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Total Synthesis and Bioactivity of 18(\(R\))-Hydroxyeicosapentaenoic Acid

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Abstract

Resolvins are family of lipid mediators derived from omega-3 polyunsaturated fatty acids, which are generated during the resolution phase of acute inflammation. Resolvin E1 is biosynthesized from eicosapentaenoic acid via 18(\(R\))-hydroxyeicosapentaenoic acid (18R-HEPE) in the Cox-2 and lipoygenase mediated pathway and has proven to exhibit potent anti-inflammatory activity. We report herein the first total chemical synthesis of 18R-HEPE and demonstrate that this compound displays in vivo bioactivity by blocking neutrophil infiltration in a murine model of zymosan-induced peritonitis.

Inflammation plays a central role in the onset and progression of Alzheimer’s disease, atherosclerosis,\(^{1}\) and cancer,\(^{2,3}\) in addition to arthritis and periodontal disease.\(^{4,5}\) Recently, Serhan and co-workers have identified novel oxygenated products that display potent anti-inflammatory activity within resolving inflammatory exudates. Derived from omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA), these compounds have been termed E- and D-series resolvins, respectively.\(^{6–11}\) As an example, resolvin E1 (RvE1) is a metabolite of EPA, which is produced by neutrophils from 18(\(R\))- hydroxy-5(\(Z\)),8(\(Z\)),11(\(Z\)),14(\(Z\)),16(\(E\))-eicosapentaenoic acid (18R-HEPE) through a 5-lipoxygenase-mediated pathway.\(^{12,13}\) RvE1 serves as an on-demand negative feedback switch that dramatically reduces inflammatory responses, including neutrophil and dendritic cell migration and interleukin-12 production.\(^{14}\) Efforts to generate synthetic analogues of resolvins,\(^{15–21}\) as well as other lipid mediators that possess significant anti-inflammatory and pro-resolution properties, have been recently reported. Herein, we report the first total chemical synthesis of 18R-HEPE and characterize its anti-inflammatory activity in vivo.
Our retrosynthetic approach for the synthesis of 18R-HEPE is outlined in Scheme 1.
According to this strategy, the E,Z-conjugated diene system of 18R-HEPE is constructed
using Cu(I)–Pd(0) coupling as the key step. This approach uses the terminal acetylene 7
and the vinyl iodide 13 as requisite building blocks.

The synthesis of 7 began with cross coupling of commercially available 4-chlorobut-2-yn-1-
ol and hex-5-ynoic acid methyl ester 2, in the presence of CuI, which afforded 3 in 74%
yield.22,23 The alcohol 3 was converted to the corresponding bromide 4 in the presence of
CBr₄/PPh₃.24 Subsequent coupling of 4 with 1(trimethylsilyl)-1,4-pentadiyne in the
presence of CuI, NaI, and K₂CO₃ afforded tetrayne 5 in 71% yield. Selective hydrogenation
of 5 with Brown’s P-2 Ni method gave the TMS-protected acetylenic triene 6 in 58% yield
with high isomeric purity.25–28 Liberation of the terminal acetylene then led to the key
intermediate 7 in 91% yield (Scheme 2).

