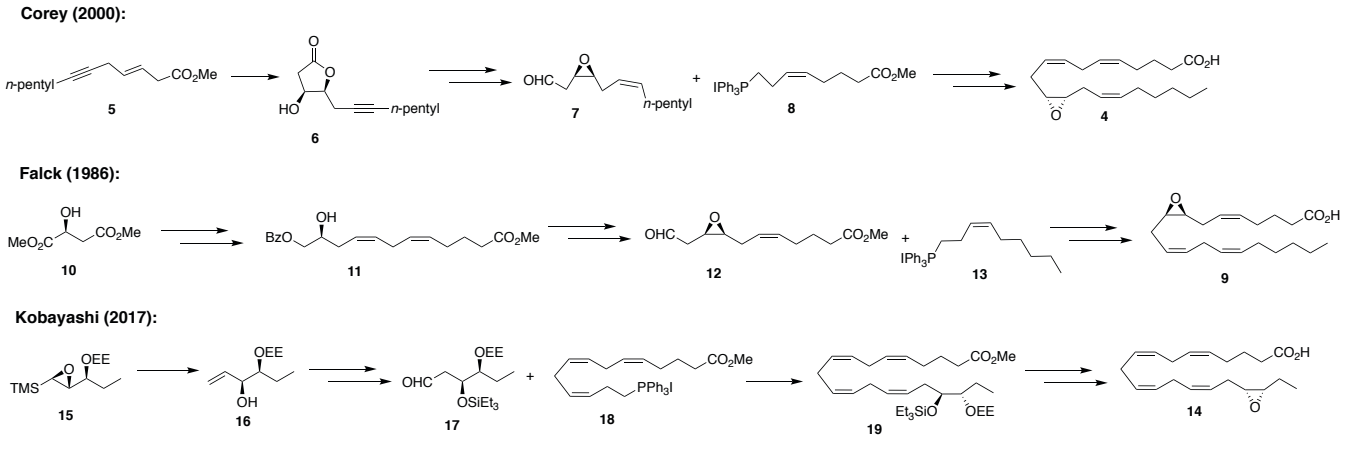
(EET) (**4**), which proceeded through asymmetric dihydroxylation of **5**, elaboration of **6** to the epoxide **7**, and Wittig reaction with **8**. An analogous synthesis of 8,9-EET (**9**), beginning with dimethyl malate (**10**) was reported in 1986 by Falck and colleagues.[10] In this route, several steps convert **10** to **11**, and vanadium-catalyzed epoxidation of **11** preferentially affords one diastereomer, which was then cleaved and oxidized to the aldehyde **12** and condensed with **13**.

Scheme 1. DHA (**1**) and EDP metabolites **2** and **3**. EDPs are shown as racemic.



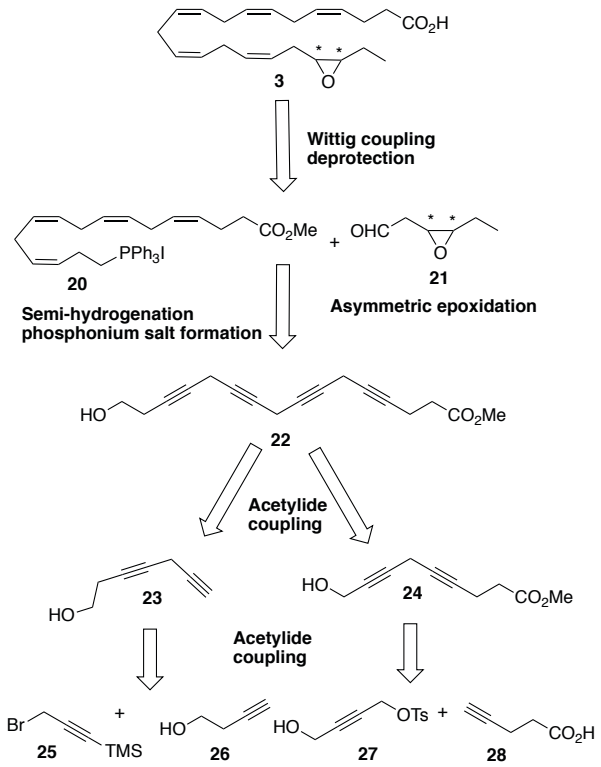
Similarly, the asymmetric total synthesis of the EPA metabolite 17,18-epoxyeicosatetraenoic acid (17,18-EEQ) (**14**) was published in 2017 by Kobayashi et al, which employs sodium dimsylate-mediated opening of the silylepoxide **15**, conversion of **16** to **17** via protection, hydroboration, and oxidation, and condensation with **18** to yield epoxide precursor **19**.[11] While elegant, these syntheses require multiple steps to prepare the chiral epoxides or their surrogates, and/or are relatively early-divergent, thus making adaptation of these routes to prepare analogues (especially those containing modifications or bioisosteres of the epoxide moiety) difficult. No total synthesis of **2**, **3**, nor any other EDP positional isomer has been performed as of this date. In this communication, we describe the first asymmetric total synthesis of 19,20-EDP via a highly convergent, late-stage diversifiable route that should be amenable to the preparation of EDP analogues. This route includes direct asymmetric epoxidation of a homoallylic alcohol, and, to the best of our knowledge, is the first synthesis of an epoxy fatty acid to employ this strategy.

Scheme 2. Previous syntheses of epoxy fatty acids.



RESULTS AND DISCUSSION

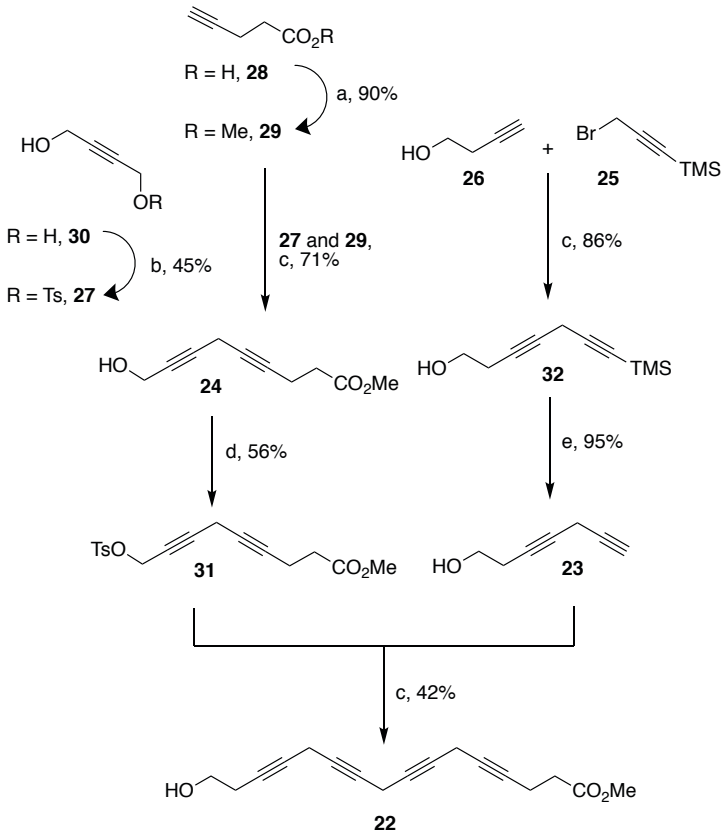
Scheme 3. Retrosynthetic analysis of **3**.



Retrosynthetic analysis of **3** is depicted in Scheme 3. The pentaenoate structure would be disconnected at the 16,17-olefin to an appropriate Wittig precursor (**20**) and *beta*-epoxyaldehyde **21** (which we envisaged as accessible via asymmetric epoxidation of a homoallylic alcohol). The skipped polyene in **20** would be installed as alkynes (i.e., tetrayne **22**), which would be deconstructed further to diynes **24** (C1-9) and **23** (C10-C16, see Scheme 1 for numbering). Assembly of the skipped diynes **24** and

23 would be accomplished via Cu-catalyzed acetylide coupling, the effectiveness of which has already been demonstrated in the total synthesis of DHA[12] and 17,18-EEQ.[11] Compounds **23** and **24** would, correspondingly, be prepared from the readily accessible precursors **25**-**28**.

Scheme 4. Assembly of tetrayne **22**.

