Stereoselective Syntheses of Polyunsaturated Fatty Acids, 13-(*S*)-HODE and 15-(*S*)-HETE
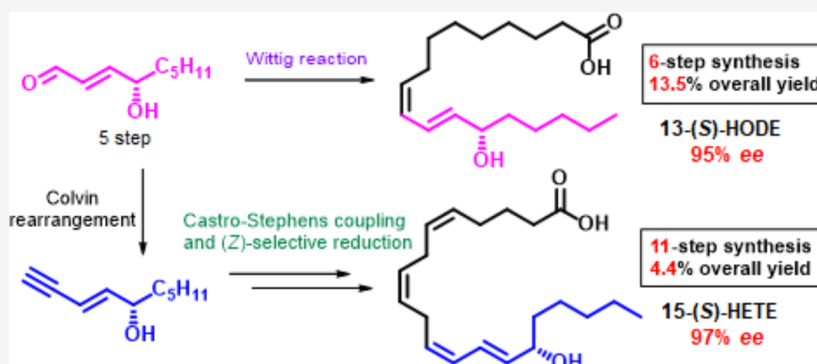
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ABSTRACT: Polyunsaturated fatty acids and their metabolites have been reported in which their pathway has potential for the modulation of cancer cell growth. 13-(*S*)-HODE and 15-(*S*)-HETE, both of which are main metabolites of 15-LOXs, play an important role as endogenous ligands in biological systems. However, the modification of 13-(*S*)-HODE and 15-(*S*)-HETE in pharmaceutical applications has not been explored widely. Herein, we report the stereoselective syntheses of 13-(*S*)-HODE, 15-(*S*)-HETE, and its derivatives to enable the synthesis of bioactive fatty acid analogues.

■ INTRODUCTION

Polyunsaturated fatty acids (PUFAs), such as linoleic acid (LA), arachidonic acid (AA), and its metabolites, have been reported to possess a variety of biological activities, including inhibition of cancer metastasis, anti-inflammatory, and antioxidant activities.[1a,b] LA is metabolized into 13-(*S*)-hydroxyoctadecadienoic acid (13-(*S*)-HODE) by 15-lipoxygenase (15-LOX-1). 13-(*S*)-HODE has been reported to have biological activities such as an endogenous ligand of peroxisome proliferator-activated receptor γ (PPAR-γ), which is known to inhibit cancer metastasis in several animal tumor models, including colon cancer.[2,3] 13-(*S*)-HODE is also capable of regulating biological functions related to inflammation pathways.[4a] 15-LOX-2 metabolizes AA to 15-(*S*)-hydroxyeicosatetraenoic acid (15-(*S*)-HETE). It has been reported that 15-(*S*)-HETE, an endogenous PPAR-γ ligand, could induce the papillary thyroid cancer (PTC) cell growth inhibition and apoptosis of tumor cells, which was adjusted by PPAR-γ activity.[4b,c] Furthermore, the antiproliferative effects of 15-(*S*)-HETE on cancer cells are attributed to its activation of this PPAR-γ.[4d] Therefore, 13-(*S*)-HODE and 15-(*S*)-HETE are attractive potential molecules for targeting cancer metastasis and inflammation-related disease. Several 13-(*S*)-HODE isomers and analogues have been studied to understand the relationship between their chemical structure and biological activities.[5a,b] However, structural modifications of 13-(*S*)-HODE and 15-(*S*)-HETE for pharmaceutical applications have not yet been

extensively investigated. The facile synthesis of enantiomerically and geometrically pure 13-(*S*)-HODE and 15-(*S*)-HETE is necessary for structural optimization and biological evaluation.

Several total syntheses of 13-(*S*)-HODE and 15-(*S*)-HETE have been reported to date. Two representative studies are summarized in Figure 1A. Recently, Vik et al. synthesized 13-(*S*)-HODE using a chiral pool strategy starting from a commercially available enantiopure epoxide using optically active *O*-silylated glycidols.[6a] In this approach, the Grignard addition and subsequent functionalization to produce (*E*)-vinyl iodide for a Sonogashira cross-coupling reaction are key reactions toward the synthesis of 13-(*S*)-HODE in 12 synthetic steps with an overall yield of 7.5%. The first total synthesis of 15-(*S*)-HETE was reported by Nicolaou et al.[6b] in 1985. The key step involved the cross-coupling reaction between the diene-yne intermediate and the enantioenriched vinyl bromide as a chiral starting material, followed by reduction with Lindlar conditions, deprotection with HF-pyridine, and ester hydrolysis in 11 steps

A. Previous synteses
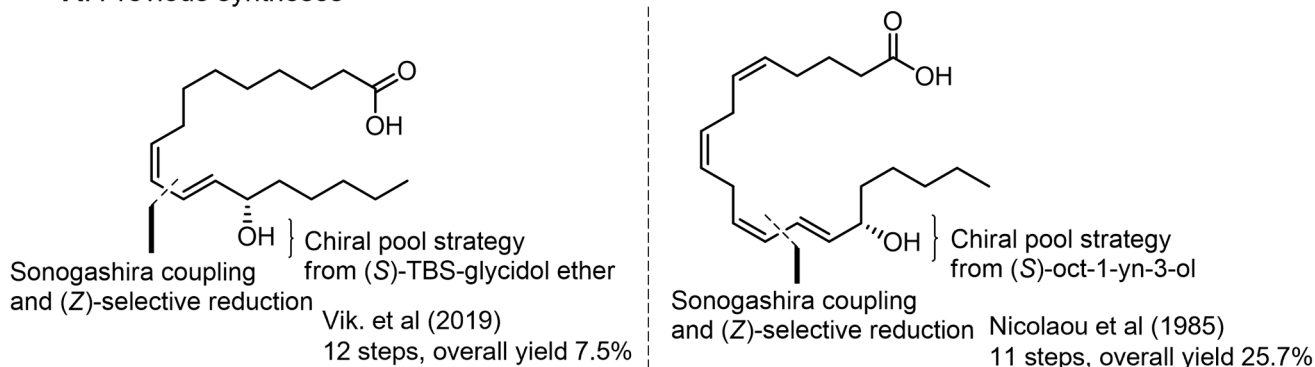

Sonogashira coupling
and (Z)-selective reduction

Chiral pool strategy
from (S)-TBS-glycidol ether

Vik. et al (2019)
12 steps, overall yield 7.5%

Sonogashira coupling
and (Z)-selective reduction

Chiral pool strategy
from (S)-oct-1-yn-3-ol

Nicolaou et al (1985)
11 steps, overall yield 25.7%

B. This work

Wittig reaction

6 steps (*ee* ≥ 95%)
overall yield 13.5%

13-(*S*)-HODE (**7a**)

5a
5 steps
from (*E*)-olefinic alcohol

Colvin rearrangement

Castro–Stephens coupling
and (*Z*)-selective reduction

3 steps (*ee* ≥ 97%)
overall yield 37.8%
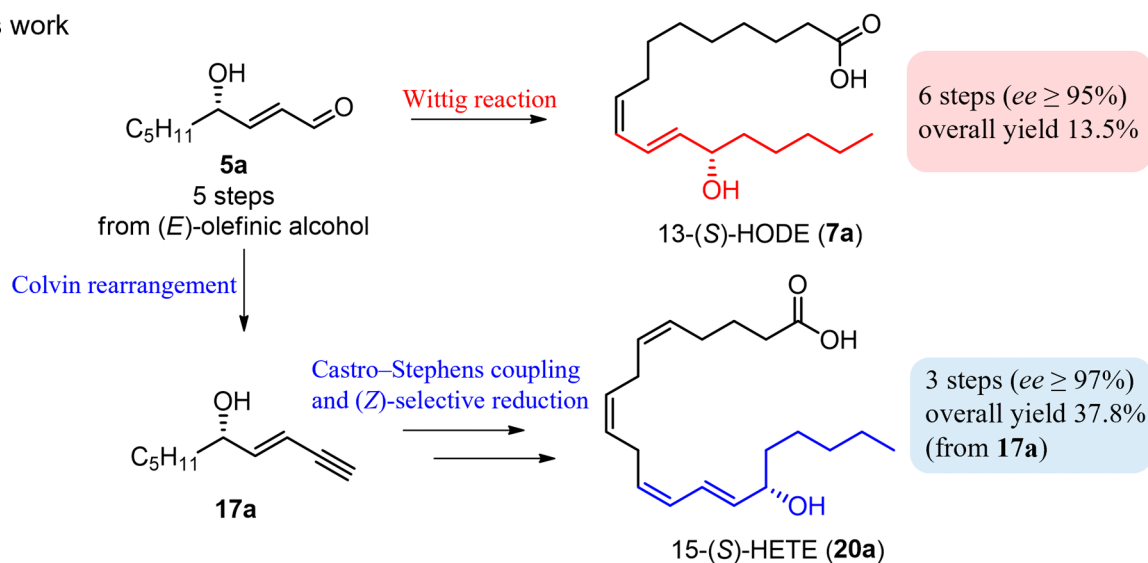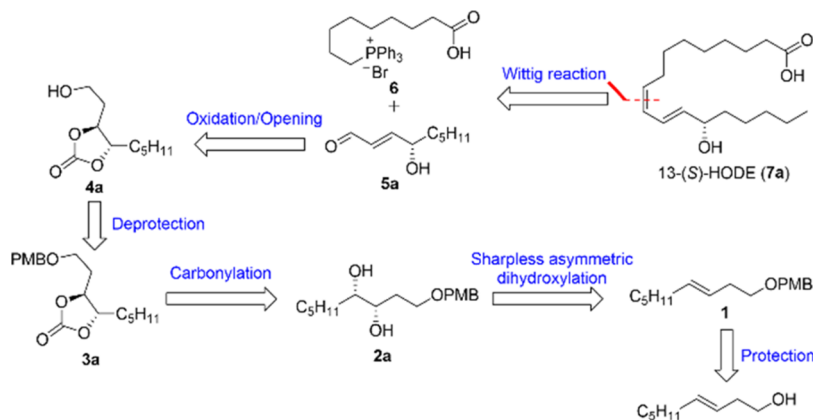(from **17a**)

17a

15-(*S*)-HETE (**20a**)

Figure 1. (A) Previous syntheses of 13-(*S*)-HODE (**7a**) and 15-(*S*)-HETE (**20a**). (B) Our synthetic work of 13-(*S*)-HODE (**7a**) and 15-(*S*)-HETE (**20a**).

**Scheme 1. Retrosynthesis of the Core Structure for 13-(*S*)-HODE (7a)**

with an overall yield of 25.7% (*ee* ≥ 95%). Herein, we have developed a stereoselective synthesis of 13-(*S*)-HODE, its analogues, and its application to the synthesis of 15-(*S*)-HETE in a concise synthetic approach (Figure 1B).