The synthesis of vinyl iodide fragment 13 was achieved from commercially available
bis(trimethylsilylacetylene) 8, which was converted to the corresponding ketone 9 via
treatment with propionyl chloride in the presence of AlCl₃ as an activator.29 The known
Noyori’s asymmetric transfer hydrogenation produced the chiral TMS-acetylenic alcohol
10.30–34 In contrast to published work using 5–10% of the Noyori catalyst (R,R)-
TSDPEN)Ru(p-cymene) Cl₂,32–34 a simple modification of this procedure leads to higher
turnover numbers. Thus, freshly prepared catalyst (0.01%) was added to the degassed 2-
propanol under argon atmosphere, and this was followed by slow addition of TMS-
acetylenic ketone 9 in 2-propanol over 3 h. The reaction mixture was stirred for 12 h, the
solvent evaporated, and the product purified by flash chromatography to give the chiral
alcohol 10 in 81% yield with very high enantioselectivity.35–39 TIPS protection of the free
hydroxyl functionality followed by selective desilylation of the TMS group with potassium
carbonate afforded alkyne 12 in 95% yield. Hydrostannylation of 12 was achieved by
heating with Bu₃SnH in the presence of AIBN as an initiator, followed by exchanging the
stannane for iodine. The key vinyl iodide fragment 13 was obtained in 72% overall yield and
the Cu(I)–Pd(0) coupling reaction with 7 investigated.40–43 Thus, slow addition of the
alkyne 7 (2 equiv) over a 2 h period using a syringe pump to a reaction mixture containing
vinyl iodide 13 (1 equiv), tetrakis-triphenylphosphine palladium (0) (0.05 equiv), and copper
iodide (0.1 equiv) produced the desired coupled product 14 in 88% yield. Under these
reaction conditions, only a minimal amount (<5%) of glacier coupling of alkyne 7 was
observed. The triple bond was selectively reduced by zinc–copper couple to provide the
protected HEPE 15 in 56% yield.44 All other (Z)-selective methods, such as Lindlar
degumination, palladium(0) poisoned with BaSO₄, and Brown’s P-2 Ni protocol failed to
produce 15, leading only to the recovery of the starting material. Deprotection of the TIPS
ether in 15 with excess TBAF followed by alkaline hydrolysis of the methyl ester afforded
18R-HEPE 1 (Scheme 3).

The biological activity of 18R-HEPE 1 was examined using a murine model of peritonitis
(Figure 1). Eight-week-old male C57BL/6 mice were injected intraperitoneally with
zymosan A (1 mg/mL) in sterile saline. 18R-HEPE (2.5 μg) was suspended in 5 μL of
ethanol and dissolved in 95 μL of sterile saline. Test compound or vehicle alone was
administered intraperitoneally at the time of zymosan A injection and 1 h later. Mice were
sacrificed 4 h after zymosan injection, and peritoneal lavage was performed to characterize
the inflammatory cell infiltrate by flow cytometry. 18R-HEPE significantly reduced
neutrophil (PMN) infiltration as compared to vehicle alone (6.06 × 10⁶ ± 0.94 × 10⁶ vs
10.52 × 10⁶ ± 2.20 × 10⁶; n = 8/group, *p < 0.01).

In summary, the total synthesis of 18R-HEPE was achieved in a convergent manner using
terminal acetylene 7 and vinyl iodide 13 fragments. These fragments were coupled using
Cu(I)–Pd-(0) to obtain the E,Z-conjugated diene system of 18R-HEPE. Synthetic 18R-HEPE proved to be biologically active by blocking neutrophil infiltration in a murine peritonitis model.

**EXPERIMENTAL SECTION**

**General Experimental Methods**

All reagents were purchased from a commecial supplier and used as received, unless otherwise indicated. 4-Chloro-2-butyn-1-ol, hex-5-ynoic acid methyl ester, and 1-trimethylsilyl-1,4-pentadiyne were purchased from commercial suppliers. All reactions were carried out under nitrogen with anhydrous solvents, unless otherwise stated. All organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum. $^1$H and $^{13}$C were recorded with a Varian 400 MHz spectrometer with CDCl$_3$ solvent. High resolution ESI-mass spectra were recorded by the Emory University Mass Spectrometry Center using a JEOL JMS-SX102 instrument.

**Synthesis of 10-Hydroxydeca-5,8-diynoic Acid Methyl Ester (3)**

4-Chloro-2-butyn-1-ol (3.0 g, 28.7 mmol) and hex-5-ynoic acid methyl ester (3.62 g, 28.7 mmol) were added to a suspension of CuI (11.0 g, 57.4 mmol), NaI (8.61 g, 57.4 mmol), and K$_2$CO$_3$ (5.94 g, 43 mmol) in 10 mL of anhydrous DMF under Ar atmosphere. The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH$_4$Cl, and the lipophilic products were extracted with Et$_2$O. The combined organic extracts were washed with water and brine and dried with Na$_2$SO$_4$. After rotary evaporation of solvents, the residue was chromatographed on silica gel to afford alcohol 3 (4.1 g, 74% yield) as colorless oil: $R_f = 0.25$ (30% EtOAc in hexanes); IR (neat) 3405, 2245, 1730, 1025 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 4.18 (t, $J = 2.4$ Hz, 2H), 3.61 (s, 3H), 3.11 (p, $J = 2.0$ Hz, 2H), 2.37 (t, $J = 7.2$ Hz, 2H), 2.16 (tt, $J = 7.0$ Hz, $J = 2.0$ Hz, 2H), 1.74 (p, $J = 7.2$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 173.9, 80.4, 79.8, 78.8, 74.7, 51.8, 51.2, 33.0, 23.9, 18.3, 9.9; ESI-HRMS calcd for C$_{11}$H$_{14}$O$_3$ [M + Na] 217.0835, obsd 217.08346.