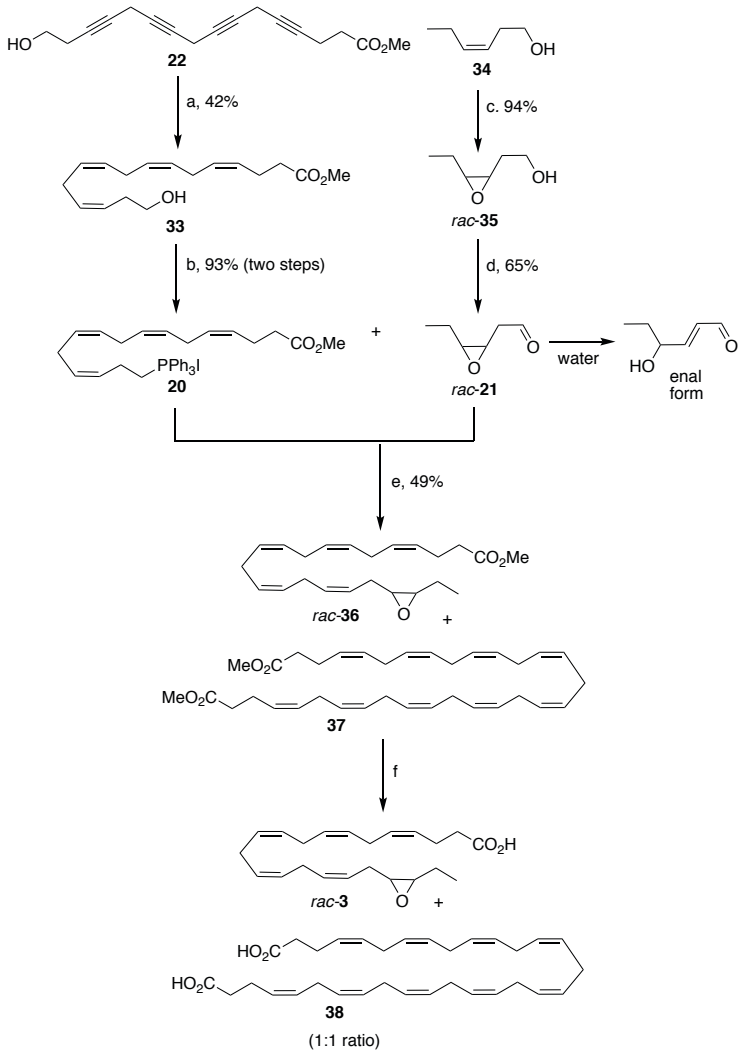


Reagents and Conditions: (a) MeOH, cat. H_2SO_4, r.t.; (b) TsCl, pyridine, CH_2Cl_2, 0 ˚C; (c) Cs_2CO_3, CuI, NaI, DMF, r.t.; (d) TsCl, DMAP, CH_2Cl_2, 0 ˚C - r.t.; (e) TBAF in THF, AcOH, THF, -15 ˚C.

Commencing the preparation of the carboxylate-containing diyne **24**, commercially available pentynoic acid **28** was first protected as its methyl ester **29** (Scheme 4),[13] commercially available butynediol **30** was converted to monotosylate **27**,[14] and Cu-catalyzed acetylene coupling of **27** and **29** afforded diyne **24**.[15] Tosylation was then employed to convert **24** to a suitable electrophile (**31**). The C10-C16 diyne fragment (as **32**) was prepared from commercially available alcohol and protected propargyl bromide **26** and **25** (respectively); deprotection of **32** (to yield **23**) was performed with TBAF in the presence of acid to minimize isomerization.[16] With both **31** and **23** in hand, the acetylide coupling method was employed to produce tetrayne **22** in moderate yield (presumably because of the instability of the

skipped poly-ynes – **22** must be stored at -80 ˚C otherwise it will darken and decompose into organic-insoluble material), although similar yields are reported in the literature.[13]

Scheme 5. Reduction and Wittig coupling (and homocoupling).

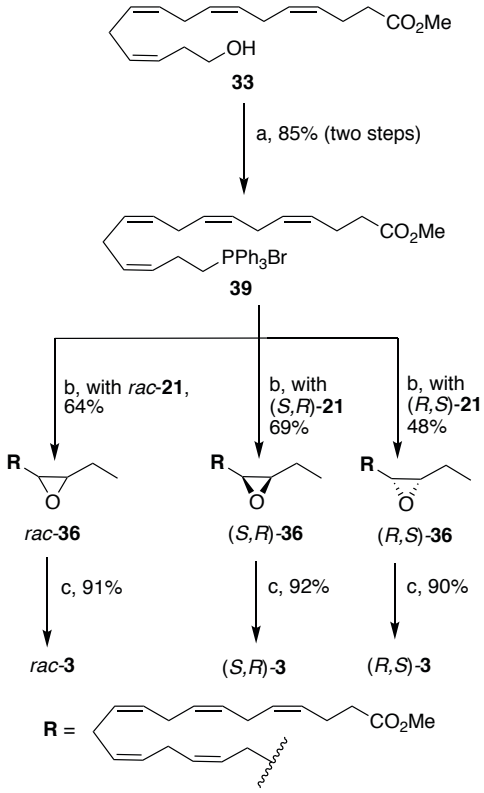


Reagents and Conditions: (a) H_2, $Ni(OAc)_2$, $NaBH_4$, ethylenediamine, MeOH, r.t.; (b) *i.* PPh_3, I_2, imidazole, ether/MeCN, 0 ˚C - r.t., *ii.* PPh_3, MeCN, reflux; (c) *m*-CPBA, CH_2Cl_2, 0 ˚C - r.t.; (d) Dess-Martin periodinane, CH_2Cl_2, r.t.; (e) *i.* NaHMDS, THF, -78 ˚C, *ii.* toluene, **21**, -100 ˚C to -15 ˚C; (f) LiOH, THF/H_2O (4:1), r.t.

Efforts next focused on semi-hydrogenation of **22** to tetraene **33** (Scheme 5). A prior report described performing this hydrogenation with Lindlar catalyst in the presence of pyridine and 2-methyl-2-butene on a similar scaffold,[13] but in the case of **22**, the reaction yielded only dark-colored material and, as assessed by TLC, a complex mixture of products with polarity between the tetrayne and tetraene (presumably enynes), even after multiple days. Contrarily, hydrogenation with freshly prepared nickel boride and ethylenediamine afforded this reduction in approximately 50 minutes.[11,16] Some minor impurities

(possibly overreduction products) were observed, but they were separated from **33** by flash chromatography. Compound **33** was then converted to the intermediate iodide, and immediate treatment with triphenylphosphine in acetonitrile under reflux conditions provided the phosphonium salt **20** in excellent yield (Scheme 5).[17] With **20** in hand, the *beta*-epoxyaldehyde **21** was prepared next (as its racemate *rac*-**21** to test the utility of the Wittig reaction). The commercially available homoallylic alcohol **34** was converted to the epoxide **35** with *m*-CPBA. Treatment of **35** with Dess-Martin periodinane afforded the aldehyde *rac*-**21** within minutes. The aqueous workup for Dess-Martin oxidations (sodium thiosulfate and bicarbonate) cannot be employed in this case, as exposure to water rapidly isomerizes the *beta*-epoxy-aldehyde to the ring-opened enal (confirmed by NMR).[18] The reaction mixture was simply diluted with hexanes and filtered, and concentration afforded the crude aldehyde, which was used immediately because of concerns about its stability.

Scheme 6. Synthesis of **39** and assembly of **3**.



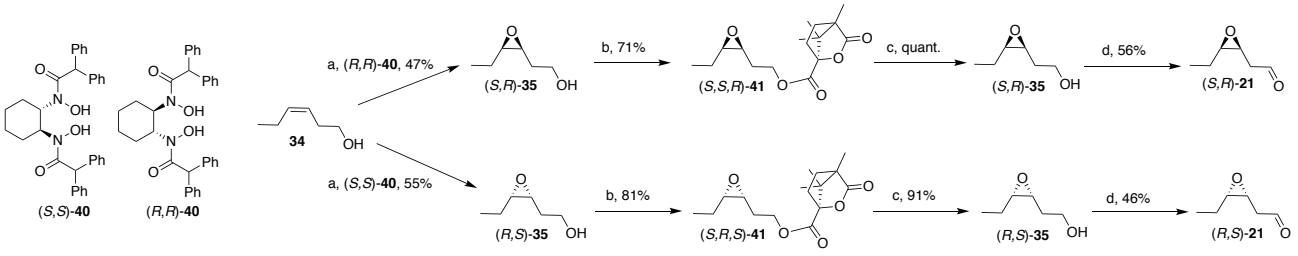
Reagents and Conditions: (a) *i.* PPh_3, CBr_4, imidazole, CH_2Cl_2, 0 ˚C - r.t., *ii.* PPh_3, MeCN, reflux; (b) *i.* NaHMDS, THF, -78 ˚C, *ii.* toluene, **21** in toluene, -78 ˚C - r.t.; (c) LiOH, THF/H_2O, 0 ˚C - r.t.