■ **RESULTS AND DISCUSSION**

The retrosynthetic analysis of 13-(*S*)-HODE is depicted in Scheme 1. The structure of 13-(*S*)-HODE would be disconnected at 9,10-olefin to an appropriate Wittig precursor

6 and (*E*)-α,β-unsaturated aldehyde **5a**. The aldehyde **5a**, the key intermediate, can be prepared from the carbonate **3a** by sequential *p*-methoxybenzyl (PMB) deprotection and 2-iodoxybenzoic acid (IBX)-mediated oxidation.[6c] The precursor carbonate **3a** is assembled by carbonylation between dimethyl carbonate (DMC) and the chiral vicinal diol **2a**, which can be achieved via Sharpless asymmetric dihydroxylation (AD)[7a] and deprotection process. The commercially available olefin is protected with a PMB group.

Scheme 2. Synthesis of 13-(S)-HODE (7a) and 13-(R)-HODE (7b)
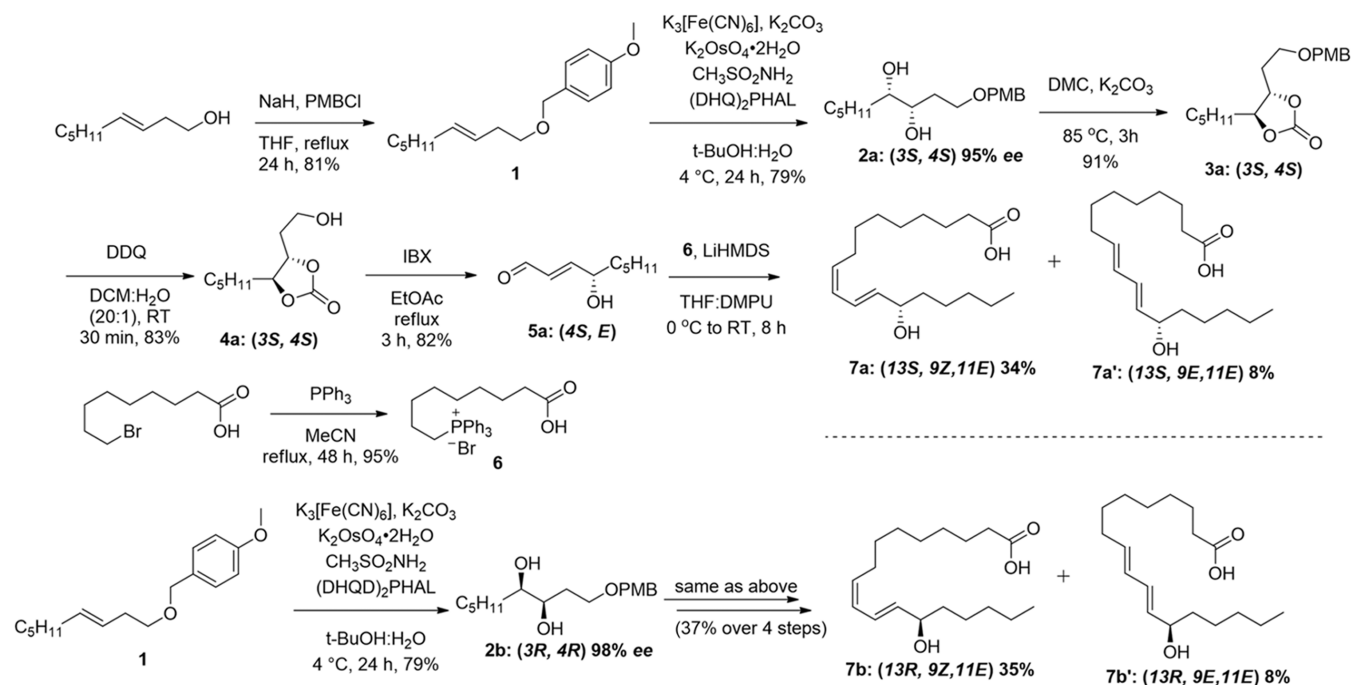
The synthesis of 13-(S)-HODE is shown in Scheme 2. For the stereoselective synthesis of 13-(S)-HODE, the construction of **2a** was achieved via the stereoselective dihydroxylation of olefin **1**. Asymmetric dihydroxylation of alkene **1** has proven to be a facile transformation from substituted alkenes to chiral diol product **2a**.[8a,b] However, the stereoselectivity of the reaction was low in the *cis*-alkene ligand system (entries 5−8, Table 1)

Table 1. Asymmetric Dihydroxylation of *trans*-Homoallylic and *cis*-Homoallylic Alcohols and Ether Derivatives with Chiral Ligands

| entry	substrate	R	ligand	% yield[a]	% ee[b]
1	(E)-alkene	H	(DHQ)$_2$PHAL	81	85[c] (S,S)
2	(E)-alkene	H	(DHQD)$_2$PHAL	70	88[c] (R,R)
3	(E)-alkene	PMB	(DHQ)$_2$PHAL	79	95 (S,S)
4	(E)-alkene	PMB	(DHQD)$_2$PHAL	79	99 (R,R)
5	(Z)-alkene	H	(DHQ)$_2$PHAL	94	75[c] (S,S)
6	(Z)-alkene	H	(DHQD)$_2$PHAL	95	80[c] (R,R)
7	(Z)-alkene	PMB	(DHQ)$_2$PHAL	82	38 (S,S)
8	(Z)-alkene	PMB	(DHQD)$_2$PHAL	70	24 (R,R)

[a]Isolated yield. [b]Determined using chiral HPLC analysis. [c]Determined the *ee* value of the final product using chiral HPLC analysis.

compared to the *trans*-alkene ligand system (entries 1−4, Table 1). It was known that the surrounding chiral environment of the *cis*-alkene ligand negatively impacts the chirality of the AD process.[7b] In our study, enantioselectivity on *trans*-alkene (entries 3 and 4) was high (>95% *ee*) through the AD reaction with PMB protection, while that of *cis*-alkene (entries 7 and 8) was low with 28−34% *ee* (Table 1). It should be noted that PMB protection of the homoallylic alcohol affects the enantioselectivity of the AD-PHAL ligand system (Table 1). Pioneering work with Sharpless dihydroxylation on the allylic substrate was reported by Corey and co-workers.[7b] Indeed, the presence of PMB-protected allylic ether moiety in the alkene provided high stereoselectivity through increased aromatic stacking interaction

and decreased steric repulsion between the *trans*-alkene group and the methoxyquinone wall of the PHAL ligand.[7c] The poor stereoselectivity in AD when using a PHAL-class ligand might have resulted from the substituent (entries 7 and 8) because of unfavorable steric interaction between the bulky protecting group and binding pocket.[7d] In contrast, free allylic alcohols (entries 1 and 2) cannot participate in π-stacking interaction with the catalyst pocket and prefer to be solvated, resulting in low enantioselectivities.[7b] Therefore, the PHAL-class ligand was not effective for *cis*-alkene substrates, while *trans*-alkene substrates (entries 3 and 4) gave the best result for diol compounds (**2a**, **2b**). The syntheses of (E)-α,β-unsaturated aldehydes **5a** were achieved in 33% yield over five synthetic steps. The known (E)-non-3-en-1-ol was protected by the PMB group. The diol **2a** was obtained via Sharpless asymmetric *cis*-dihydroxylation of **1** in 79% yield (95% *ee*, determined by chiral high-performance liquid chromatography (HPLC)). This diol **2a** was treated with DMC in the presence of a catalytic amount of K$_2$CO$_3$ to form the corresponding chiral vicinal carbonate **3a** in 91% yield.[9a] The carbonate synthesis was carried out under mild conditions because the PMB-protecting group significantly suppressed undesirable reactions. Without the PMB-protecting group on the alcohol, harsh conditions such as pyridine and triphosgene were required, which led to undesirable results, including low yield and byproducts. Furthermore, it was unsuitable for large-scale reactions because the reaction rate was difficult to control. The PMB group could be conveniently removed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9b] in 83% yield. After the removal of the PMB group, the IBX-promoted reaction of carbonate compound **4a** afforded (E)-α,β-unsaturated aldehyde **5a** in 82% yield.

For the preparation of 13-(S)-HODE, the key step was the Wittig reaction between (E)-α,β-unsaturated aldehyde **5a** and phosphonium salt **6** derived from 9-bromononanoic acid.[9c] The LiHMDS/THF/DMPU-mediated Wittig reaction gave high (Z)-selectivity (9Z/9E = 8:2) in 42% yield. This might be due to

Scheme 3. Synthesis of 13-(S)-HODE Analogues
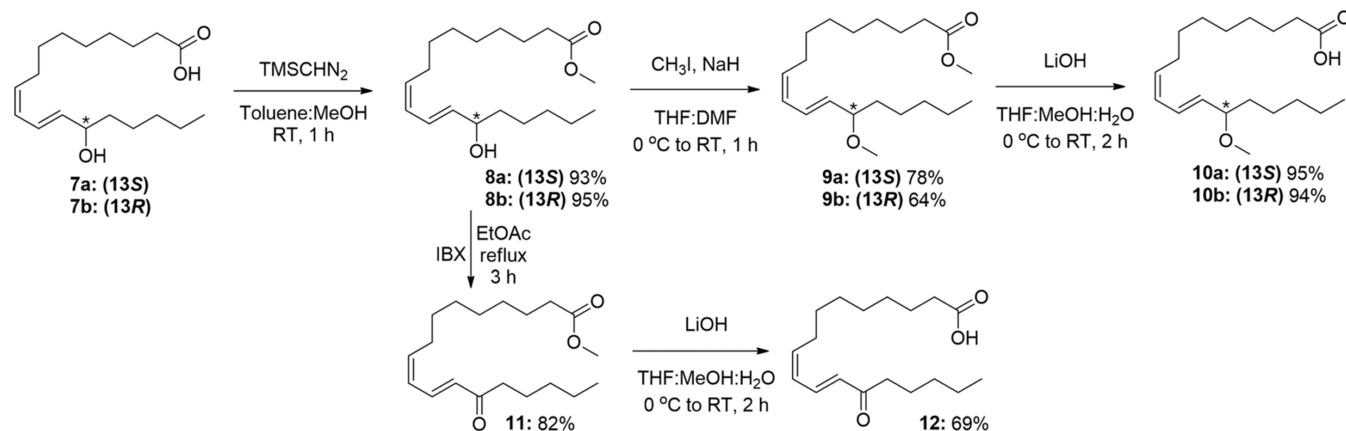


the interaction of DMPU with organolithium reagents, as previously reported.[10a,b] The (Z)-isomer could be separated from the (E)-isomer by using normal silica gel chromatography (conditions: hexane/diethyl ether (3:7) containing 1% glacial acetic acid). The (Z) and (E) isomers (7a and 7a′) were confirmed by comparing the coupling constants of vicinal hydrogen atoms of the isomers, for (Z)-isomer 7a, J_{H-9} = 10.8 Hz, and for (E)-isomer 7a′, J_{H-9} = 15.0 (see the Supporting Information). However, KHMDS instead of LiHMDS in the Wittig reaction generated the product in low yield, while dimethylformamide (DMF) instead of DMPU produced the byproduct.