**Synthesis of 10-Bromodeca-5,8-diynoic Acid Methyl Ester (4)**

A solution of PPh$_3$ (6.09 g, 23.2 mmol) in dry CH$_2$Cl$_2$ (15 mL) was added dropwise to a stirred solution of alcohol 3 (4.1 g, 21.1 mmol) and CBr$_4$ (7.45 g, 23.2 mmol) in 15 mL of dry CH$_2$Cl$_2$ at 0 °C. Then the mixture was stirred for another 1.5 h at 0 °C. The solvent was evaporated, and the residue was diluted with Et$_2$O and filtered through a short pad of Celite. The filtrate was concentrated and then chromatographed on silica gel to provide bromide 4 (5.33 g, 85% yield) as a yellow oil: $R_f = 0.7$ (10% EtOAc in hexanes); IR (neat) 2948, 2920, 2845, 2250, 1730, 1305, 1210 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 3.88 (t, $J = 2.4$ Hz, 2H), 3.65 (s, 3H), 3.18 (p, $J = 2.0$ Hz, 2H), 2.40 (t, $J = 7.2$ Hz, 2H), 2.22 (tt, $J = 7.0$ Hz, $J = 2.0$ Hz, 2H), 1.78 (p, $J = 7.2$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 173.9, 80.4, 79.8, 78.8, 74.7, 51.8, 51.2, 33.0, 23.9, 18.3, 9.9; ESI-HRMS calcd for C$_{11}$H$_{13}$O$_2$Br [M + H] 257.01717, obsd 257.01685.

**Synthesis of 15-(Trimethylsilyl)pentadeca-5,8,11,14-tetraynoic Acid Methyl Ester (5)**

Bromide 4 (1.4 g, 5.4 mmol) and 1-trimethylsilyl-1,4-pentadiyne (0.96 g, 7.1 mmol) were added to a suspension of CuI (1.1 g, 6.0 mmol), NaI (0.89 g, 6.0 mmol), and K$_2$CO$_3$ (0.98 g, 7.1 mmol) in 5 mL of anhydrous DMF under Ar atmosphere. The mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH$_4$Cl, and the lipophilic products were extracted with EtOAc. The combined organic extracts were washed with water and brine and dried with Na$_2$SO$_4$. After rotary evaporation of solvents, the residue was chromatographed on silica gel to afford 5 (1.2 g, 71% yield) as an oil: $R_f = 0.4$ (12% EtOAc in hexanes); IR (neat) 2960, 2922, 2855, 2190, 1735, 1250.

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Synthesis of (5Z,8Z,11Z)-15-(Trimethylsilyl)pentadeca-5,8,11-trien-14-ynoic Acid Methyl Ester (6)

Ni(OAc)₂ · 4H₂O (1.3 g, 5.1 mmol) was dissolved in 20 mL of 95% ethanol and placed under a balloon of H₂ atmosphere. NaBH₄ (194 mg, 5.1 mmol) was added to this solution, followed after 20 min by ethylenediamine (1.2 g, 20.4 mmol). The diyne 5 (0.8 g, 2.56 mmol) dissolved in 5 mL of absolute ethanol was added, and the reaction was stirred under H₂ atmosphere at room temperature for an additional 4 h. After 4 h, the reaction mixture was filtered through a pad of Celite, and the ethanol was removed in vacuo. The reaction mixture was redissolved in EtOAc (50 mL) and washed with saturated NH₄Cl (30 mL) followed by brine (30 mL). The EtOAc layer was dried, concentrated, and purified by chromatography over silica gel to afford the title compound 6 as colorless oil (475 mg, 58% yield):