The union of **20** and *rac*-**21** was attempted using the conditions reported by Corey.[9] A fraction with TLC polarity consistent with the 19,20-EDP methyl ester *rac*-**36** was obtained in 49% yield. Although the *Z/E* ratio appeared to be very good by NMR (≥95%), with only minor impurities present, ^{1}H-NMR indicated the presence of another, inseparable product. Following saponification, this second product could be separated from *rac*-**3**. Based on NMR and mass spectrometry, it was likely to be di-acid **38** which presumably arose via oxidative homocoupling of the ylide derived from **20**[19] (which yielded **37**) and was present in an approximate 1:1 ratio with *rac*-**36**. Attempting to reproduce this reaction proved immediately problematic; in addition to the homocoupling issue, different batches of **20** gave widely variable results or no reaction at all (assessed by TLC), even when different solvents or temperatures were used. Additionally, **20** appeared to be very sensitive, rapidly darkening in solution and when exposed to light, suggesting possible disproportionation and production of elemental iodine. Although phosphonium iodides have been used to prepare similar skipped polyene systems, [9-11,17] we decided to switch to the bromide **39** (which was predicted to be more stable) to remove possible interference by iodine, and **39** was prepared from **33** (Scheme 6). Pleasingly, **39** did not darken upon dissolution or exposure to light and was readily amenable to condensation with **21**, although homocoupling was still an issue, even when all solvents employed in the Wittig reaction were sonicated and sparged with argon to remove oxygen. Nonetheless, subjecting all components of the reaction to three freeze-pump thaw cycles (see Experimenal Section) completely attenuated the homocoupling, and *rac*-**36** was obtained in 64% yield (at -78 ˚C, which afforded an impurity distribution identical to the material obtained at -100 ˚C). Saponification afforded *rac*-**3** in excellent yield. HPLC (C18, reverse-phase) indicated that this material had a purity of just over 93%, and preparative HPLC readily afforded very pure *rac*-**3**.

Encouraged by the promising results obtained from the racemic synthesis, efforts next turned to preparing **21** in as its single enantiomers. Although there are many reported procedures for asymmetric epoxidation of allylic alcohols, homoallylic alcohols are more challenging substrates. The Yamamoto group has reported asymmetric epoxidation of **34** employing transition metals (e.g., tungsten, vanadium, hafnium, and zirconium)[20-22] and *bis*-hydroxamic acid (BHA) ligands. The most accessible (commercially

and synthetically) of these ligands are the diphenylacetyl ligands (*R*,*R*)- and (*S*,*S*)-**40**, which can be used with either hafnium or zirconium, although the former generally affords higher yields and enantioselectivities.[22] Ligands (*R,R*)-**40** and (*S,S*)-**40** were synthesized using the previously reported procedures[22,23] and asymmetric epoxidation was then attempted (Scheme 7). Although yields were lower than reported (45-60% after 72 h), the epoxidation did proceed with both ligands; no differences were observed between commercially available (*R,R*)-**40** and (*R,R*)-**40** synthesized in-house. Chiral HPLC (of the benzoate derivative, see Supporting Information, SI Figure 1) indicated that the obtained enantioselectivity was lower than reported[22] (reported: 94 %ee, 97 %er; obtained: 80 %ee, 90 %er). Attempts were then made to remove the unwanted enantiomer. A previous report indicated that liquid enantioenriched epoxy alcohols could be converted to solid benzoate or *p*-nitrobenzoate derivatives (and the major enantiomer purified by crystallization[24]), but these aryl ester derivatives of **35** were oils. A chiral auxiliary approach was employed instead. A sample of (*S,R*)-**35** obtained from the epoxidation was treated with commercially available (*S*)-camphanic chloride to yield the camphanoate ester, enriched in (*S,S,R*)-**41**. Although the diastereomers were not separable by TLC (in multiple solvent systems), a crystalline solid was obtained by cooling the enriched hexane solution of (*S,S,R*)-**41**, and 71% yield of (*S,S,R*)-**41** [based on the theoretical yield of (*S,S,R*)-**41**] was obtained after three crystallizations from hexanes, and cleavage of the auxiliary (LiOH, THF/H_2O, 0 ˚C, 90 min) yielded enantiopure (*S,R*)-**35** (with an er of approximately 97:3, determined via chiral HPLC of the benzoate derivative) in nearly quantitative yield.

Scheme 7. Asymmetric epoxidation to prepare enantiopure *beta*-epoxyaldehydes.



Reagents and Conditions: (a) CHP, 2 mol% BHA ligand, Hf(O-*t*Bu)$_4$, 4 mol% DMPU, 4 Å mol. sieves, toluene, 0 ˚C - r. t.; (b) *i.* (*S*)-camphanic chloride, Et_3N, CH_2Cl_2, r.t. *ii.* Recrystallization from hexanes; (c) LiOH, THF/H_2O, 0 ˚C; (d) Dess-Martin periodinane, CH_2Cl_2, r.t.

Similarly, enantioenriched (*R,S*)-**35** was converted to ester (*S,R,S*)-**41**, which had even poorer solubility in hexanes. Two crystallizations afforded diastereomerically pure (*S,R,S*)-**41** in 81% yield. After cleavage of the auxiliary, (*R,S*)-**35** was obtained [with an er of approximately 98:2 (see Supporting Information, SI Figure 2) as assessed by chiral HPLC of the benzoate derivative]. The alcohols were then converted to the aldehydes via Dess-Martin oxidation, and aldehydes (*S,R*)-**21** and (*R,S*)-**21** were obtained, and as with the racemic aldehyde, Wittig condensation with **39** afforded 19(*S*),20(*R*)-EDP methyl ester (*S,R*)-**36** and 19(*R*),20(*S*)-EDP methyl ester (*R,S*)-**36**, (respectively) in good yields, and these were saponified to yield (*S,R*)-**3** and (*R,S*)-**3** (Scheme 6). The purity of the partially purified crude **3** obtained was approximately 92% in all three cases (as assessed by HPLC; some of the impurities are proposed to be small amounts of compounds containing the 16,17-*E* double bond as suggested by their very similar retention times to **3**). Preparative HPLC (C18) easily afforded very pure (>99.5%) *rac*-**3**, (*S,R*)-**3** and (*R,S*)-**3** (see Supporting Information, Figure S4). Chiral HPLC indicated (*S,R*)-**3** to be ~96.5% the *S,R*-isomer [confirmed by comparison to an authentic standard of (*S,R*)-**3**], and (*R,S*)-**3** to be ~98% the *R,S*-isomer, indicating that racemization does not occur to any appreciable degree during Wittig coupling (see Supporting Information, Figure S5).

CONCLUSIONS

In conclusion, we completed the first asymmetric total synthesis of 19,20-epoxydocosapentaenoic acid, utilizing hafnium-catalyzed asymmetric epoxidation and Wittig condensation. Although the asymmetric epoxidation (by Yamamoto's method) did not yield the reported enantiopurity, conversion of the obtained epoxyalcohols to their (*S*)-camphanoate derivative allowed for easy crystallization of the major isomer. Our synthesis proceeds in only eight steps (beginning with **28**, 3.1% overall yield of *rac*-**3** is obtained) and we were able to prepare >20 mg each of racemic and enantiopure **3** by this route, highlighting its suitability for preparing larger amounts of **3** for biological studies. Additionally **39** is an attractive, late-divergent precursor to prepare analogues of **3** (notably 19,20-epoxide isosteres, an appealing point from which to begin structure-activity relationship studies). Compound **39** can be

prepared readily on gram scale. Synthesis of various EDP analogues is now in progress, and these studies will be reported in due course.

EXPERIMENTAL SECTION

General Procedures. Chemicals were purchased from commercial vendors and were used as received without further purification. ^{1}H-NMR spectra were recorded at 500 MHz on an Agilent DD2 Spectrometer; ^{13}C-NMR spectra were recorded at 126 MHz using the same instrument, and all ^{13}C-NMR spectra are proton-decoupled. Flash chromatography was performed on a Buchi Reveleris X2 flash purification system (equipped with an evaporative light scattering detector), using Buchi HP SiO_2 or GraceResolv SiO_2 cartridges, and monitoring/collecting using both UV absorption and ELSD, or on a Teledyne Isco CombiFlash RF Lumen flash purification system, using the same columns and detection methods. TLC was performed on Analtech Uniplate 250 micron glass TLC plates; visualization was performed with potassium permanganate ($KMnO_4$) stain, and where appropriate, short-wave (254 nm) UV light. Mass spectrometry was performed at the Michigan State University Mass Spec and Metabolomics Facility. Data were collected using a Waters Xevo G2-XS QTOF system (using electrospray ionization-time of flight) and processed with MassLynx software. Polarimetry was performed using a Perkin Elmer 341 Polarimeter in a 10 cm cell. HPLC was performed using a Shimadzu Prominence LC-20AT analytical pump and SPD- 20A UV-vis detector, monitoring at 205 and 208 nm, at a flow rate of 1 mL/min. Chiral HPLC for epoxy fatty acids was performed using a Phenomenex Lux cellulose-3 column (250 x 4.6 mm, 5 μm, 1000 Å) eluting with isocratic 45% 50 mM ammonium bicarbonate (NH_4HCO_3) in methanol (35 min), with a sample concentration of 0.5 mM. Chiral HPLC for epoxy benzoates was performed using a Daicel Chiralcel OJ-H column (250 x 4.6 mm, 5 μm) eluting with isocratic 2% *i*-PrOH in hexanes (with 0.05% formic acid added to each solvent), monitoring at 205 and 254 nm for 30 min, at a flow rate of 0.5 mL/min, with a sample concentration of 0.3 mM). Achiral HPLC (for determining chemical purity) was performed using a Zorbax Eclipse XDB C18 column (250 x 4.6 mm, 5 μm, 100 Å), eluting with a gradient of 60% acetonitrile (MeCN) in water (H_2O) +0.05% formic acid in each solvent (5 min) to 90% MeCN in H_2O +0.05% formic acid (over 50 min) to 90% MeCN in

H_2O +0.05% formic acid (5 min), with a sample concentration of ~30 mM. Preparative HPLC was performed using a Phenomenex Kinetex C18 column (250 x 21.2 mm, 5 μm, 100 Å) Shimadzu Prominence LC-20AP preparative pump and SPD-20A UV-vis detector, monitoring at 205 and 208 nm, at a flow rate of 21.2 mL/min.