As shown in Scheme 3, synthetic approaches to the analogues of 13-(S)-HODE were presented by modifications to its functional groups. The hydroxyl group of 13-(S)-HODE at the C-13 position was replaced by other functional groups such as methoxy and ketone. Methylation of the carboxylic acid group of 13-(S)-HODE and 13-(R)-HODE was achieved by treating trimethylsilyldiazomethane (TMSCHN$_2$)[11a] without affecting the free −OH group at the C-13 to provide compounds (8a, 8b) in high yield. These ester intermediates were utilized to modify the −OH group at the C-13 position. Compounds (8a, 8b) were treated with excess iodomethane using sodium hydride to give the methylated compounds (9a, 9b) in 64−78% yield. The secondary alcohol at C-13 was oxidized using IBX[11b] to provide ketone 11 in 82% yield. Ester hydrolysis of the 13-HODE analogues (9a, 9b, and 11) was achieved by the treatment of LiOH to give the final carboxylic acid compounds (10a, 10b, and 12), respectively.

With the enantiomeric-enriched (95% ee) key intermediate 5, we expanded its application for the synthesis of 15-(S)-HETE. Retrosynthetic analysis of 15-(S)-HETE is shown in Scheme 4. The key reaction for building the 15-(S)-HETE core is Castro-Stephens coupling reaction[12a] of 14 and 17a. The synthesis of 15-(S)-HETE is shown in Scheme 5. The first fragment, diyne 14, was prepared in a two-step sequence starting from commercial 1,4-dichlorobut-2-yne and methyl hex-5-ynoate. Copper-catalyzed cross-coupling reaction[12b] and Appel reaction[12c] using NaI delivered the diyne 14. The preparation of 17a was achieved through three-step reactions, including the protection of 5a with p-methoxybenzyl-2,2,2-trichloroacetimidates (PMB-TCAIs),[12d] Colvin rearrangement[12e,f] of the benzyl ether 15a with TMSCHN$_2$ and lithium diisopropylamide (LDA), and the deprotection step of the terminal alkyne 16a with DDQ.

Scheme 4. Retrosynthesis of the Core Structure for 15-(S)-HETE (20a)
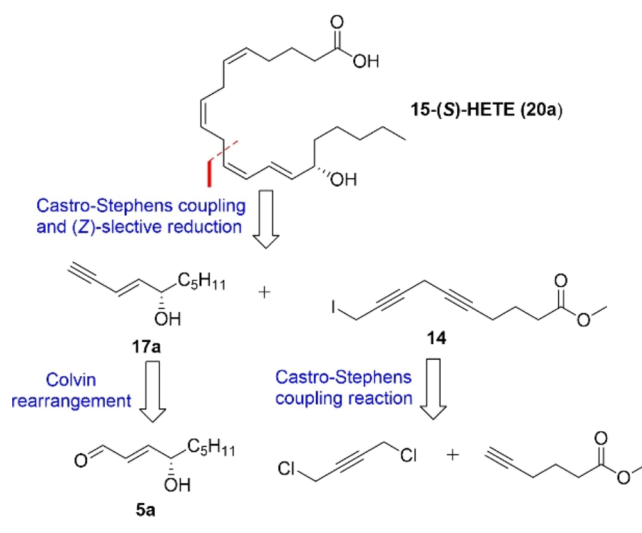
Castro-Stephens coupling of diyne 14 and compound 17a with the treatment of CuI, NaI, and Cs$_2$CO$_3$ proceeded successfully to give triyne 18a in 94% yield. Partial hydrogenation of the triple bonds under hydrogen gas with the Brown catalyst (P2−Ni)[13a] with ethylenediamine (EDA), a well-known method to stop the reaction of alkynes at the stage of desired cis-alkenes without causing overhydrogenation to alkanes.[12a,b] However, partial reduction of 18a was not achieved, resulting in giving a mixture of the major product 19a and a diene-yne intermediate (C11−C12)[12a,13b] of 18a in a proportion of 4:1 as determined by NMR and reversed-phase HPLC (RP-HPLC; data not shown). Without separation of the mixture, this diene-yne intermediate was converted into compound 19a using a Zn(Cu/Ag) catalyst.[12a] Finally, compound 20a was synthesized by ester hydrolysis of 19a with aqueous LiOH in 68% yield.

The synthesis and analytical characterization of 13-(S)-HODE and 15-(S)-HETE were compared with previously reported data.[6a,b] The overall yield of the current method from the commercially available (E)-olefinic alcohol was 13.5% over 6 synthetic steps, while the overall yield of 13-(S)-HODE by the reported method was 7.5% over 12 steps. The overall yield for 15-(S)-HETE was 37.8% (ee ≥ 97%) from the key intermediate 17a and 4.4% from the starting material (E)-olefinic alcohol.

Scheme 5. Synthesis of 15-(S)-HETE (20a) and 15-(R)-HETE (20b)
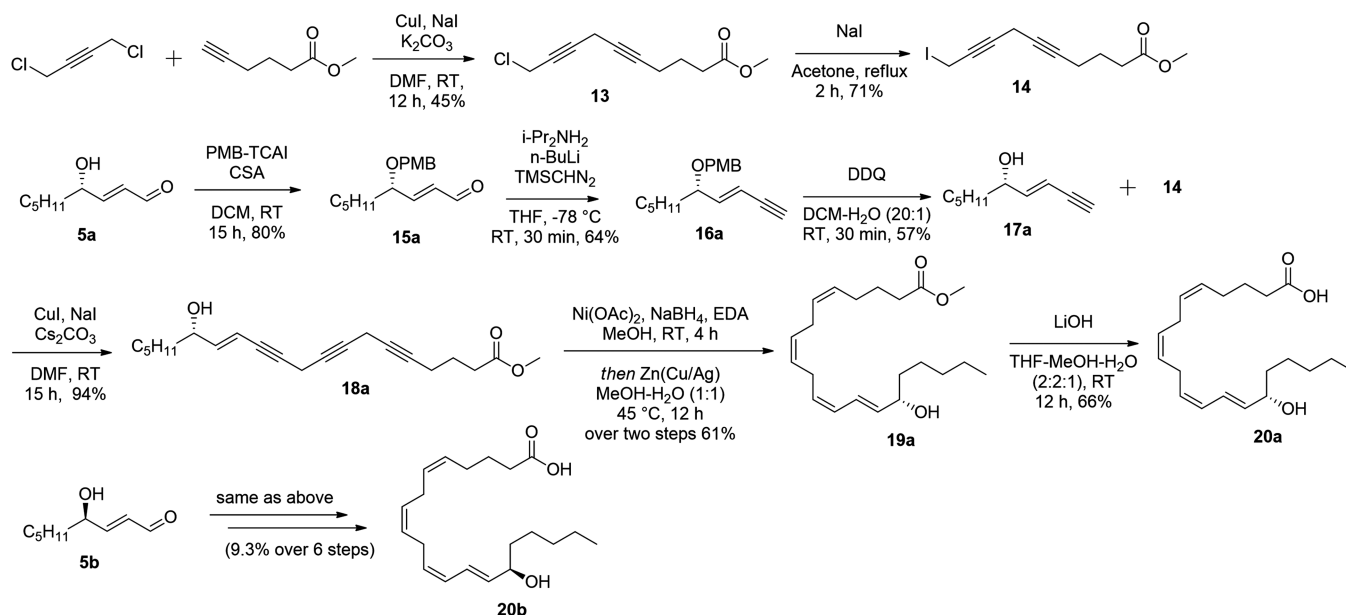
■ CONCLUSIONS

In conclusion, the stereoselective synthesis of 13-(S)-HODE was successfully accomplished in 6 synthetic steps from commercial (E)-olefin alcohol. The analogues of 13-(S)-HODE were synthesized from the intermediate fatty acid ester by methylation, oxidation, and hydrolysis. This synthetic route was applied to modify the hydroxyl group at position C-13. By structural modification of the chiral intermediate, the synthesis of 15-(S)-HETE was achieved in 3 synthetic steps from the key chiral alkyne. These results may pave the way for further development of the synthesis of various 13-(S)-HODE, 15-(S)-HETE, and their analogues.

■ EXPERIMENTAL SECTION

General Information. All of the chemicals and solvents used in the reaction were purchased from Sigma-Aldrich, TCI, or Alfa Aesar and were used without further purification. All reactions were carried out in oven-dried glassware under an inert atmosphere, and the reaction temperature was controlled by an oil bath. Reactions were monitored by thin layer chromatography (TLC) on 0.25 mm Merck precoated silica gel plates (60 F254). Reaction progress was monitored by TLC analysis using a UV lamp and/or $KMnO_4$ staining or p-anisaldehyde staining solution for detection purposes. Column chromatography was performed on silica gel (230−400 mesh, Merck, Darmstadt, Germany). ^{1}H and ^{13}C NMR spectra were recorded at room temperature (298 K) in $CDCl_3$ (7.26 ppm/77.16 ppm), CD_3OD (3.31 ppm/49.00 ppm), or CD_3CN/D_2O (2.53 and 4.79 ppm/1.32 and 118.26 ppm) on a Bruker Ultrashield 600 MHz Plus spectrometer and referenced to an internal solvent. NMR solvents, including $CDCl_3$, CD_3OD, CD_3CN, and D_2O, were used as received from the Eurisotop company. Chemical shifts are reported in parts per million (ppm). Coupling constants (J) are given in Hertz. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double of doublet; dt, double of triplet; and br, broad for ^{1}H NMR data. High-resolution mass spectra (HRMS) were recorded on an Agilent 6530 Accurate mass Q-TOF LC/MS spectrometer. Reversed-phase high-performance liquid chromatography (RP-HPLC) purification using a semipreparative column (Phenomenex Gemini-NX C18, 110 Å, 150 mm × 10 mm, 5 μm) was performed on Agilent 1260 Infinity (Agilent). The purity of all final compounds was measured by analytical RP-HPLC on an Agilent 1260 Infinity (Agilent) with a C_{18} column (Phenomenex, 150 mm × 4.6 mm, 3 μm, 110 Å) using water (containing 0.1% FA) and acetonitrile

(ACN; containing 0.1% FA) as the mobile phase. All compounds were monitored at a UV detector: 220 nm. The purities of the tested compounds were >95%. Melting point (mp) was measured using a Q2000 DSC (TA Instruments, New Castle, DE). Optical rotation was measured at λ = 589 nm, corresponding to the sodium D line, at the indicated temperature using a Krüss P8000 polarimeter.