**Rf** = 0.75 (12% EtOAc in hexanes); IR (neat) 2964, 2904, 2150, 1737, 1680, 1550, 1459, 1415, 1353, 1262, 1198 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ = 3.65 (s, 3H), 3.15 (t, J = 2.4 Hz, 2H), 3.10 (dt, J = 2.4 Hz, J = 1.6 Hz, 2H), 3.07 (p, J = 2.4 Hz, 2H), 2.39 (t, J = 7.6 Hz, 2H), 2.18 (tt, J = 7.0 Hz, J = 2.0 Hz, 2H), 1.74 (p, J = 7.2 Hz, 2H), 0.12 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ = 173.8, 99.6, 85.3, 80.2, 80.1, 79.7, 75.2, 74.8, 74.1, 51.7, 33.0, 23.9, 18.3, 11.1, 10.4, 9.9, 0.1 (3C); ESI-HRMS calcd for C₁₉H₂₄O₂Si [M + H] 313.16184, obsd 313.16189.

Synthesis of (5Z,8Z,11Z)-Pentadeca-5,8,11-trien-14-ynoic Acid Methyl Ester (7)

Cesium fluoride (154 mg, 1.01 mmol) was added to the alkyne 6 (160 mg, 0.51 mmol) dissolved in DMF (2 mL) and stirred at room temperature for 3 h. After 3 h, the reaction mixture was diluted with EtOAc (10 mL) and NH₄Cl (10 mL) followed by brine (10 mL). The aqueous layer was back-extracted with EtOAc (10 mL), and the combined organic layers were dried, concentrated, and purified by chromatography over silica gel to afford the terminal alkyne 7 as a colorless oil (121 mg, 91% yield):

**Rf** = 0.70 (12% EtOAc in hexane); IR 3300, 2990, 2958, 2920, 2840, 2120, 1730, 1640, 1450, 1240, 910 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ = 5.45–5.44 (m, 2H), 5.36–5.32 (m, 4H), 3.64 (s, 3H), 2.99 (t, J = 2.4 Hz, 2H), 2.79 (dt, J = 2.4 Hz, J = 1.6 Hz, 2H), 2.76 (p, J = 2.4 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 2.07 (tt, J = 7.0 Hz, J = 2.0 Hz, 2H), 1.68 (p, J = 7.2 Hz, 2H), 0.13 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ = 174.2, 129.9, 129.2, 128.9, 128.8, 124.5, 105.2, 84.5, 51.7, 33.8, 27.2, 28.7, 25.8, 24.9, 18.8, 0.3 (3C); ESI-HRMS calcd for C₁₉H₂₃O₃Si [M – H] 317.19289, obsd 317.19337.

Synthesis of 1-(Trimethylsilyl)-1-pentyn-3-one (9)

Bis-(trimethylsilylacetylene) (3.0 g, 17.6 mmol) and propionyl chloride (1.68 g, 17.6 mmol) were dissolved in dichloromethane (60 mL) and the mixture cooled to 0 °C. To this solution was added aluminum chloride (2.3 g, 17.6 mmol), and the reaction mixture was stirred for 3 h. After 3 h, the mixture was poured in to 3 N HCl (50 mL) and extracted with Et₂O (3 × 30 mL). The combined organic layer was dried, concentrated and purified by chromatography over silica gel (1% EtOAC/hexane) to afford the title compound 9 (2.41 g, 89% yield) as a colorless oil:

**Rf** = 0.8 (3% EtOAc in hexanes); IR (neat) 2964, 2904, 2150, 1737, 1680, 1459, 1415, 1353, 1262, 1198 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ = 2.53 (dd, J = 6.4 Hz, J = 12.0 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H), 0.18 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ = 188.5, 101.9, 97.7, 38.7, 8.1, –0.6 (3C); ESI-HRMS calcd for C₆H₁₄OSi [M + H] 155.08865, observed 155.08865.
Synthesis of 1-Trimethylsilyl-1-pentyn-3(\(E\))-Iodo-3(\(R\))-Triisopropylsiloxylpentene (13)