4-Hydroxybut-2-yn-1-yl 4-Toluenesulfonate (27). Compound **27** was prepared from alcohol **30** by the literature method.[14] Spectral data for the obtained product were consistent with those previously reported. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 4.74 (t, *J* = 1.8 Hz, 2 H), 4.17 (d, *J* = 6.0 Hz, 2 H), 2.46 (s, 3 H), 1.54 (t, *J* = 6.1 Hz, 1 H).

Methyl Pent-4-ynoate (29). Prepared by the literature method.[13] Acid **28** (2.00 g, 20.4 mmol) was diluted in MeOH (20 mL) and ten drops of concd. H_2SO_4 were added. The mixture was stirred at room temperature for 48 h and then partitioned between H_2O (50 mL) and ether (100 mL). The layers were separated, and the aqueous phase was extracted with ether (2 x 70 mL). The ether layer was then washed with sat. aq. $NaHCO_3$, H_2O, and sat. aq. NaCl (80 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was passed through a short silica plug, eluting with 3:1 CH_2Cl_2/ether to afford the product as a clear, colorless volatile oil (2.066 g, 90%) upon concentration. Spectral data for the obtained product were consistent with those previously reported:[13] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.71 (s, 3 H), 2.56 (ddd, *J* = 8.1, 6.3, 1.7 Hz, 2 H), 2.51 (tdd, *J* = 6.7, 3.1, 1.4 Hz, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H). Rf (3:2 hexane/EtOAc): 0.86.

General Procedure for Cu-catalyzed Acetylide Coupling. A round-bottomed flask was charged with Cs_2CO_3 (1.3 equiv. relative to bromide or tosylate), NaI (1.3 equiv. relative to bromide or tosylate), and anhydrous CuI (1.3 equiv. relative to bromide or tosylate). The solids were azeotroped three times with toluene and dried under high vacuum, and then diluted with anhydrous DMF (around 1-1.5 mL/mmol of bromide or tosylate) under argon. The bromide or tosylate was then added, followed by the terminal alkyne (1.3 equiv. relative to the bromide or tosylate), and the mixture was stirred rapidly overnight at room temperature in the dark. The mixture was then diluted with EtOAc (typically around 3 x the reaction volume) and filtered through a pad of Celite; the pad was then washed with EtOAc until no further product

was detected in the filtrate by TLC. The filtrate was washed with sat. aq. NH_4Cl, and the aqueous layer was extracted 3 x with EtOAc. The organic layer was then washed twice with H_2O, followed by sat. aq. NaCl (equal volumes), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was then purified by flash column chromatography (SiO_2), eluting with hexanes/EtOAc as described below, to yield the desired product.

Methyl 9-Hydroxynona-4,7-diynoate (**24**). The title compound was prepared by the general procedure from **27** (6.00 g, 25.0 mmol), and **29** (3.64 g, 32.4 mmol), using 10.6 g Cs_2CO_3 (32.4 mmol), 4.86 g NaI (32.4 mmol), and 6.18 g CuI (32.4 mmol) in 40 mL DMF. After workup and purification (80 g cartridge, eluting with 20-30% EtOAc in hexanes over 30 min), the desired product (retention time, 10.6 min) was obtained as a yellow oil (3.19 g, 71%) after drying in vacuo. Spectral data for the obtained product were consistent with those previously reported:[13] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 4.25 (t, J = 2.1 Hz, 2 H), 3.69 (s, 3 H), 3.17 (p, J = 2.2 Hz, 2 H), 2.54-2.46 (m, 4 H); the hydroxyl proton is not visible because of exchange with residual water. Rf (3:2 hexane/EtOAc): 0.2.

7-(Trimethylsilyl)hepta-3,6-diyn-1-ol (32). The title compound was prepared by the general procedure from **25** (3.84 g, 20.0 mmol), and **26** (1.68 g, 24.0 mmol), using 7.80 g Cs_2CO_3 (24.0 mmol), 3.6 g NaI (24.0 mmol), and 4.56 g CuI (24.0 mmol). After workup and purification (80 g cartridge, eluting with a gradient of hexanes to 15% EtOAc in hexanes over 35 minutes), the product (retention time, 30 min) was obtained as an orange oil (3.18 g, 88%) after drying in vacuo. Spectral data for the obtained product were consistent with those previously reported:[16] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.71 (t, J = 6.2 Hz, 2 H), 3.21 (t, J = 2.4 Hz, 2 H), 2.45 (tt, J = 6.2, 2.4 Hz, 2 H), 1.75 (br s, 1 H), 0.16 (s, 9 H). Rf (3:1 hexane/EtOAc): ~0.25.

Methyl 16-Hydroxyhexadeca-4,7,10,13-tetraynoate (22). The title compound was prepared by the general procedure from **31** (3.16 g, 9.44 mmol), and **23** (1.33 g, 12.3 mmol), using 4.00 g Cs_2CO_3 (12.3 mmol), 1.80 g NaI (12.3 mmol), and 2.28 g CuI (12.3 mmol). After workup and purification (80 g cartridge, eluting with a gradient of 30-45% EtOAc in hexanes over 24 minutes), the product (retention time, 7.7 min) was obtained as a pale orange amorphous semisolid (1.079 g, 42%) after drying in vacuo.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.71 (t, *J* = 6.1 Hz, 2 H), 3.70 (s, 3 H), 3.16-3.15 (m, 4 H), 3.12-3.11 (m, 2 H), 2.54-2.43 (m, 6 H); the hydroxyl group is visible as a broadened baseline at ca. 1.8 ppm; ^{13}C-NMR (126 MHz; $CDCl_3$): δ 172.5, 78.7, 76.1, 74.9, 74.7, 74.6, 74.4, 74.2, 61.1, 51.8, 33.3, 23.1, 14.6, 9.8, 9.76; some signals overlap or are obscured by the solvent peak. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}O_3^+$ 271.1329; found, 271.1332.

Methyl 9-(Tosyloxy)nona-4,7-diynoate (31). Compound **24** (4.50 g, 25.0 mmol) was diluted in dichloromethane (80 mL) and cooled to 0 ˚C. TsCl (5.72 g, 30.0 mmol) was added, followed by DMAP (4.58 g, 37.5 mmol), upon which the mixture turned an orange-brown color. The mixture was stirred at 40 min at 0 ˚C and then 20 min at room temperature and was then washed with 0.5 M HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were washed with 0.5 M HCl, H_2O, and sat. aq. NaCl (100 mL of each), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography (80 g cartridge, eluting with a gradient of hexanes to 30% EtOAc in hexanes over 35 minutes) to yield the product (retention time, 26.4 min) as a yellow syrup (4.64 g, 56%) after drying in vacuo. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.3 Hz, 2 H), 4.69 (t, *J* = 2.1 Hz, 2 H), 3.70 (s, 3 H), 3.04 (q, *J* = 2.1 Hz, 2 H), 2.53-2.45 (m, 7 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 172.3, 145.0, 133.1, 129.8, 128.1, 84.2, 79.3, 73.2, 72.1, 58.1, 33.2, 21.7, 14.5, 9.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}O_5S^+$ 335.0948; found, 335.0950.

Hepta-3,6-diyn-1-ol (23). Compound **32** (2.38 g, 13.2 mmol) was diluted in dry THF (55 mL) and cooled to -10 ˚C under argon. TBAF (1 M in THF, 13.2 mL, 13.2 mmol) and AcOH (0.755 mL, 13.2 mmol) were added simultaneously and dropwise. The mixture was stirred for 1.5 h, and additional TBAF and AcOH (0.3 equiv. of each) were added. The mixture was warmed to room temperature and stirred for 1 h, and then diluted with ether (60 mL). The mixture was washed with water (100 mL), the aqueous layer was extracted with ether (2 x 30 mL), and the organic layers were washed with sat. aq. NaCl and dried over anhydrous sodium sulfate. After concentration, the residue was azeotroped twice from *n*-heptane (50 mL) to remove AcOH and then passed through a short SiO_2 plug (eluting with ether) to yield the product

as a yellow oil (1.36 g, 95%) after drying in vacuo. Spectral data for the obtained product were consistent with those previously reported[16]: ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.71 (t, J = 6.2 Hz, 2 H), 3.17 (q, J = 2.5 Hz, 2 H), 2.45 (tt, J = 6.2, 2.4 Hz, 2 H), 2.07 (t, J = 2.7 Hz, 1 H); the hydroxyl group is visible as a broadened baseline at ca. 1.8 ppm.