(E)-1-Methoxy-4-((non-3-en-1-yloxy)methyl)benzene (1). To a solution of (E)-non-3-en-1-ol (8.0 g, 56.2 mmol) in tetrahydrofuran (THF, 160 mL) were added NaH (60%, 3.14 g, 78.7 mmol), PMBCl (9.0 mL, 66 mmol), and tetra-n-butylammonium bromide (187 mg, 0.56 mmol). The reaction mixture was heated under reflux for 24 h, poured into saturated NH_4Cl solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using Hex/EtOAc (98:2) to give the product as a colorless oil in 81% yield (12.0 g). R_f = 0.25 (Hex/EtOAc (98:2), $KMnO_4$ stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, J = 8.58 Hz, 2H), 6.88 (d, J = 8.64 Hz, 2H), 5.49 (dt, J = 15.3, 6.7 Hz, 1H), 5.41 (dt, J = 15.3, 6.7 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.45 (t, J = 7.0 Hz, 2H), 2.30 (q, J = 6.7 Hz, 2H), 1.98 (q, J = 6.7 Hz, 2H), 1.38−1.23 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ159.3, 132.8, 130.9, 129.4, 129.4, 126.4, 114.0, 114.0, 72.7, 70.2, 55.5, 33.3, 32.8, 31.6, 29.4, 22.8, 14.3.

(3S,4S)-1-((4-Methoxybenzyl)oxy)nonane-3,4-diol (2a). To a mixture of $K_3[Fe(CN)_6]$ (18.7 g, 57.2 mmol, 3.0 equiv), K_2CO_3 (7.88 g, 57.2 mmol, 3.0 equiv), and (DHQ)$_2$PHAL (142.6 mg, 0.19 mmol, 1.0 mol %) in t-BuOH·H_2O (1:1, 200 mL) cooled at 4 °C was added K_2OsO_4·$2H_2O$ (28.8 mg, 0.076 mmol, 0.4 mol %) followed by methanesulfonamide (1.80 g, 19.0 mmol, 1.0 equiv). After the mixture was stirred for 5 min at 4 °C, compound **1** (5.0 g, 19.0 mmol) was added in one portion. The reaction mixture was stirred at 4 °C for 24 h and then quenched with solid Na_2SO_3 (3.6 g, 28.6 mmol, 1.5 equiv). The stirring was continued for an additional 45 min, the solid was removed in vacuum filtration, and then the filtrates were extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel using Hex/EtOAc (3:1) to give crude product **2a** as white solids. The residue was purified by recrystallization in Hex/EtOAc (20:1) to afford the desired pure product **2a** as a white solid (4.46 g, 79%, 95% ee). The enantiomeric ratio was determined by chiral HPLC [250 mm × mm, 5 μm, Daicel Chiralpak-IG, 90:10 to 0:100 hexane/methyl tert-butyl ether (MTBE) containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 10.7 min [97.8%, (S,S)-isomer], 11.5 min [2.2%, (R,R)-isomer]. Mp 40−41 °C; R_f = 0.25 (Hex/EtOAc

(7:3), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$), 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.71−3.62 (m, 3H), 3.41 (m, 1H), 3.19 (d, J = 3.9 Hz, 1H), 2.52 (d, J = 8.4 Hz, 1H), 1.90−1.70 (m, 2H), 1.51−1.23 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 159.6, 130.0, 129.6, 129.6, 114.1, 114.1, 74.5, 73.9, 73.3, 68.5, 55.5, 33.7, 33.4, 32.1, 25.6, 22.8, 14.2; HRMS (ESI) m/z: [M + Na]$^+$ calculated for C$_{17}$H$_{28}$O$_4$Na$^+$ 319.1880; found 319.1856.

(3R,4R)-1-((4-Methoxybenzyl)oxy)nonane-3,4-diol (2b). White solid (4.50 g, 79%, 98% *ee*); mp 40−41 °C; R_f = 0.25 (Hex/EtOAc (7:3), KMnO$_4$ stain). The enantiomeric ratio was determined by chiral HPLC [250 mm × mm, 5 μm, Daicel Chiralpak-IG, 80:20 to 0:100 hexane/MTBE containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 10.7 min [0.7%, (*S,S*)-isomer], 11.5 min [99.2%, (*R,R*)-isomer]. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.71−3.62 (m, 3H), 3.41 (m, 1H), 3.19 (d, J = 3.9 Hz, 1H), 2.52 (d, J = 8.4 Hz, 1H), 1.90−1.70 (m, 2H), 1.51−1.23 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 159.5, 130.0, 129.6, 129.6, 114.1, 114.1, 74.5, 73.9, 73.2, 68.4, 55.5, 33.7, 33.3, 32.1, 25.6, 22.8, 14.2; HRMS (ESI) m/z: [M + Na]$^+$ calculated for C$_{17}$H$_{28}$O$_4$Na$^+$ 319.1880; found 319.1865.

(4S,5S)-4-(2-((4-Methoxybenzyl)oxy)ethyl)-5-pentyl-1,3-dioxolan-2-one (3a). Compound **2a** (3.5 g, 11.8 mmol) was dissolved in dimethyl carbonate (1.5 mL, 17.7 mmol, 1.5 equiv), and K$_2$CO$_3$ was added as a catalyst (98 mg, 0.71 mmol, 0.06 equiv) and the resulting mixture was stirred 85 °C for 3 h. Then, methanol and excess dimethyl carbonate were distilled at 30 °C under reduced pressure. The residue was purified by column chromatography on silica gel using Hex/EtOAc (9:1) to give the product as a colorless oil in a 91% yield (3.48 g). R_f = 0.25 (Hex/EtOAc (9:1), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.22 (d, J = 8.6, 2H), 6.88 (d, J = 8.6, 2H), 4.45−4.39 (m, 3H), 4.33 (m, 1H), 3.80 (s, 3H), 3.60−3.57 (m, 2H), 2.00−1.94 (m, 2H), 1.70−1.59 (m, 2H), 1.49−1.23 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 159.5, 154.8, 130.0, 129.6, 129.6, 114.0, 114.0, 82.4, 79.8, 73.2, 65.2, 55.4, 34.2, 33.8, 31.4, 24.4, 22.5, 14.1; HRMS (ESI) m/z: [M + Na]$^+$ calculated for C$_{18}$H$_{26}$O$_5$Na$^+$ 345.1672; found 345.1639.

(4R,5R)-4-(2-((4-Methoxybenzyl)oxy)ethyl)-5-pentyl-1,3-dioxolan-2-one (3b). Colorless oil (3.65 g, 96%); R_f = 0.25 (Hex/EtOAc (9:1), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.22 (d, J = 8.6, 2H), 6.88 (d, J = 8.6, 2H), 4.45−4.39 (m, 3H), 4.33 (m, 1H), 3.80 (s, 3H), 3.60−3.57 (m, 2H), 2.00−1.94 (m, 2H), 1.70−1.59 (m, 2H), 1.49−1.23 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 159.5, 154.8, 130.0, 129.6, 129.6, 114.0, 114.0, 82.4, 79.7, 73.2, 65.2, 55.4, 34.2, 33.8, 31.4, 24.5, 22.5, 14.0; HRMS (ESI) m/z: [M + Na]$^+$ calculated for C$_{18}$H$_{26}$O$_5$Na$^+$ 345.1672; found 345.1650.

(4S,5S)-4-(2-Hydroxyethyl)-5-pentyl-1,3-dioxolan-2-one (4a). To a stirred solution of **3a** (3.3 g, 10.2 mmol) in a mixed solvent of DCM (40 mL) and H$_2$O (2 mL) was added DDQ (3.47 g, 15.3 mmol, 1.5 equiv) at 4 °C. After 30 min, the mixture was diluted with water and extracted with DCM. The extract was washed with water and brine, dried over MgSO$_4$, and concentrated in vacuo after filtration. The residue was purified by column chromatography on silica gel using Hex/EtOAc (8:2) to give the product as a colorless oil in 83% yield (1.71 g). R_f = 0.25 (Hex/EtOAc (7:3), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 4.48 (m, 1H), 4.35 (m, 1H), 3.81 (m, 2H), 2.14 (br s, 1H), 1.98−1.88 (m, 2H), 1.77−1.65 (m, 2H), 1.51−1.27 (m, 6H), 0.88 (t, J = 6.96 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 155.0, 82.5, 79.7, 58.2, 36.3, 33.6, 31.5, 24.4, 22.5, 14.1; HRMS (ESI) m/z: [M + H]$^+$ calculated for C$_{10}$H$_{19}$O$_4$ 203.1278; found 203.1263.

(4R,5R)-4-(2-Hydroxyethyl)-5-pentyl-1,3-dioxolan-2-one (4b). Colorless oil (1.79 g, 82%); R_f = 0.25 (Hex/EtOAc (7:3), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 4.48 (m, 1H), 4.35 (m, 1H), 3.81 (m, 2H), 2.15 (br s, 1H), 1.98−1.88 (m, 2H), 1.77−1.65 (m, 2H), 1.51−1.27 (m, 6H), 0.88 (t, J = 6.96 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 155.0, 82.5, 79.7, 58.2, 36.3, 33.6, 31.5, 24.4, 22.5, 14.1; HRMS (ESI) m/z: [M + H]$^+$ calculated for C$_{10}$H$_{19}$O$_4$ 203.1278; found 203.1273.

(S,E)-4-Hydroxynon-2-enal (5a). To a stirred solution of compound **4a** (100 mg, 0.49 mmol) in EtOAc (10 mL) was added 2-iodoxybenzoic

acid (IBX, 45% w/w with stabilizer) (615 mg, 0.98 mmol, 2.0 equiv) under an Ar atmosphere. The resulting suspension was refluxed for 3−4 h (TLC monitoring). The reaction was cooled to room temperature, and the solid was removed through vacuum filtration. The filtrates were washed with saturated NaHCO$_3$(aq), brine, dried over MgSO$_4$, and concentrated. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (98:2) as an eluent to afford product **5a** in 82% yield (63 mg) as a colorless oil. R_f = 0.25 (DCM/EtOAc, 98:2. KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.57 (d, J = 7.8 Hz, 1H), 6.82 (dd, J = 15.7, 4.8 Hz, 1H), 6.30 (ddd, J = 15.7, 7.8, 1.6 Hz, 1H), 4.42 (q, J = 4.8 Hz, 1H), 2.01 (s, 1H), 1.68−1.57 (m, 2H), 1.49−1.41 (m, 1H), 1.41−1.35 (m, 1H), 1.35−1.26 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 193.9, 159.3, 130.9, 71.3, 36.7, 31.8, 25.1, 22.7, 14.2; HRMS (ESI) m/z: [M + H]$^+$ calculated for C$_9$H$_{17}$O$_2$ 157.1223; found 157.1226.