Alkyn e12 (200 mg, 0.83 mmol) was taken in a round-bottom flask to which AIBN (14 mg, 0.083 mmol) and tributyltin hydride (360 mg, 1.24 mmol) were added and heated to 130 °C for 3 h. After 3 h, the reaction was allowed to cool down to room temperature and cooled to 0 °C. To this was added a solution of I\(_2\) (630 mg, 2.49 mmol) dissolved in CH\(_2\)Cl\(_2\) (5 mL). The reaction was slowly warmed to room temperature and stirred for additional 12 h. After 12 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (30 mL) and washed with saturated aq Na\(_2\)S\(_2\)O\(_3\) (10 mL) and saturated aq NH\(_4\)Cl (10 mL). The CH\(_2\)Cl\(_2\) layer was then dried, concentrated, and purified by chromatography over silica gel (1% EtOAc in hexane) to
Synthesis of 18(R)-(5Z,8Z,11Z,16E)-Triisopropylsilyloxy-5,8,11-trien-14-ynoic Acid Methyl Ester (14)

Piperidine (56 μL, 0.57 mmol) and cuprous iodide (6 mg, 0.028 mmol) were added at room temperature to a solution of vinyl iodide 13 (105 mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium (17 mg, 0.014 mmol). To this solution was added dieneyne 7 (140 mg, 0.57 mmol) in benzene (2 mL) dropwise over a period of 2 h. The mixture was stirred for an additional 6 h, diluted with EtOAc (10 mL), and washed with a saturated solution of NH₄Cl (10 mL) and brine (10 mL). The EtOAc layer was collected, dried over Na₂SO₄, and purified by chromatography over silica gel (eluent: 8% EtOAc in hexanes) to afford the protected HEPE 14 (243 mg, 88% yield) as a colorless oil; IR (neat) 1733, 1670, 1665, 735, 710 cm⁻¹; [α] D² = 6.0 (c 0.6, CHCl₃); 1H NMR (CDCl₃, 400 MHz) δ = 6.0 (dd, J = 6.4 Hz, J = 15.2 Hz, 1H), 6.03–5.96 (m, 1H), 5.62 (dd, J = 6.4 Hz, J = 14.8 Hz, 1H), 5.45 - 5.30 (m, 7H), 4.21 (q, J = 6.0 Hz, 1H), 3.65 (s, 3H), 3.07 (dd, J = 2.0 Hz, J = 6.4 Hz, 1H), 2.91 (t, J = 2.4 Hz, 1H), 2.80 (t, J = 5.6 Hz, 2H), 2.77 (t, J = 5.2 Hz, 2H), 2.28 (t, J = 7.6 Hz, 2H), 2.08 (dd, J = 6.8 Hz, J = 13.6 Hz, 2H), 1.69 (dt, J = 15.6 Hz, J = 14.8 Hz, 2H), 1.57 (m, 2H), 1.05 (m, 2H), 0.82 (t, J = 7.6 Hz, 3H); 13CNMR (CDCl₃, 100 MHz) δ = 175.0, 145.4, 128.9, 128.8, 129.7, 127.8, 124.8, 109.3, 88.1, 78.8, 73.9, 51.8, 33.6, 31.0, 29.5, 26.7, 25.8, 25.0, 24.9, 24.8, 18.3 (6C), 12.5 (3C), 8.7; ESI-HRMS calcd for C₃₀H₅₀O₃Si [M + H] 487.36020, obsd 487.36043.

Synthesis of 18(R)-(5Z,8Z,11Z,14Z,16E)-Triisopropylsilyloxyeicosapentaenoic Acid Methyl Ester (15)