Methyl (4*Z*,7*Z*,10*Z*,13*Z*)-16-hydroxyhexadeca-4,7,10,13-tetraenoate (33). Nickel acetate tetrahydrate (1.192 g, 4.79 mmol) was diluted in anhydrous MeOH (80 mL) and $NaBH_4$ (0.205 g, 5.39 mmol) was added. The black mixture was stirred for 10 minutes at room temperature and then flushed and placed under a hydrogen atmosphere (using a hydrogen-filled balloon). Ethylenediamine (1.06 mL) was added, and the mixture was allowed to equilibrate for 10 min before tetrayne **22** (1.079 g, 4.00 mmol) was added as a solution in 5 mL MeOH. TLC indicated the reaction was complete within 50 min. The reaction was diluted with EtOAc/hexanes (1:1, 100 mL) and filtered through a silica plug, and the plug was washed with 1:1 EtOAc/hexanes until no further product was detected in the filtrate by TLC. The filtrate was washed with sat. aq. NH_4Cl (100 mL), and the aqueous phase was extracted with EtOAc (3 x 50 mL). The organic layers were washed with sat. aq. NaCl (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography, eluting with 15% EtOAc in hexanes (80 g cartridge, 35 minutes). Pure fractions (retention time, 24.7 min) were pooled, and impure fractions were re-chromatographed using the same solvent system. A total of 0.453 g (41%) of the title compound was obtained as a colorless oil after drying in vacuo. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.56-5.54 (m, 1 H), 5.44-5.35 (m, 7 H), 3.68-3.64 (m, 5 H), 2.88-2.83 (m, 6 H), 2.41-2.35 (m, 6 H), 1.52 (t, J = 5.4 Hz, 1 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 173.7, 131.1, 129.3, 128.24, 128.16, 128.1, 128.00, 127.8, 125.6, 62.2, 51.6, 34.0, 30.9, 25.8, 25.7, 25.6, 22.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{27}O_3^+$ 279.1955; found, 279.1957.

((3*Z*,6*Z*,9*Z*,12*Z*)-16-Methoxy-16-oxohexadeca-3,6,9,12-tetraen-1-yl)triphenylphosphonium Iodide (20). Triphenylphosphine (0.548 g, 2.09 mmol) and imidazole (0.153 g, 2.25 mmol) were diluted in anhydrous MeCN/anhydrous ether (5:1.7 mL) and cooled to 0 ˚C. Iodine (0.470 g, 1.85 mmol) was added, and the mixture was warmed to room temperature and stirred for 20 min, upon which the yellow

suspension was then cooled back to 0 ˚C. A solution of **33** (0.448 g, 1.61 mmol) in MeCN/anhydrous ether (5:1.7, 3 mL) was then added slowly, and the mixture was warmed to room temperature and stirred for 30 min. After 30 min, a 1/3 portion of all reagents (0.182 g PPh_3, 0.051 g imidazole, and 0.157 g I_2) was added, and after a total of 1 h, the reaction was complete. The mixture was diluted with 4:1 hexane/EtOAc (40 mL) and filtered through a short silica plug to yield the crude iodide. The iodide was immediately diluted in anhydrous MeCN (10 mL) and added to PPh_3 (0.485 g, 1.85 mmol) in a sealable tube. The solution was sparged with argon and the tube was sealed and heated at reflux for 18 h. The mixture was then concentrated, and the residue was washed 4 x with 1:1 hexane/benzene (10 mL) and then dried in vacuo to yield a pale-orange viscous oil (0.976 g, 93%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.89-7.84 (m, 6 H), 7.83-7.79 (m, 3 H), 7.73-7.69 (m, 6 H), 5.65 (dtd, *J* = 10.5, 7.0, 1.6 Hz, 1 H), 5.43-5.18 (m, 8 H), 3.90-3.84 (m, 2 H), 3.66 (s, 3 H), 2.77 (t, *J* = 5.7 Hz, 2 H), 2.67 (t, *J* = 7.1 Hz, 2 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 2.50-2.46 (m, 2 H), 2.37-2.35 (m, 4 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 173.6, 135.19, 135.17, 133.8, 133.7, 130.6, 130.5, 130.4, 129.1, 128.6, 128.3, 128.0, 127.9, 127.3, 126.5, 126.4, 118.4, 117.7, 51.6, 33.9, 25.60, 25.56, 23.5, 23.1, 22.8, 20.39, 20.36; the signal at 25.60 appears to be two separate peaks. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{40}O_2P^+$ 523.2760; found, 523.2769. Rf (8:1 hexane/EtOAc): 0.0.

((3*Z*,6*Z*,9*Z*,12*Z*)-16-Methoxy-16-oxohexadeca-3,6,9,12-tetraen-1-yl)triphenylphosphonium Bromide (39). Triphenylphosphine (0.553 g, 2.11 mmol) and imidazole (0.155 g, 2.28 mmol) were diluted in dry CH_2Cl_2 (8 mL) and cooled to 0 ˚C under argon. CBr_4 (0.622 g, 1.87 mmol) was added, and the mixture was warmed to room temperature, stirred for 20 min, and cooled back to 0 ˚C. The alcohol **33** (0.453 g, 1.63 mmol) was added as a solution in dry CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 1 h, upon which another 1/3 equivalent of PPh_3, CBr_4, and imidazole were added; after 30 min, this procedure was repeated, and the reaction was complete after 2 h. The mixture was diluted with hexanes/EtOAc (8:1, 50 mL) and filtered through a small silica plug, which was washed until no product was detected in the filtrate by TLC (via $KMnO_4$ staining). The filtrate and washings were concentrated, and the residue was purified by flash column chromatography (25 g cartridge, eluting with

a gradient of hexanes to 10% EtOAc in hexanes over 25 minutes) to yield the bromide (retention time, 15 min) as a clear, colorless oil (0.473 g, 85%) after drying in vacuo. The intermediate bromide (0.205 g, 0.601 mmol) was immediately diluted in anhydrous MeCN (5 mL) in a sealable vial and PPh_3 (0.307 g, 1.17 mmol) was added. The vial was flushed with argon, sealed, and the mixture was heated to reflux (ca. 100 ˚C) for 48 h, upon which an additional equivalent of PPh_3 (0.158 g, 0.601 mmol) was added and heating continued. After a total of 96 h, the mixture was cooled and concentrated. The remaining residue was washed with 50% hexanes in benzene until no PPh_3 was detected in the washings by TLC (typically 6 x 5 mL). The remaining transparent pale-orange gum was dried in vacuo to yield the desired product (0.374 g, quant with several % benzene). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.91-7.87 (m, 6 H), 7.81-7.78 (m, 3 H), 7.72-7.68 (m, 6 H), 5.67-5.62 (m, 1 H), 5.40-5.16 (m, 7 H), 4.03-3.97 (m, 2 H), 3.65 (s, 3 H), 2.77 (t, J = 5.8 Hz, 2 H), 2.66 (t, J = 7.1 Hz, 2 H), 2.57 (t, J = 7.2 Hz, 2 H), 2.48 (dt, J = 4.7, 0.8 Hz, 2 H), 2.36 (d, J = 2.0 Hz, 4 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 173.5, 136.0, 135.0, 133.8, 133.7, 130.5, 130.4, 130.1, 129.1, 128.5, 128.3, 128.2, 128.0, 127.9, 127.4, 126.8, 126.7, 118.7, 118.0, 51.6, 33.9, 25.5, 23.1, 22.8, 22.7, 20.44, 20.41; the signal at 25.5 appears to be two overlapping peaks. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{40}O_2P^+$ 523.2760; found, 523.2775. Rf (8:1 hexane/EtOAc): 0.0.

Racemic 2-(3-Ethyloxiran-2-yl)ethan-1-ol (*rac*-35). Alcohol **34** (1.00 g, 10.00 mmol) was diluted in CH_2Cl_2 (40 mL) and cooled to 0 ˚C. A slurry of *m*-CPBA (3.98 g, 15.00 mmol of approximately 65% w/w *m*-CPBA) in CH_2Cl_2 (20 mL) was added, and the mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of 2 M sodium thiosulfate: sat. $NaHCO_3$ (1:1, 90 mL). The layers were separated, and the aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (4 x 50 mL). The organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography (40 g cartridge, eluting with a gradient of 25-60% EtOAc in hexanes over 30 minutes, retention time ~8-12 min) to yield the title compound (retention time ~8-12 min) as a clear and colorless oil (1.09 g, 94%) after drying in vacuo. Spectral data are consistent with those previously reported:[24] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.92-3.82 (m, 2 H), 3.11 (dt, J = 8.1, 4.3 Hz, 1 H), 2.92 (td, J = 6.4, 4.3 Hz, 1 H), 1.88 (dddd, J = 14.4, 6.8, 5.4, 4.6 Hz, 1 H), 1.70

(dddd, J = 14.5, 7.8, 6.8, 5.4 Hz, 1 H), 1.65-1.48 (m, 2 H), 1.05 (t, J = 7.5 Hz, 3 H); the hydroxyl proton broadens into residual water around 1.7 ppm. Rf (3:1 hexane/EtOAc): ~0.1.