(R,E)-4-Hydroxynon-2-enal (5b). Colorless oil (106 mg, 86%), R_f = 0.25 (DCM/EtOAc, 98:2. KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.58 (d, J = 7.9 Hz, 1H), 6.82 (dd, J = 15.7, 4.7 Hz, 1H), 6.30 (ddd, J = 15.7, 7.9, 1.4 Hz, 1H), 4.42 (q, J = 4.8, 1H), 1.87 (s, 1H), 1.68−1.57 (m, 2H), 1.45 (m, 1H), 1.42−1.36 (m, 1H), 1.36−1.27 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 193.8, 159.2, 130.8, 71.3, 36.7, 31.8, 25.1, 22.7, 14.2; HRMS (ESI) m/z: [M + H]$^+$ calculated for C$_9$H$_{17}$O$_2$ 157.1223; found 157.1229.

(8-Carboxyoctyl)triphenylphosphonium Bromide (6). Triphenylphosphine (5.9 g, 22.2 mmol, 1.5 equiv) was dissolved in 90 mL of freshly dried ACN in a 100 mL round-bottomed flask. A 9-bromononanoic acid (3.5 g, 14.8 mmol) in 10 mL of ACN was slowly added to the stirred triphenylphosphine solution. The reagents readily dissolved, and the orange-colored reaction mixture was heated under reflux for 48 h at 90 °C under Ar. The solvent of the reaction mixture was then evaporated, and the (8-carboxyalkyl)triphenylphosphonium bromide salts were obtained as slightly yellow oils, which proved insoluble in toluene. Toluene (20 mL) was added to each slight yellow oil, and the mixture was heated under reflux for 30 min. The toluene phase was decanted, and the cleaning process was repeated with 20 mL of toluene. Afterward, 30 mL of anhydrous diethyl ether was added to the oily residue, and recrystallization in the refrigerator resulted in a slightly yellow solid. The obtained solid was triturated with diethyl ether, and the precipitate was filtered off and washed several times with anhydrous diethyl ether. Drying overnight in a vacuum produced white powders of product **6** in 95% yield (7.02 g) without any need for further purification. R_f = 0.1 (Hex/EtOAc 7:3). KMnO$_4$ stain; ^{1}H NMR (600 MHz, DMSO) δ 11.95 (s, 1H), 7.91−7.76 (m, 15H), 3.63−3.56 (m, 2H), 2.15 (t, J = 7.4 Hz, 2H), 1.51 (m, 2H), 1.48−1.40 (m, 4H), 1.25 (m, 2H), 1.22−1.14 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 174.4, 134.9, 133.6, 130.2, 118.9, 118.3, 33.6, 29.7, 29.6, 28.4, 27.9, 24.4, 21.7, 20.3; HRMS (ESI) m/z: calculated for C$_{27}$H$_{32}$O$_2$P$^+$ 419.2134; found 419.2146.

(S,9Z,11E)-13-Hydroxyoctadeca-9,11-dienoic Acid (7a). (8-Carboxyoctyl)triphenylphosphonium bromide **6** (1.43 g, 2.88 mmol, 1.5 equiv) was suspended in anhydrous N,N'-dimethylpropyleneurea (DMPU) (5 mL) under an argon atmosphere. 1.5 M lithium bis(trimethylsilyl)amide (LiHMDS) solution in THF (6.14 mL, 9.22 mmol, 4.80 equiv) was added within 40 min to the suspension at 0 °C and stirring was continued at 0 °C for further 15 min. The resulting dark red solution was cooled to 0 °C and (*S,E*)-4-hydroxynon-2-enal **5a** (300 mg, 1.92 mmol) dissolved in THF (2 mL) was added within 40 min; after the addition, the reaction mixture was allowed to warm to room temperature. A TLC check after 8 h indicated the completion of the reaction. 1.0 M HCl$_{(aq)}$ was added to the reaction mixture until an acidic pH was obtained. The aqueous phase was extracted with EtOAc (3 × 40 mL), and the combined extracts were dried over MgSO$_4$. After evaporation to dryness, the crude mixture was purified by column chromatography using hexane/diethyl ether (8:2) containing 1% glacial acetic acid to give (*S,9Z,11E*)-13-hydroxyoctadeca-9,11-dienoic acid **7a** in an 8:2 ratio (*Z/E*). Yield: 192 mg (34%, 95% *ee*) as a colorless oil. R_f = 0.25 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain). The enantiomeric ratio was determined by chiral HPLC [250 mm × 4.6 mm, 5 μm, Daicel Chiralpak-IG, 80:20 to 0:100 hexane/MTBE containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 6.4 min

[2.5%, (*R*,*R*)-isomer], 11.6 min [97.5%, (*S*,*S*)-isomer]. $[\alpha]_D^{28}$ = +10.8 (*c* 1.0, CHCl$_3$), Lit.[14] $[\alpha]_D^{25}$ = +9.3 (*c* 1.29, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.49 (dd, *J* = 15.2, 10.8 Hz, 1H, H-11), 5.97 (t, *J* = 10.8 Hz, 1H, H-10), 5.66 (dd, *J* = 15.2, 6.8 Hz, 1H, H-12), 5.44 (dt, *J* = 10.8, 7.2 Hz, 1H, H-9), 4.17 (q, *J* = 6.8 Hz, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.20−2.15 (m, 2H), 1.66−1.60 (m, 2H), 1.55 (m, 2H), 1.41−1.36 (m, 3H), 1.36−1.27 (m, 11H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 179.2, 136.0, 133.1, 128.1, 126.1, 73.2, 37.5, 34.1, 32.0, 29.6, 29.1, 29.1, 29.0, 27.8, 25.3, 24.8, 22.8, 14.3; HRMS (ESI): [M − H]$^-$ calculated for C$_{18}$H$_{31}$O$_3^-$, 295.2278; found, 295.2289.

(R,9Z,11E)-13-Hydroxyoctadeca-9,11-dienoic Acid (7b). Colorless oil (195.6 mg, 35%, 99% *ee*); R_f = 0.25 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain). The enantiomeric ratio was determined by chiral HPLC [250 mm × 4.6 mm, 5 μm, Daicel Chiralpak-IG, 80:20 to 0:100 Hex/MTBE containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 6.4 min [99.9%, (*R*,*R*)-isomer], 11.6 min [0.1%, (*S*,*S*)-isomer]. $[\alpha]_D^{28}$ = −9.73 (*c* 1.0, CHCl$_3$), Lit.[14] $[\alpha]_D^{25}$ = −9.3 (*c* 1.21, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.49 (dd, *J* = 15.2, 10.8 Hz, 1H, H-11), 5.97 (t, *J* = 10.8 Hz, 1H, H-10), 5.66 (dd, *J* = 15.2, 6.8 Hz, 1H, H-12), 5.44 (dt, *J* = 10.8, 7.7 Hz, 1H, H-9), 4.17 (q, *J* = 6.8 Hz, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.20−2.15 (m, 2H), 1.66−1.60 (m, 2H), 1.55 (m, 2H), 1.41−1.36 (m, 3H), 1.36−1.27 (m, 11H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 179.2, 136.0, 133.1, 128.1, 126.1, 73.2, 37.5, 34.2, 32.0, 29.6, 29.1, 29.1, 29.0, 27.8, 25.3, 24.8, 22.8, 14.3; HRMS (ESI): [M − H]$^-$ calculated for C$_{18}$H$_{31}$O$_3^-$, 295.2278; found, 295.2271.

(S,9E,11E)-13-Hydroxyoctadeca-9,11-dienoic Acid (7a′). White solid (49.3 mg, 8%); mp 54−55 °C; R_f = 0.20 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.16 (dd, *J* = 15.0, 10.8 Hz, 1H, H-11), 6.01 (dd, *J* = 15.6, 10.8 Hz, 1H, H-10), 5.68 (dt, *J* = 15.0, 7.2 Hz, 1H, H-9), 5.57 (dd, *J* = 15.6, 7.2 Hz, 1H, H-12), 4.11 (q, *J* = 7.2 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.65−1.59 (m, 2H), 1.59−1.46 (m, 2H), 1.37−1.34 (m, 3H), 1.35−1.26 (m, 11H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 179.5, 135.5, 133.7, 131.1, 129.7, 73.1, 37.4, 34.1, 32.7, 31.9, 29.2, 29.2, 29.1, 29.0, 25.2, 24.8, 22.7, 14.2; HRMS (ESI): [M − H]$^-$ calculated for C$_{18}$H$_{31}$O$_3^-$, 295.2278; found, 295.2286.

(R,9E,11E)-13-Hydroxyoctadeca-9,11-dienoic Acid (7b′). White solid (45.1 mg, 8%); mp 54−55 °C; R_f = 0.20 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.16 (dd, *J* = 15.2, 10.4 Hz, 1H, H-11), 6.01 (dd, *J* = 15.1, 10.4 Hz, 1H, H-10), 5.68 (dt, *J* = 15.1, 7.1 Hz, 1H, H-12), 5.57 (dd, *J* = 15.2, 7.2 Hz, 1H, H-9), 4.11 (q, *J* = 7.2 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.07 (q, *J* = 7.1 Hz, 2H), 1.65−1.59 (m, 2H), 1.59−1.46 (m, 2H), 1.37−1.34 (m, 3H), 1.35−1.26 (m, 11H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 179.5, 135.5, 133.7, 131.1, 129.7, 73.1, 37.4, 34.1, 32.7, 31.9, 29.2, 29.1, 29.1, 29.0, 25.2, 24.8, 22.7, 14.2; HRMS (ESI): [M − H]$^-$ calculated for C$_{18}$H$_{31}$O$_3^-$, 295.2278; found, 295.2278.

(S,9Z,11E)-13-Methyl 13-Hydroxyoctadeca-9,11-dienoate (8a). To a stirred solution of compound **7a** (1.5 g, 5.1 mmol) in 20 mL of toluene/MeOH (3:2), a 0.6 M solution of trimethylsilyldiazomethane (TMSCHN$_2$) in hexane (7.95 mL, 13.3 mmol, 2.6 equiv) was added dropwise until the yellow color persisted. The mixture was stirred for 30−60 min at room temperature and concentrated to give the corresponding methyl ester. The residue was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as an eluent to afford the product **8a** in 93% yield (1.46 g) as a colorless oil. R_f = 0.25 (Hex/EtOAc, 9:1. KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.48 (dd, *J* = 15.2, 11.0 Hz, 1H, H-11), 5.96 (t, *J* = 11.0 Hz, 1H, H-10), 5.65 (dd, *J* = 15.2, 6.9 Hz, 1H, H-12), 5.42 (dt, *J* = 11.0, 7.4 Hz, 1H, H-9), 4.15 (q, *J* = 6.9 Hz, 1H), 3.65 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.16 (q, *J* = 7.4 Hz, 2H), 1.63−1.59 (m, 2H), 1.58−1.53 (m, 1H), 1.53−1.46 (m, 1H), 1.42−1.33 (m, 3H), 1.33−1.25 (m, 11H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 174.5, 136.1, 132.9, 128.0, 125.9, 73.1, 51.7, 37.5, 34.2, 32.0, 29.7, 29.2, 29.2, 29.1, 27.8, 25.3, 25.1, 22.8, 14.2; HRMS (ESI): [M + H]$^+$ calculated for C$_{19}$H$_{33}$O$_3^+$, 309.2435; found, 309.2418.