To a solution of compound 14 (22 mg, 0.041 mmol) in MeOH/H₂O (1:1, 20 mL) was added activated zinc powder (1 g). The reaction mixture was warmed to 40 °C and stirred for 12 h, after which the mixture was filtered on a pad of Celite. Methanol was removed under reduced pressure, and the reaction mixture was diluted with EtOAc (15 mL) and extracted. The EtOAc layer was dried, concentrated, and purified by chromatography over silica gel (8% EtOAc in hexanes) to afford the protected HEPE 15 (12 mg, 56% yield) as a colorless oil; IR (neat) 1733, 1670, 1665, 735, 710 cm⁻¹; [α] D² = −11.2 (c 0.5, CHCl₃); 1H NMR (CDCl₃, 400 MHz) δ = 6.43 (dd, J = 4.0 Hz, J = 15.2 Hz, 1H), 6.03–5.96 (m, 1H), 5.62 (dd, J = 6.4 Hz, J = 14.8 Hz, 1H), 5.45 - 5.30 (m, 7H), 4.21 (q, J = 6.0 Hz, 1H), 3.65 (s, 3H), 3.07 (dd, J = 2.0 Hz, J = 6.4 Hz, 1H), 2.91 (t, J = 2.4 Hz, 1H), 2.80 (t, J = 5.6 Hz, 2H), 2.77 (t, J = 5.2 Hz, 2H), 2.28 (t, J = 7.6 Hz, 2H), 2.08 (dd, J = 6.8 Hz, J = 13.6 Hz, 2H), 1.69 (dt, J = 15.6 Hz, J = 14.8 Hz, 2H), 1.57 (m, 2H), 1.02 (m, 21H), 0.82 (t, J = 7.6 Hz, 3H); 13CNMR (CDCl₃, 100 MHz) δ = 174.1, 137.4, 129.2, 129.1, 128.8, 128.7, 126.6, 126.5, 128.2, 128.1, 124.8, 73.9, 51.8, 33.6, 31.4, 31.0, 26.7, 25.9, 24.9, 24.8, 18.3 (6C), 12.5 (3C), 8.7; ESI-HRMS calcd for C₃₀H₅₀O₃Si [M + H] 489.37640, obsd 489.37378.

Synthesis of 18(R)-Hydroxy-(5Z,8Z,11Z,14Z,16E)-eicosapentaenoic Acid (1)

Compound 15 (10 mg, 0.02 mmol) was dissolved in THF (1 mL) to which a 1 M TBAF in THF solution (0.1 mL, 0.1 mmol) was added under Ar atmosphere and stirred at room temperature for 10 h. The reaction was monitored by TLC, and after 10 h, the reaction was diluted with EtOAc (5 mL) and washed with saturated aq NH₄Cl (2 × 5 mL). The organic phase was extracted and concentrated under reduced pressure. The resulting crude was...
subsequently dissolved in THF/H$_2$O (1:1, 2 mL), and the reaction was allowed to stir at room temperature for 5 h. After 5 h, the organic phase was removed under reduced pressure and carefully acidified to pH 5 using 1 N HCl. The aqueous layer was extracted with EtOAc (3 × 5 mL), dried, concentrated, and purified by chromatography over silica gel (40% EtOAc in hexanes) to afford I (4.6 mg, 71% yield) as colorless oil: $R_f$ = 0.3 (40% EtOAc in hexanes); IR (neat) 3510, 3475, 1730, 1665, 735, 710 cm$^{-1}$; $[\alpha]_{D}^{19}$ −17.9 (c 0.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 6.51 (dd, $J$ = 4.0 Hz, $J$ = 15.2 Hz, 1H), 5.99 (t, $J$ = 10.8 Hz, 1H), 5.63 (dd, $J$ = 6.4 Hz, $J$ = 14.8 Hz, 1H), 5.39–5.33 (m, 7H), 4.09 (q, $J$ = 5.6 Hz, 1H), 2.95 (t, $J$ = 2.4 Hz, 2H), 2.83 (t, $J$ = 5.6 Hz, 2H), 2.78 (t, $J$ = 5.2 Hz, 2H), 2.30 (t, $J$ = 7.6 Hz, 2H), 2.08 (dd, $J$ = 6.8 Hz, $J$ = 13.6 Hz, 2H), 1.68 (dt, $J$ = 15.6 Hz, $J$ = 14.8 Hz, 2H), 1.57 (m, 2H), 0.87 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 177.9, 136.0, 130.4, 129.2, 129.0, 128.4, 128.8, 128.4, 128.1, 127.8, 125.7, 74.2, 33.2, 30.3, 30.0, 26.6, 26.3, 25.9, 24.7, 9.9; ESI-HRMS calcd for C$_{20}$H$_{30}$O$_{3}$ [M − H]$^-$, expected 317.21222, obsd 317.21244.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**References**


Figure 1.
Synthetic 18R-HEPE reduces neutrophil infiltration in a murine model of zymosan-induced peritonitis (*p < 0.01).
Scheme 1.
Retrosynthetic Analysis for 18R-HEPE

\[ 18R-\text{HEPE (1)} \rightarrow \text{7} + \text{13} \]
Scheme 2.
Synthesis of Alkyne Fragment 7
Scheme 3.
Synthesis of 18R-HEPE