2-((2*S*,3*R*)-3-Ethyloxiran-2-yl)ethan-1-ol (*S,R*-35).[22] In a glovebox, activated 4 Å molecular sieves (1 g), and (*R*,*R*)-**40** (0.054 g) were combined in anhydrous toluene (5 mL), and Hf(O*t*-Bu)$_4$ (0.040 mL) and anhydrous DMPU (0.025 mL) were added. The mixture was stirred in the glovebox for 1 h, removed, and cooled to 0 ˚C, upon which alcohol **34** (0.500 g, 5 mmol) and cumene hydroperoxide (1.3 mL of 80% CHP) were added in succession. The mixture was allowed to warm to room temperature slowly over 4 h and stirred at room temperature for 72 h. MeOH (2 mL) was then added, and the mixture was stirred for 10 min, diluted with EtOAc, and filtered. The filter cake was washed with EtOAc (50 mL) and the filtrate was concentrated and the residue was purified by flash column chromatography (25 g cartridge, eluting with a gradient of 20-60% EtOAc in hexanes over 20 minutes) to afford the epoxyalcohol (*S,R*)-**35** (retention time ~15 min) as a clear and colorless oil (0.272 g, 47%) after drying in vacuo; analytical data are identical to *rac*-**35**. Rf (3:1 hexane/EtOAc): ~0.1. To determine the ee/er, a small sample of the epoxyalcohol (0.0116 g, 0.1 mmol) was benzoylated in 0.8 mL CH_2Cl_2 using 16.0 µL pyridine (0.2 mmol), 12.8 µL BzCl (0.11 mmol), and catalytic DMAP. After 30 min, the solvent was removed and the residue plugged through a short SiO_2 plug with 40:60 hexanes/CH_2Cl_2 to yield the benzoate (unquantified, confirmed by TLC comparison to racemic benzoate). Chiral HPLC (see the above conditions) at 0.3 mM indicated the *S,R* and *R,S* enantiomers were present in a ratio of 91:9 (205 nm).

2-((2*S*,3*R*)-3-Ethyloxiran-2-yl)ethyl (*S*)-Camphanoate (*S,S,R*-41). Enantioenriched (*S,R*)-**35** (from the asymmetric epoxidation, 0.272 g, 2.34 mmol) was diluted in dry CH_2Cl_2 (7 mL). Et_3N (0.651 mL, 4.68 mmol) was added, followed by (*S*)-camphanic chloride (0.507 g, 2.34 mmol), dropwise, in CH_2Cl_2 (2 mL). After 20 min, additional Et_3N (0.325 mL, 2.34 mmol) and (*S*)-camphanic chloride (0.223 g, 1.02 mmol, in 1 mL CH_2Cl_2). After a total of 40 min, the mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with 0.5 M HCl, sat aq. $NaHCO_3$, and sat. aq. NaCl (30 mL each). The organic layer was dried over anhydrous sodium sulfate and concentrated, and the residue was purified by flash column chromatography (25 g cartridge, eluting with a gradient of hexanes to 30% EtOAc in hexanes

over 20 minutes, retention time 13.2 min), to yield a viscous syrup (0.620 g). This was diluted in hexanes and cooled to -20 ˚C, upon which fine needles precipitated. The crystals were collected and an additional crop was obtained upon cooling of the mother liquor. The combined crystals were subjected two additional crystallizations from hexanes to afford the product as fine, low-melting, colorless needles (0.442 g, 71%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 4.41 (t, *J* = 6.4 Hz, 2 H), 3.03 (dt, *J* = 7.6, 4.3 Hz, 1 H), 2.92 (td, *J* = 6.3, 4.4 Hz, 1 H), 2.45 (ddd, *J* = 13.5, 10.8, 4.2 Hz, 1 H), 2.07-1.98 (m, 2 H), 1.93 (ddd, *J* = 13.2, 10.8, 4.6 Hz, 1 H), 1.86-1.80 (m, 1 H), 1.70 (ddd, *J* = 13.3, 9.3, 4.1 Hz, 1 H), 1.60-1.50 (m, 2 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 1.06 (t, *J* = 7.5 Hz, 3 H), 0.97 (s, 3 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 178.1, 167.5, 91.1, 63.1, 58.0, 54.8, 54.2, 54.0, 30.7, 28.9, 27.3, 21.1, 16.8, 10.6, 9.7; one carbon is not visible or overlaps with another signal. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{24}NaO_5^+$ 319.1516; found, 319.1517; $[\alpha]^{20}_D$ (*c* = 0.30, MeOH) -18.0˚.

Compound (*S,S,R*)-**41** (0.507 g, 1.71 mmol) was diluted in THF/H_2O (10:2.5 mL) and cooled to 0 ˚C under argon. LiOH (2 M, 2.56 mL, 5.12 mmol) was added dropwise, and the mixture was stirred at 0 ˚C for 90 min. The mixture was then warmed to room temperature, partitioned between EtOAc and sat. aq. NaCl (20 mL each) and the organic layers were separated. The aqueous phase was extracted with EtOAc (5 x 15 mL), and the organic layers were washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, filtered to remove particulates, and concentrated to yield the title compound as a pale yellow oil (0.209 g, quant.). Derivatization to the benzoate (as described above) and chiral HPLC indicated an er of 96.8:3.2 (see Supporting Information, Figure S1). NMR data are identical to that for (*S,R*)-**35** obtained directly from asymmetric epoxidation, to *rac*-**35**, and to the data reported in the literature.[21] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.92-3.82 (m, 2 H), 3.11 (dt, *J* = 8.2, 4.2 Hz, 1 H), 2.92 (td, *J* = 6.3, 4.4 Hz, 1 H), 1.92-1.85 (m, 1 H), 1.74-1.50 (m, 4 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

2-((2*R*,3*S*)-3-Ethyloxiran-2-yl)ethan-1-ol (*R,S*-35).[22] The procedure for the synthesis of (*R,S)*-**35** was identical to (*SR*)-**35**, but employing (*S,S*)-**40** instead. After workup and purification as above, the epoxy alcohol (*R,S*)-**35** (retention time ~15 min) was obtained as a clear and colorless oil (0.322 g, 55%)

after drying in vacuo; analytical data are identical to *rac*-**35**. Rf (3:1 hexane/EtOAc): ~0.1. To determine the ee/er, a small sample of the epoxyalcohol (0.0116 g, 0.1 mmol) was benzoylated in 0.8 mL CH_2Cl_2 using 16.0 µL pyridine (0.2 mmol), 12.8 µL BzCl (0.11 mmol), and catalytic DMAP. After 30 min, the solvent was removed and the residue plugged through a short SiO_2 plug with 40:60 hexanes/CH_2Cl_2 to yield the benzoate (unquantified, confirmed by TLC comparison to racemic benzoate). Chiral HPLC (see the above conditions) at 0.3 mM indicated the *R,S* and *S,R* enantiomers were present in a ratio of 89.6:10.4 (254 nm).

2-((2*R*,3*S*)-3-Ethyloxiran-2-yl)ethyl (*S*)-Camphanoate (*S,R,S*-41). Enantioenriched (*R,S*)-**35** (from the asymmetric epoxidation, 0.280 g, 2.41 mmol) was diluted in dry CH_2Cl_2 (7 mL), and the mixture was cooled to 0 ˚C. Et_3N (0.671 mL, 4.82 mmol) was added, followed by (*S*)-camphanic chloride (0.522 g, 2.41 mmol), dropwise, in CH_2Cl_2 (2 mL). After 20 min, additional Et_3N (0.325 mL, 2.34 mmol) and (*S*)-camphanic chloride (0.230 g, 1.06 mmol, in 1 mL CH_2Cl_2). After a total of 40 min, the mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with 0.5 M HCl, sat aq. $NaHCO_3$, and sat. aq. NaCl (30 mL each). The organic layer was dried over anhydrous sodium sulfate and concentrated, and the residue was purified by flash column chromatography (25 g cartridge, eluting with a gradient of hexanes to 30% EtOAc in hexanes over 20 minutes), to yield a viscous syrup (retention time, 12.1 min). Two crystallizations from hexanes at -20 ˚C (as above) afforded the pure camphanoate as low-melting colorless needles (0.523 g, 81%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 4.45-4.37 (m, 2 H), 3.04 (dt, *J* = 7.7, 4.3 Hz, 1 H), 2.93 (td, *J* = 6.3, 4.4 Hz, 1 H), 2.44 (ddd, *J* = 13.5, 10.7, 4.2 Hz, 1 H), 2.07-1.98 (m, 2 H), 1.93 (ddd, *J* = 13.2, 10.8, 4.6 Hz, 1 H), 1.84 (ddt, *J* = 14.3, 7.8, 6.3 Hz, 1 H), 1.70 (ddd, *J* = 13.3, 9.3, 4.1 Hz, 1 H), 1.60-1.50 (m, 2 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 1.06 (t, *J* = 6.7 Hz, 3 H), 0.97 (s, 3 H); ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 167.5, 91.0, 63.1, 58.0, 54.8, 54.2, 53.9, 30.7, 28.9, 27.4, 21.1, 16.74, 16.72, 10.5, 9.7; one of the carbonyl carbons is not visible. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{24}NaO_5^+$ 319.1516; found, 319.1522; $[\alpha]^{20}_D$ (*c* = 0.30, MeOH) +6.0˚.