(R,9Z,11E)-Methyl 13-Hydroxyoctadeca-9,11-dienoate (8b). Colorless oil (1.0 g, 95%); R_f = 0.25 (Hex/EtOAc, 9:1), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.48 (dd, *J* = 15.2, 11.0 Hz, 1H, H-11), 5.97

(t, *J* = 11.0 Hz, 1H, H-10), 5.67 (dd, *J* = 15.2, 6.9 Hz, 1H, H-12), 5.43 (dt, *J* = 11.0, 7.7 Hz, 1H, H-9), 4.16 (q, *J* = 6.9 Hz, 1H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.17 (q, *J* = 7.7 Hz, 2H), 1.65−1.55 (m, 4H), 1.55−1.47 (m, 1H), 1.41−1.35 (m, 3H), 1.32 (d, *J* = 16.6 Hz, 11H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 174.5, 136.2, 133.0, 128.0, 125.9, 73.1, 51.7, 37.5, 34.3, 32.0, 29.7, 29.2, 29.2, 29.1, 27.9, 25.3, 25.1, 22.8, 14.2; HRMS (ESI): [M + H]$^+$ calculated for C$_{19}$H$_{33}$O$_3^+$, 309.2435; found, 309.2428.

(S,9Z,11E)-Methyl 13-Methoxyoctadeca-9,11-dienoate (9a). To a solution of NaH (60% in mineral oil, 182 mg, 4.58 mmol, 4.75 equiv) in DMF (2.0 mL) was added a solution of compound **8a** (300 mg, 0.97 mmol, 10.3 equiv) in THF (2.0 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 20 min, and an iodomethane (612 μL, 9.95 mmol, 10.3 equiv) was added at 0 °C. The reaction mixture was stirred at room temperature for 30 min. More iodomethane (305 μL, 4.98 mmol, 5.15 equiv) was added, and the reaction mixture was stirred for another 25 min. The reaction mixture was quenched with saturated NaHCO$_{3(aq)}$ (50 mL), and the mixture was poured into brine (50 mL) and EtOAc (100 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel using Hex/EtOAc (98:2) gave the product as a colorless oil in 78% yield (246 mg). R_f = 0.25 (Hex/EA (98:2), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.42 (dd, *J* = 15.2, 11.1 Hz, 1H, H-11), 5.99 (t, *J* = 11.1 Hz, 1H, H-10), 5.47 (dd, *J* = 15.2, 7.7 Hz, 1H, H-12), 5.43 (dt, *J* = 11.1, 7.4 Hz, 1H, H-9), 3.67 (s, 3H), 3.57 (q, *J* = 7.7 Hz, 1H), 3.26 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.18 (q, *J* = 7.4 Hz, 2H), 1.66−1.57 (m, 3H), 1.50−1.42 (m, 1H), 1.41−1.34 (m, 3H), 1.33−1.25 (m, 11H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 174.5, 134.0, 132.7, 128.0, 127.9, 82.6, 56.3, 51.6, 35.9, 34.3, 32.0, 29.7, 29.3, 29.3, 29.2, 27.9, 25.3, 25.1, 22.8, 14.3; HRMS (ESI): [M + Na]$^+$ calculated for C$_{20}$H$_{36}$O$_3$Na$^+$, 347.2556; found, 347.2528.

(R,9Z,11E)-Methyl 13-methoxyoctadeca-9,11-dienoate (9b). Colorless oil (200 mg, 64%); R_f = 0.25 (Hex/EtOAc (98:2), KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.42 (dd, *J* = 15.2, 11.0 Hz, 1H, H-11), 5.99 (t, *J* = 11.0 Hz, 1H, H-10), 5.47 (dd, *J* = 15.2, 7.7 Hz, 1H, H-12), 5.43 (dt, *J* = 11.0, 7.4 Hz, 1H, H-9), 3.67 (s, 3H), 3.57 (q, *J* = 7.7 Hz, 1H), 3.26 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.18 (q, *J* = 7.4 Hz, 2H), 1.60 (m, 4H), 1.49−1.42 (m, 1H), 1.41−1.34 (m, 3H), 1.33−1.25 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 174.5, 134.0, 132.7, 128.0, 127.9, 82.6, 56.3, 51.7, 35.9, 34.3, 32.1, 29.7, 29.3, 29.3, 29.2, 27.9, 25.3, 25.1, 22.8, 14.3; HRMS (ESI): [M + Na]$^+$ calculated for C$_{20}$H$_{36}$O$_3$Na$^+$, 347.2556; found, 347.2548.

(S,9Z,11E)-13-Methoxyoctadeca-9,11-dienoic Acid (10a). Compound **9a** (0.31 mmol, 100 mg) was dissolved in a mixture of MeOH (8 mL), THF (8 mL), and water (4 mL). Then, LiOH (9.24 mmol, 221 mg, 30 equiv) was added at 0 °C. The mixture was stirred under argon at 0 °C for 30 min and then at RT for an additional 2 h. A TLC check after 2 h indicated the completion of the reaction. Then, 1 M HCl$_{(aq)}$ was added to the reaction mixture until an acidic pH was obtained, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and evaporated. After evaporation to dryness, the crude mixture was purified by column chromatography using Hex/ether (7:3) containing 1% glacial acetic acid to give the product as a colorless oil in 95% yield (90.8 mg). R_f = 0.25 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.43 (dd, *J* = 15.2, 11.0 Hz, 1H, H-11), 5.99 (t, *J* = 11.0 Hz, 1H, H-10), 5.48 (dd, *J* = 15.2, 7.4 Hz, 1H, H-12), 5.43 (dt, *J* = 11.0, 7.6 Hz, 1H, H-9), 3.58 (q, *J* = 7.4 Hz, 1H), 3.27 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.66−1.57 (m, 2H), 1.50−1.43 (m, 1H), 1.41−1.36 (m, 2H), 1.36−1.30 (m, 8H), 1.27 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 179.8, 133.9, 132.7, 128.0, 127.9, 82.6, 56.3, 35.8, 34.2, 32.0, 29.7, 29.3, 29.2, 29.2, 27.9, 25.3, 24.9, 22.8, 14.3; HRMS (ESI): [M − H]$^-$ calculated for C$_{19}$H$_{33}$O$_3^-$, 309.2435; found, 309.2426.

(R,9Z,11E)-13-Methoxyoctadeca-9,11-dienoic Acid (10b). Colorless oil (135 mg, 94%); R_f = 0.25 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain); ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.43 (dd, *J* = 15.2, 11.0 Hz, 1H, H-11), 5.99 (t, *J* = 11.0 Hz, 1H, H-10), 5.48 (dd, *J* = 15.2, 7.6

Hz, 1H, H-12), 5.43 (dt, J = 11.0, 7.4 Hz, 1H, H-9), 3.58 (q, J = 7.6 Hz, 1H), 3.27 (s, 3H), 2.35 (t, J = 7.5 Hz, 2H), 2.18 (q, J = 7.4 Hz, 2H), 1.63 (m, 2H), 1.59 (m, 1H), 1.50−1.42 (m, 1H), 1.42−1.36 (m, 2H), 1.33 (m, 8H), 1.30−1.24 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 179.7, 133.9, 132.7, 128.0, 127.9, 82.6, 56.3, 35.8, 34.2, 32.0, 29.7, 29.2, 29.1, 29.1, 27.9, 25.3, 24.9, 22.8, 14.3; HRMS (ESI): [M − H]$^-$ calculated for C$_{19}$H$_{33}$O$_3^-$, 309.2435; found, 309.2439.

(9Z,11E)-Methyl 13-oxooctadeca-9,11-dienoate (11). Compound **8a** (200 mg, 0.64 mmol) was dissolved in ethyl acetate (50 mL), treated with 2-iodoxybenzoic acid (IBX, 45% w/w with stabilizer) (3.6 g, 5.76 mmol, 9.0 equiv), and kept under reflux at 85 °C. After 90 min, the mixture was filtered to remove unreacted IBX as a white solid. The filtrate was dried and the residue was purified by column chromatography (Hex/EtOAc (98:2)) to give the product as a colorless oil in 82% yield (163 mg). R_f = 0.25 (Hex/EA (98:2), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 7.48 (dd, J = 15.3, 11.5 Hz, 1H, H-11), 6.17 (d, J = 15.4 Hz, 1H, H-12), 6.12 (t, J = 11.2 Hz, 1H, H-10), 5.89 (dt, J = 10.7, 7.8 Hz, 1H, H-9), 3.67 (s, 3H), 2.55 (t, J = 7.4 Hz, 2H), 2.33−2.28 (m, 4H), 1.63 (m, 4H), 1.45−1.39 (m, 2H), 1.36−1.28 (m, 10H), 0.90 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 201.3, 174.5, 142.6, 137.1, 129.6, 127.2, 51.7, 41.3, 34.3, 31.7, 29.5, 29.3, 29.2, 29.2, 28.5, 25.1, 24.3, 22.7, 14.1; HRMS (ESI): [M + Na]$^+$ calculated for C$_{19}$H$_{32}$O$_3$Na$^+$, 331.2243; found, 331.2225.

(9Z,11E)-13-Oxooctadeca-9,11-dienoic Acid (12). Compound **11** (0.44 mmol, 136 mg) was dissolved in a mixture of MeOH (8 mL), THF (8 mL), and water (4 mL). Then, LiOH (13.2 mmol, 316 mg, 30 equiv) was added at 0 °C. The mixture was stirred under argon at 0 °C for 30 min and then at RT for an additional 2 h. A TLC check after 2 h indicated the completion of the reaction. Then, 1 M HCl$_{(aq)}$ was added to the reaction mixture until an acidic pH was obtained, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and evaporated. After evaporation to dryness, the crude mixture was purified by column chromatography using Hex/ether (8/2) containing 1% glacial acetic acid to give the product as a white solid in 69% yield (90 mg). Mp 40−41 °C (Lit.[14] 39.5−41.5 °C); R_f = 0.25 (Hex/ether (8:2) with 0.1% AcOH, KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 7.49 (dd, J = 15.3, 11.6 Hz, 1H, H-11), 6.17 (d, J = 15.3 Hz, 1H, H-12), 6.11 (t, J = 11.6 Hz, 1H, H-10), 5.92−5.87 (m, 1H, H-9), 2.54 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 2.30 (q, J = 7.4 Hz, 2H), 1.67−1.59 (m, 4H), 1.41 (m, 2H), 1.37−1.27 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 201.6, 179.4, 142.8, 137.3, 129.5, 127.2, 41.4, 34.1, 31.7, 29.4, 29.1, 29.1, 29.0, 28.5, 24.8, 24.3, 22.7, 14.1; HRMS (ESI): [M + Na]$^+$ calculated for C$_{18}$H$_{30}$O$_3$Na$^+$, 317.2087; found, 317.2067.

Methyl 10-Chlorodeca-5,8-diynoate (13). To a mixture of K$_2$CO$_3$ (630 mg, 4.5 mmol, 1.0 equiv), CuI (870 mg, 4.5 mmol, 1.0 equiv), and NaI (684 mg, 4.5 mmol, 1.0 equiv) in anhydrous DMF (10 mL) were added 1,4-dichloro-2-butyne (1.8 mL, 18.4 mmol, 4.0 equiv) and methyl 5-hexynoate (591 μL, 4.5 mmol, 1.0 equiv) under Ar. The reaction mixture was stirred for 12 h and then diluted with Hex/EtOAc (50 mL, 1:1) and passed through a pad of Celite to remove insoluble material. The filtrates were washed with saturated NaHCO$_{3(aq)}$, brine, dried over MgSO$_4$, and concentrated. The residue was purified by flash chromatography on silica gel using Hex/EtOAc (95:5) as the eluent to afford the product in 45% yield (440 mg) as a yellow liquid. R_f = 0.25 (Hex/EtOAc (95:5), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 4.12 (t, J = 2.2 Hz, 2H), 3.66 (s, 3H), 3.18 (p, J = 2.2 Hz, 2H), 2.41 (t, J = 7.2 Hz, 2H), 2.22 (tt, J = 7.2, 2.2 Hz, 2H), 1.80 (p, J = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 173.8, 81.7, 80.2, 75.3, 74.0, 51.8, 33.0, 30.9, 24.0, 18.3, 10.1; HRMS (ESI-TOF$^+$) m/z calculated for C$_{11}$H$_{14}$ClO$_2$ [M + H]$^+$: 213.0677, found 213.0676. This compound was previously reported in the analytical data.[12b]

Methyl 10-Iododeca-5,8-diynoate (14). To a solution of **13** (1.09 g, 5.12 mmol) in 40 mL of acetone was added NaI (1.53 g, 10.2 mmol, 2.0 equiv) at RT. After the reaction mixture was refluxed for 2 h, it was cooled to room temperature and quenched with 10 mL of H$_2$O. The mixture was extracted with diethyl ether (2 × 50 mL) and washed with brine. The organic layer was dried over anhydrous MgSO$_4$ and

concentrated. The residue was purified by flash chromatography on silica gel using Hex/EtOAc (95:5) as an eluent to afford product **14** in 71% yield (1.11 g) as a yellow liquid. R_f = 0.25 (Hex/EtOAc (95:5), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 3.68 (t, J = 2.4 Hz, 2H), 3.67 (s, 3H), 3.15 (p, J = 2.4 Hz, 2H), 2.43 (t, J = 7.2 Hz, 1H), 2.23 (tt, J = 7.2, 2.4 Hz, 2H), 1.81 (p, J = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 173.8, 80.4, 80.1, 77.3, 74.2, 51.8, 33.0, 24.0, 18.4, 10.4, −18.0. Compound **14** could not be detected by Q-TOF-MS in either positive or negative ionization mode.

(S,E)-4-((4-Methoxybenzyl)oxy)non-2-enal (15a). To a solution of **5a** (250 mg, 1.60 mmol) in DCM (10 mL) were added PMB-TCAl (675 mg, 2.40 mmol, 1.5 equiv) and camphorsulfonic acid (92.5 mg, 0.40 mmol, 0.25 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 15 h and then quenched with saturated NaHCO$_{3(aq)}$ (30 mL). The mixture was poured into DCM (50 mL). The phases were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with brine, dried over MgSO$_4$, filtered, and evaporated. After evaporation to dryness, the crude mixture was purified by chromatography on silica gel using Hex/EtOAc (95:5) to give the product as a light-yellow oil in 80% yield (354 mg). R_f = 0.25 (Hex/EtOAc (95:5), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 9.59 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.73 (dd, J = 15.8, 6.2 Hz, 1H), 6.27 (ddd, J = 15.8, 7.9, 0.8 Hz, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.34 (d, J = 11.4 Hz, 1H), 4.04 (q, J = 6.2 Hz, 1H), 3.80 (s, 3H), 1.70−1.63 (m, 1H), 1.60−1.54 (m, 1H), 1.45−1.37 (m, 1H), 1.35−1.22 (m, 5H), 0.87 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 193.7, 159.5, 157.8, 132.5, 130.1, 129.6, 114.1, 77.8, 71.2, 55.5, 34.9, 31.8, 25.0, 22.7, 14.2.

(R,E)-4-((4-Methoxybenzyl)oxy)non-2-enal (15b). Colorless oil (296 mg, 67%); R_f = 0.25 (Hex/EtOAc (95:5), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 9.59 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.73 (dd, J = 15.8, 6.2 Hz, 1H), 6.27 (ddd, J = 15.8, 7.9, 0.8 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.34 (d, J = 11.4 Hz, 1H), 4.04 (q, J = 6.2 Hz, 1H), 3.80 (s, 3H), 1.70−1.64 (m, 1H), 1.61−1.54 (m, 1H), 1.45−1.37 (m, 1H), 1.35−1.22 (m, 5H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR$\{^1H\}$ (151 MHz, CDCl$_3$) δ 193.7, 159.6, 157.8, 132.5, 130.1, 129.6, 114.1, 77.8, 71.2, 55.5, 34.9, 31.8, 25.0, 22.7, 14.2.

(S,E)-1-((Dec-3-en-1-yn-5-yloxy)methyl)-4-methoxybenzene (16a). To a solution of i-Pr$_2$NH (152 μL, 1.08 mmol, 3.0 equiv) in THF (3 mL) was added n-BuLi (2.5 M in hexane, 345 μL, 0.86 mmol, 2.4 equiv) at 0 °C under an argon atmosphere. After being stirred at 0 °C for 30 min, the solution was cooled to −78 °C, and TMSCHN$_2$ (2.0 M in hexane, 720 μL, 1.44 mmol, 4.0 equiv) was added at −78 °C. After 15 min, **15a** (100 mg, 0.36 mmol) in THF (2 mL) was added, and then the cooling bath was removed. The solution was stirred at room temperature for 30 min and diluted with saturated NH$_4$Cl$_{(aq)}$. The resulting mixture was extracted with EtOAc twice. The extract was washed with brine, dried over MgSO$_4$, and concentrated in vacuo after filtration. The residue was purified by column chromatography on silica gel using Hex/EtOAc (98:2) to give the product as a light brown oil in 64% yield (63 mg). R_f = 0.25 (Hex/EtOAc (98:2), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$), 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.16 (dd, J = 16.0, 6.2 Hz, 1H), 5.65 (dt, J = 16.0, 1.9 Hz, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.76 (q, J = 6.2 Hz, 1H), 2.91 (d, J = 1.9 Hz, 1H), 1.64−1.58 (m, 1H), 1.52−1.45 (m, 1H), 1.41−1.33 (m, 1H), 1.32−1.21 (m, 5H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR$\{^1H\}$ (151 MHz, CDCl$_3$) δ 159.4, 146.6, 130.7, 129.5, 114, 110.5, 81.9, 78.9, 77.9, 70.4, 55.5, 35.5, 31.9, 25.1, 22.8, 14.2; HRMS (ESI): [M + H]$^+$ calculated for C$_{18}$H$_{25}$O$_2^+$, 273.1849; found, 273.1864.

(R,E)-1-((Dec-3-en-1-yn-5-yloxy)methyl)-4-methoxybenzene (16b). Colorless oil (280 mg, 58%); R_f = 0.25 (Hex/EtOAc (98:2), KMnO$_4$ stain); ^1H NMR (600 MHz, CDCl$_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.16 (dd, J = 16.1, 7.1 Hz, 1H), 5.65 (dt, J = 16.1, 1.9 Hz, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.76 (q, J = 7.1 Hz, 1H), 2.91 (d, J = 1.9 Hz, 1H), 1.64−1.58 (m, 1H), 1.52−1.45 (m, 1H), 1.41−1.33 (m, 1H), 1.32−1.21 (m, 5H), 0.87 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CDCl$_3$) δ 159.4, 146.6, 130.7, 129.5, 114.0, 110.5, 81.9, 78.9, 77.9, 70.4, 55.5,

35.5, 31.9, 25.1, 22.8, 14.0; HRMS (ESI): $[M + H]^+$ calculated for $C_{18}H_{25}O_2^+$, 273.1849; found, 273.1856.

(S,E)-Dec-3-en-1-yn-5-ol (17a). To a stirred solution of **16a** (264 mg, 0.97 mmol) in a mixed solvent of DCM (2 mL) and H_2O (0.1 mL) was added DDQ (330 mg, 1.46 mmol, 1.5 equiv) at 4 °C. After 30 min, the mixture was diluted with water (5 mL) and DCM (30 mL) and extracted with DCM. The excess of $NaHSO_3$ (1 g), EtOAc (30 mL), MeOH (3 mL), and water (2 mL) was added to the DCM layer to remove the remaining aldehyde and discarded the aqueous layer (This process was repeated further two times). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo after filtration. The residue was purified by column chromatography on silica gel using Hex/EtOAc (8:2) to give the product as a light brown oil in 57% yield (84 mg). R_f = 0.25 (Hex/EtOAc (8:2), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.24 (dd, J = 16.0, 5.9 Hz, 2H), 5.69 (dt, J = 16.0, 2.1 Hz, 1H), 4.16 (q, J = 5.9 Hz, 1H), 2.88 (d, J = 2.1 Hz, 1H), 1.63 (s, 1H), 1.56−1.51 (m, 2H), 1.42−1.35 (m, 1H), 1.34−1.26 (m, 5H), 0.88 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.9, 108.8, 81.9, 78.0, 72.3, 37.1, 31.9, 25.1, 22.8, 14.2.

(R,E)-dec-3-en-1-yn-5-ol (17b). Colorless oil (136 mg, 60%); R_f = 0.25 (Hex/EtOAc (8:2), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.25 (dd, J = 16.0, 6.1 Hz, 1H), 5.69 (dt, J = 16.0 Hz, 2.1 Hz, 1H), 4.17 (q, J = 6.1 Hz, 1H), 2.88 (d, J = 2.1 Hz, 1H), 1.56−1.51 (m, 2H), 1.42−1.35 (m, 1H), 1.34−1.26 (m, 5H), 0.89 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.9, 108.8, 81.9, 78, 72.3, 37.1, 31.9, 25.1, 22.8, 14.2.