Compound (*S,R,S*)-**41** (0.523 g, 1.76 mmol) was diluted in THF/H_2O (10:2.5 mL) and cooled to 0 ˚C under argon. LiOH (2 M, 2.64 mL, 5.28 mmol) was added dropwise, and the mixture was stirred at 0

˚C for 90 min. The mixture was then warmed to room temperature, partitioned between EtOAc and sat. aq. NaCl (20 mL each) and the organic layers were separated. The aqueous phase was extracted with EtOAc (5 x 15 mL), and the organic layers were washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, filtered to remove particulates, and concentrated to yield the title compound as a pale yellow oil (0.186 g, 91%). Derivatization to the benzoate (As described above) and chiral HPLC indicated er of approximately 98:2 (see Supporting Information, Figure S2). NMR data are identical to that for (*R,S*)**-35** obtained directly from asymmetric epoxidation, to *rac*-**35**, and to the data reported in the literature.[22] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.92-3.82 (m, 2 H), 3.11 (dt, *J* = 8.2, 4.2 Hz, 1 H), 2.92 (td, *J* = 6.3, 4.4 Hz, 1 H), 1.92-1.85 (m, 1 H), 1.74-1.49 (m, 4 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

Racemic 2-(3-Ethyloxiran-2-yl)acetaldehyde (*rac*-21).[25] Alcohol *rac*-**35** (0.166 g, 1.43 mmol) was diluted in anhydrous CH_2Cl_2 (2 mL) and added dropwise to a stirring solution of Dess-Martin periodinane (0.697 g, 1.64 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 20 min, upon which TLC indicated completion. The mixture was poured into hexanes (40 mL) and filtered. The filtrate was concentrated to approximately 5 mL in volume and re-filtered, and the filter cake was washed with hexanes (3 x 1 mL). Concentration afforded the title compound as a yellow oil (0.106 g, 65%) after drying in vacuo. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 9.88 (s, 1 H), 3.37-3.34 (m, 1 H), 2.99 (td, *J* = 6.3, 4.3 Hz, 1 H), 2.77-2.65 (m, 2 H), 1.61-1.45 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H). This aldehyde was used immediately without further characterization or purification because of concerns about its stability; attempts at chromatographic purification of this compound result in decomposition. Rf (3:1 hexane/EtOAc): ~0.4.

2-((2*S*,3*R*)-3-Ethyloxiran-2-yl)acetaldehyde (*S,R*-21). Alcohol (*S,R*)-**35** (0.166 g, 1.43 mmol) was diluted in anhydrous CH_2Cl_2 (2 mL) and added dropwise to a stirring solution of Dess-Martin periodinane (0.697 g, 1.64 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 20 min, upon which TLC indicated completion. The mixture was poured into hexanes (40 mL) and filtered. The filtrate was concentrated to approximately 5 mL in volume and re-filtered, and the filter cake was washed with hexanes (3 x 1 mL). Concentration afforded the title compound as a yellow oil (0.091

g, 56%) after drying in vacuo. NMR data are identical to *rac*-**21**; This aldehyde was used immediately without further characterization or purification because of concerns about its stability; attempts at chromatographic purification of this compound result in decomposition. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 9.88 (t, *J* = 1.3 Hz, 1 H), 3.36 (ddd, *J* = 6.6, 5.5, 4.3 Hz, 1 H), 2.99 (td, *J* = 6.4, 4.2 Hz, 1 H), 2.77-2.65 (m, 2 H), 1.59-1.46 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H). Rf (3:1 hexane/EtOAc): ~0.4.

2-((2*R*,3*S*)-3-Ethyloxiran-2-yl)acetaldehyde (*R,S*-21). Alcohol (*R,S*)-**35** (0.166 g, 1.43 mmol) was diluted in anhydrous CH_2Cl_2 (2 mL) and added dropwise to a stirring solution of Dess-Martin periodinane (0.697 g, 1.64 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 20 min, upon which TLC indicated completion. The mixture was poured into hexanes (40 mL) and filtered. The filtrate was concentrated to approximately 5 mL in volume and re-filtered, and the filter cake was washed with hexanes (3 x 1 mL). Concentration afforded the title compound as a yellow oil (0.075 g, 46%) after drying in vacuo. NMR data are identical to *rac*-**21**; This aldehyde was used immediately without further characterization or purification because of concerns about its stability; attempts at chromatographic purification of this compound result in decomposition. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 9.88 (t, *J* = 1.3 Hz, 1 H), 3.36 (ddd, *J* = 6.6, 5.6, 4.3 Hz, 1 H), 2.99 (td, *J* = 6.4, 4.2 Hz, 1 H), 2.77-2.65 (m, 2 H), 1.61-1.46 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H). Rf (3:1 hexane/EtOAc): ~0.4.

Wittig Test Reaction: Preparation of *rac*-3 and 38. Compound **20** (0.214 g, 0.329 mmol) was diluted in anhydrous THF (2 mL) and cooled to -78 ˚C. NaHMDS (1 M in THF, 0.329 mL, 0.329 mmol) was added dropwise under argon. The bright orange solution was stirred at -79 ˚C for 45 min, anhydrous toluene (10 mL) was added, and the mixture was cooled to -100 ˚C in a liquid nitrogen/MeOH bath. The aldehyde *rac*-**21** (0.025 g, 0.219 mmol) was then added dropwise in 0.5 mL toluene. The mixture was slowly warmed to -15 ˚C over 3 h, and then quenched by the addition of an equal volume of 25% w/v aqueous NH_4OAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography (24 g cartridge eluting with a gradient of hexanes to 10% EtOAc in hexanes over 20 min) to yield the **36**-containing fraction [retention

time ~12 min, Rf (8:1 hexane/EtOAc): ~0.4] as a clear oil (0.038 g, based on the yield of *rac*-**36**). ^{1}H-NMR indicated this to be a 1:1 mixture of *rac*-**36** and homocoupled product **37** (see Supporting Information). This mixture was diluted in THF/H_2O (0.600/0.150 mL) treated with LiOH (2 M, 0.150 mL). Workup as described below and column chromatography (12 g cartridge, eluting with 30% EtOAc in hexanes for 15 min) afforded two fractions: *rac*-**3** [0.012 g, retention time 2.5 min, Rf (3:1 hexane/EtOAc): ~0.4] and **38** (0.013 g, retention time 4 min Rf (3:1 hexane/EtOAc): ~0.1], both colorless oils. The NMR for *rac*-**3** was identical to those below and previously reported. Compound **38**: ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.46-5.35 (m, 18 H), 2.85-2.83 (m, 16 H), 2.42-2.40 (m, 9 H); $^{13}C\{^1H\}$-NMR (126 MHz; $CDCl_3$): δ 180.1, 129.7, 128.2, 128.15, 128.13, 128.11, 128.0, 127.4, 34.1, 25.69, 25.66, 22.7; HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{32}H_{43}O_4^-$ 491.3167; found, 491.3167.

General Procedure for Wittig Condensation, Freeze-Pump-Thaw Method. The phosphonium bromide **39** (0.180 g, 0.298 mmol) was charged into a round-bottomed Schlenk flask and azeotroped from anhydrous benzene (3 x 3 mL) and dried under high vacuum for 30 min. The salt was then diluted in anhydrous THF (2.1 mL), and the solution was freeze-pump-thawed 3x using liquid nitrogen (one freeze-pump thaw cycle is as such: with the flask's vacuum port closed, immerse in liquid nitrogen until the mixture freezes uniformly, evacuate for approximately 3 min while still submerged in liquid nitrogen, and then close the vacuum port and warm to room temperature). Under nitrogen, the room temperature phosponium salt solution was then cooled to -78 ˚C and NaHMDS (1 M in THF, 1 equiv., 0.298 mL) was added. The solution was stirred at -78 ˚C for 45 minutes, and then anhydrous toluene (10.5 mL, freeze-pump-thawed 3 x as well) was added. A solution of **21** (0.031 g, 0.271 mmol) in 2.5 mL toluene, also freeze-pump-thawed) was added over 5-7 min. The mixture was then allowed to warm to room temperature over 3-3.5 h, and then quenched by the addition of an equal volume of 25% w/v aqueous NH_4OAc. The layers were separated, and the aqueous layer was extracted three times with an equal volume of EtOAc. The organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in a minimal amount of CH_2Cl_2 and passed through a short silica plug, eluting with 4:1 hexanes/EtOAc The filtrate was concentrated and the residue purified by column

chromatography (12 g cartridge, eluting with a gradient of hexanes to 10% EtOAc in hexanes over 22 min; retention times for EDP esters are 13-15 min, Rf values for EDP esters are 0.4 in 8:1 hexane/EtOAc) to yield the desired EDP ester (**36**) after drying in vacuo.