(S,E)-Methyl 15-Hydroxyicosa-13-en-5,8,11-triynoate (18a). To a mixture of Cs_2CO_3 (195 mg, 0.60 mmol, 1.1 equiv), CuI (114 mg, 0.60 mmol, 1.1 equiv), and NaI (90 mg, 0.60 mmol, 1.1 equiv) in anhydrous DMF (5 mL) was added **17a** (84 mg, 0.55 mmol) and diyne **14** (240 mg, 0.79 mmol, 1.4 equiv) under Ar. The reaction mixture was stirred for 15 h and then diluted with Hex/EtOAc (50 mL, 1:1) and passed through a pad of Celite to remove insoluble material. The filtrates were washed with saturated $NH_4Cl(aq)$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1) as an eluent to afford product **18a** in 94% yield (170 mg) as a brown liquid. R_f = 0.25 (Hex/EtOAc (8:2), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.11 (dd, J = 15.9, 6.3 Hz, 1H), 5.66 (dq, J = 15.9 Hz, 2.1 Hz, 1H), 4.12 (q, J = 6.3 Hz, 1H), 3.67 (s, 3H), 3.28 (q, J = 2.1 Hz, 2H), 3.13 (p, J = 2.1 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 2.23 (tt, J = 7.2, 2.1 Hz, 2H), 1.81 (p, J = 7.2 Hz, 2H), 1.61 (s, 1H), 1.56−1.46 (m, 2H), 1.41−1.34 (m, 1H), 1.34−1.24 (m, 5H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 173.9, 145.9, 109.8, 84.3, 79.7, 78.8, 75.4, 74.9, 74.2, 72.5, 51.8, 37.1, 33.1, 31.9, 25.1, 24.0, 22.8, 18.4, 14.2, 10.6, 10.0; HRMS (ESI): $[M + K]^+$ calculated for $C_{21}H_{28}O_3K^+$, 367.1670; found, 367.1696.

(R,E)-Methyl 15-Hydroxyicosa-13-en-5,8,11-triynoate (18b). Brown liquid (244 mg, 83%), R_f = 0.25 (Hex/EtOAc (8:2), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.11 (dd, J = 15.9, 6.2 Hz, 1H), 5.66 (dq, J = 15.9, 2.2 Hz, 1H), 4.13 (q, J = 6.2 Hz, 1H), 3.67 (s, 3H), 3.27 (d, J = 2.2 Hz, 2H), 3.12 (p, J = 2.2 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 2.23 (tt, J = 7.2, 2.2 Hz, 2H), 1.81 (p, J = 7.2 Hz, 2H), 1.64 (s, 1H), 1.56−1.46 (m, 2H), 1.41−1.34 (m, 1H), 1.34−1.24 (m, 5H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.5, 154.8, 130.0, 129.6, 129.6, 114.0, 114.0, 82.4, 79.7, 73.2, 65.2, 55.4, 34.2, 33.8, 31.4, 24.5, 22.5, 14.0; HRMS (ESI): $[M + K]^+$ calculated for $C_{21}H_{28}O_3K^+$, 367.1670; found, 367.1638.

(S,5Z,8Z,11Z,13E)-Methyl 15-Hydroxyicosa-5,8,11,13-tetraenoate (19a). To a solution of $Ni(OAc)_4 \cdot 4H_2O$ (240 mg, 0.96 mmol, 4.0 equiv) in anhydrous MeOH (5 mL) under H_2 gas was added $NaBH_4$ (36 mg, 0.96 mmol, 4.0 equiv) in small portions. The reaction mixture was then purged with H_2 and stirred for 20 min at RT. Then, ethylenediamine (96 μL, 1.44 mmol, 6.0 equiv) was added to the mixture. After 10 min, **18a** (80 mg, 0.24 mmol, 1.0 equiv) in MeOH (2 mL) was added. The reaction mixture was stirred at RT for 4 h and filtered through a pad of Celite with EtOAc and water. The filtrate was extracted with EA (3 × 50 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. A mixture of Zn dust (1.57 g, 24.0 mmol, 100 equiv) and $Cu(OAc)_2$ (218 mg, 1.2 mmol, 5.0 equiv) in H_2O was bubbled with Ar gas. After 20 min, $AgNO_3$ (244

mg, 1.44 mmol, 6.0 equiv) was added. The reaction mixture was stirred for 45 min and filtered using a glass filter. The remaining solid was washed with H_2O, MeOH, acetone, and EtOAc. The solid was diluted with H_2O (3 mL), and a solution of **19a** mixture in MeOH (3 mL) was added. The reaction mixture was stirred at 45 °C for 12 h and filtered through a pad of Celite with EtOAc. The filtrate was extracted with EtOAc (3 × 50 mL), and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using Hex/EtOAc (9:1) to give the product as a brown oil in a 61% yield (49 mg). R_f = 0.25 (Hex/EtOAc (9:1), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.52 (dd, J = 15.1, 11.1 Hz, 1H, H-13), 6.00 (t, J = 11.1 Hz, 1H, H-12), 5.70 (dd, J = 15.1, 6.7 Hz, 1H, H-14), 5.42−5.34 (m, 5H), 4.17 (q, J = 6.7 Hz, 1H), 3.67 (s, 3H), 2.96 (t, J = 6.2 Hz, 2H), 2.80 (t, J = 6.7 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 2.11 (q, J = 7.4 Hz, 3H), 1.70 (p, J = 7.4, 3H), 1.57−1.51 (m, 2H), 1.43−1.39 (m, 1H), 1.34−1.27 (m, 5H), 0.89 (t, J = 6.8 Hz, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 174.4, 136.9, 130.3, 129.2, 129.0, 128.8, 128.3, 127.8, 125.5, 73.0, 51.7, 37.5, 33.6, 32.0, 29.9, 26.8, 26.3, 25.9, 25.3, 25.0, 22.8, 14.3; HRMS (ESI): $[M + H]^+$ calculated for $C_{21}H_{35}O_3^+$, 335.2581; found, 335.2584.

(R,5Z,8Z,11Z,13E)-Methyl 15-Hydroxyicosa-5,8,11,13-tetraenoate (19b). Brown oil (140 mg, 64%); R_f = 0.25 (Hex/EtOAc (9:1), $KMnO_4$ stain); ^1H NMR (600 MHz, $CDCl_3$) δ 6.52 (dd, J = 15.1, 11.1 Hz, 1H, H-13), 6.00 (t, J = 11.1 Hz, 1H, H-12), 5.70 (dd, J = 15.1, 6.6 Hz, 1H, H-14), 5.42−5.33 (m, 5H), 4.17 (q, J = 6.6 Hz, 1H), 3.66 (s, 3H), 2.95 (t, J = 6.1 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 2.11 (q, J = 7.4 Hz, 2H), 1.70 (p, J = 7.4, 2H), 1.58−1.51 (m, 2H), 1.42−1.38 (m, 1H), 1.33−1.27 (m, 5H), 0.88 (t, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 174.4, 136.9, 130.3, 129.2, 129.0, 128.8, 128.3, 127.8, 125.5, 73.0, 51.7, 37.5, 33.6, 32.0, 29.9, 26.8, 26.3, 25.8, 25.3, 25.0, 22.8, 14.2; HRMS (ESI): $[M + H]^+$ calculated for $C_{21}H_{35}O_3^+$, 335.2581; found, 335.2576.

(S,5Z,8Z,11Z,13E)-15-Hydroxyicosa-5,8,11,13-tetraenoic Acid (20a). Compound **19a** (61 mg, 0.182 mmol) was dissolved in a mixture of MeOH (1.0 mL), THF (1.0 mL), and water (0.5 mL). Then, LiOH (13 mg, 0.546 mmol, 3.0 equiv) was added at 0 °C. The mixture was stirred at RT for 12 h. The reaction mixture was quenched by the addition of saturated $NH_4Cl_{(aq)}$ and diluted with EtOAc. The organic layer was extracted with EtOAc (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by HPLC (H_2O/MeCN = 7:3, 10 mL/min) to give the desired pure product **20a** as a colorless oil (39 mg, 66%, 97% *ee*). The enantiomeric ratio was determined by chiral HPLC [250 mm × 4.6 mm, 5 μm, Daicel Chiralpak-IG, 30:70 to 0:100 Hex/MTBE containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 7.5 min [98.8%, (*S,S*)-isomer], 6.6 min [1.2%, (*R,R*)-isomer]. R_f = 0.25 (Hex/ether (7:3) with 0.1% AcOH, $KMnO_4$ stain). $[α]_D^{28}$ = +3.44 (*c* 0.3, EtOH), Lit.[14b] $[α]_D^{25}$ = +23.5 (*c* 1.0, EtOH); ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (dd, J = 15.1, 11.1 Hz, 1H, H-13), 5.99 (t, J = 11.1 Hz, 1H, H-12), 5.71 (dd, J = 15.1, 6.1 Hz, 1H, H-14), 5.45−5.33 (m, 5H), 4.23 (q, J = 12.1, 6.1 Hz, 1H), 3.03−2.91 (m, 2H), 2.83 (t, J = 6.1 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 2.14 (q, J = 7.2 Hz, 2H), 1.73 (p, J = 7.2 Hz, 2H), 1.60−1.50 (m, 2H), 1.43−1.38 (m, 1H), 1.35−1.27 (m, 5H), 0.89 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 178.2, 136.3, 130.5, 129.1, 128.8, 128.1, 127.6, 125.4, 72.9, 37.5, 33.2, 32.0, 26.6, 26.4, 25.9, 25.3, 24.7, 22.8, 14.3; HRMS (ESI): $[M − H]^-$ calculated for $C_{20}H_{31}O_3^-$, 319.2278; found, 319.2298.

(R,5Z,8Z,11Z,13E)-15-Hydroxyicosa-5,8,11,13-tetraenoic Acid (20b). Colorless oil (66 mg, 55%, 98% *ee*). The enantiomeric ratio was determined by chiral HPLC [250 mm × 4.6 mm, 5 μm, Daicel Chiralpak-IG, 30:70 to 0:100 Hex/MTBE containing 0.05% glacial acetic acid, 1.0 mL/min, 220 nm, t_R = 6.6 min [99.0%, (*R,R*)-isomer], 7.6 min [0.9%, (*S,S*)-isomer]. R_f = 0.25 (Hex/ether (7:3) with 0.1% AcOH, $KMnO_4$ stain). $[α]_D^{28}$ = −3.78 (*c* 0.3, EtOH); ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (dd, J = 15.1, 11.1 Hz, 1H, H-13), 5.99 (t, J = 11.1 Hz, 1H, H-12), 5.70 (dd, J = 15.2, 6.2 Hz, 1H, H-14), 5.45−5.32 (m, 5H), 4.22 (q, J = 6.2 Hz, 1H), 3.02−2.91 (m, 2H), 2.82 (t, J = 6.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 2.13 (q, J = 7.2 Hz, 2H), 1.73 (p, J = 7.2 Hz, 2H), 1.60−1.50 (m, 2H), 1.43−1.38 (m, 1H), 1.35−1.27 (m, 5H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 178.2,

136.3, 130.5, 129.1, 128.8, 128.1, 127.6, 125.4, 72.9, 37.5, 33.2, 32.0, 26.6, 26.4, 25.9, 25.3, 24.7, 22.8, 14.3; HRMS (ESI): $[M - H]^-$ calculated for $C_{20}H_{31}O_3^-$, 319.2278; found, 319.2293.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00983.

Details of the experimental procedure and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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