All *cis*-Methyl 19,20-Epoxydocosapentaenoate (*rac*-36). By the general procedure, 0.062 g (64%) of *rac*-**36** was obtained from **39** and *rac*-**21**. The NMR data for this compound are consistent with that previously reported:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.53-5.35 (m, 10 H), 3.67 (s, 3 H), 2.96 (td, *J* = 6.4, 4.2 Hz, 1 H), 2.90 (td, *J* = 6.3, 4.3 Hz, 1 H), 2.85 (t, *J* = 4.7 Hz, 8 H), 2.42-2.36 (m, 5 H), 2.23 (dt, *J* = 14.5, 7.0 Hz, 1 H), 1.64-1.51 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

All *cis*-Methyl 19*S*,20*R*-Epoxydocosapentaenoate (*S,R*-36). By the general procedure, 0.067 g (69%) of (*S,R*)-**36** was obtained from **39** and (*S,R*)-**21**. The NMR data for this compound are consistent with that previously reported:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.54-5.34 (m, 10 H), 3.67 (s, 3 H), 2.96 (td, *J* = 6.3, 4.4 Hz, 1 H), 2.92-2.88 (m, 1 H), 2.85 (t, *J* = 4.5 Hz, 8 H), 2.44-2.35 (m, 5 H), 2.23 (dt, *J* = 14.6, 7.1 Hz, 1 H), 1.64-1.51 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

All *cis*-Methyl 19*R*,20*S*-Epoxydocosapentaenoate (*R,S*-36). By the general procedure, 0.047 g (48%) of (*R,S*)-**36** was obtained from **39** and (*R,S*)-**21**. The NMR data for this compound are consistent with that previously reported:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.54-5.33 (m, 10 H), 3.67 (s, 3 H), 2.96 (td, *J* = 6.3, 4.3 Hz, 1 H), 2.92-2.88 (m, 1 H), 2.84 (t, *J* = 4.5 Hz, 8 H), 2.44-2.35 (m, 2 H), 2.23 (dt, *J* = 14.5, 7.1 Hz, 1 H), 1.64-1.50 (m, 6 H), 1.05 (t, *J* = 7.5 Hz, 3 H).

General Procedure for Saponification. The EDP methyl ester (**36**) was diluted in THF/H_2O (4 x volume of LiOH added/1 x volume of LiOH added) and cooled to 0 ˚C under argon. 2 M aqueous LiOH (3 equiv.) was added, and the mixture was warmed to room temperature and stirred overnight. The pH was adjusted to approximately 4 by dropwise addition of formic acid, and then water and EtOAc (5 mL each) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 5 mL). The organic layer was washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was azeotroped with hexanes (3 x 10 mL) to remove residual formic acid, and the residue was purified by flash column chromatography (12 g cartridge, eluting with 5-30% EtOAc in

hexanes over 25 min; retention times for free EDPs are 13-15 min; Rf values for free EDPs are 0.3-0.4 in 3:1 hexane/EtOAc) to afford the free EDP **3**. Analytically pure samples of **3** were prepared by preparative HPLC (using the column and conditions as above). Following preparative HPLC, the solution containing the EDP was concentrated to remove acetonitrile, and the remaining water was extracted 4 x with EtOAc. The organic layer was washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was azeotroped with hexanes (3 x 10 mL) to remove residual formic acid, and the residue was purified by flash column chromatography as described above to afford **3**.

All-*cis* 19,20-Epoxydocosapentaenoic acid (*rac*-3.) By the general procedure, 0.062 g (0.173 mmol) of *rac*-**36** was deprotected to yield 0.054 g (91%) of crude *rac*-**3**, purity assessed at approximately 92% by HPLC (see Supporting Information, Figure S3). Following preparative HPLC by the general procedure, 0.026 g of pure *rac*-**3** was obtained (see Supporting Information, Figure S4). NMR data for *rac*-**3** are consistent with previous reports:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.55-5.34 (m, 10 H), 3.01 (td, J = 6.4, 4.4 Hz, 1 H), 2.97-2.93 (m, 1 H), 2.88-2.81 (m, 8 H), 2.48-2.39 (m, 5 H), 2.22 (dt, J = 14.8, 7.2 Hz, 1 H), 1.68-1.51 (m, 2 H), 1.05 (t, J = 7.5 Hz, 3 H); the carboxylic acid proton is not visible because of exchange with residual water. ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 176.0, 130.6, 129.5, 128.4, 128.2, 128.1, 128.0 (2 C), 127.8, 127.6, 124.3, 58.8, 56.9, 33.6, 26.1, 25.8, 25.7, 25.65, 25.62, 22.7, 21.0, 10.6. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{22}H_{31}O_3^-$ 343.2279; found, 343.2302.

All-*cis* 19*R*,20*S*-Epoxydocosapentaenoic acid (*R,S*-3.) By the general procedure, 0.046 g (0.128 mmol) of (*R,S*)-**36** was deprotected to yield 0.040 g (90%) of crude (*R,S*)-**3**, purity assessed at approximately 92% by HPLC. Following preparative HPLC by the general procedure, 0.023 g of pure (*R,S*)-**3** was obtained. NMR data for (*R,S*)-**3** are consistent with previous reports:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.55-5.34 (m, 10 H), 3.03-3.00 (m, 1 H), 2.97-2.94 (m, 1 H), 2.88-2.82 (m, 8 H), 2.49-2.38 (m, 5 H), 2.22 (dt, J = 14.7, 7.0 Hz, 1 H), 1.68-1.51 (m, 2 H), 1.05 (t, J = 7.5 Hz, 3 H); the carboxylic acid proton is not visible because of exchange with residual water. ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 130.6, 129.4, 128.4, 128.2, 128.1, 128.03, 128.02, 127.8, 127.6, 124.2, 58.8, 56.9, 33.5, 26.0, 25.8, 25.7, 25.64, 25.61, 22.7, 20.9, 10.6; the carboxylate carbon is not visible; HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for

$C_{22}H_{31}O_3^-$ 343.2279; found, 343.2277. Chiral HPLC (see General Procedures, and Supporting Information, Figure S5) indicated an er of 98.2:1.8 *R,S*:*S,R*. $[\alpha]^{20}_D$ (*c* = 1, MeOH) +4.7˚.

All-*cis* 19*S*,20*R*-Epoxydocosapentaenoic acid (*S,R*-3.) By the general procedure, 0.067 g (0.187 mmol) of (*S,R*)-**36** was deprotected to yield 0.059 g (92%) of crude (*S,R*)-**3**, purity assessed at approximately 92% by HPLC. Following preparative HPLC by the general procedure, 0.025 g of pure (*S,R*)-**3** was obtained. NMR data for (*S,R*)-**3** are consistent with previous reports:[8] ^{1}H-NMR (500 MHz; $CDCl_3$): δ 5.56-5.35 (m, 10 H), 3.02 (td, *J* = 6.4, 4.3 Hz, 1 H), 2.98-2.94 (m, 1 H), 2.89-2.82 (m, 8 H), 2.49-2.39 (m, 5 H), 2.22 (dt, *J* = 14.6, 7.2 Hz, 1 H), 1.69-1.48 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H); the carboxylic acid proton is not visible because of exchange with residual water. ^{13}C{^{1}H}-NMR (126 MHz; $CDCl_3$): δ 130.6, 129.4, 128.39, 128.2, 128.1, 128.05, 128.02, 127.8, 127.7, 124.2, 58.9, 56.9, 33.4, 26.0, 25.8, 25.68, 25.66, 25.6, 22.7, 20.9, 10.6; the carboxylate carbon is not visible. HRMS (ESI-TOF) m/z: [M - H]$^-$ calcd for $C_{22}H_{31}O_3^-$ 343.2279; found, 343.2286. Chiral HPLC (see General Procedures, and Supporting Information, Figure S5) indicated an er of 96.3:3.7 *S,R*:*R,S*. $[\alpha]^{20}_D$ (*c* = 1, MeOH) -4.6˚.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C-NMR spectra of new and selected known compounds, and HPLC chromatograms for purity of *rac*-**3**, *(S,R)*-**3** and *(R,S)*-**3.** This material is available free of charge via the Internet at http://pubs.acs.org

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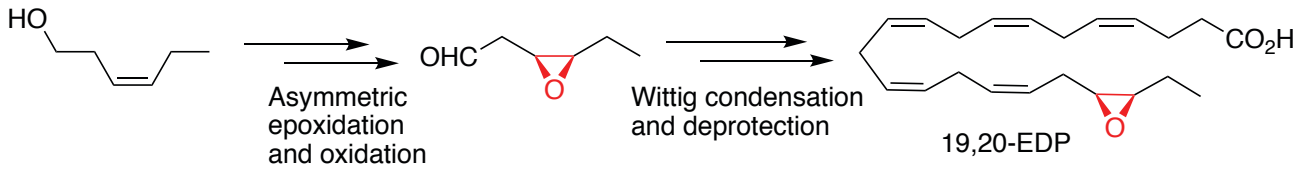

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