**Synthesis of Resolvin E3, a Proresolving Lipid Mediator, and Its Deoxy Derivatives: Identification of 18-Deoxy-resolvin E3 as a Potent Anti-inflammatory Agent**

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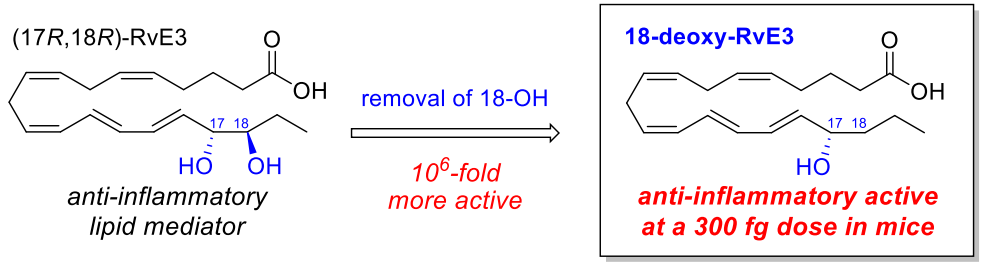



**ABSTRACT:** We synthesized RvE3 and its deoxy derivatives, 17-deoxy-RvE3 and 18-deoxy-RvE3, by a common route via Sonogashira coupling as a key step. Evaluation of their anti-inflammatory activities revealed that 18-deoxy-RvE3 was remarkably more potent than parent RvE3 and was significantly active at a 300 fg dose in mice, additionally 17-deoxy-RvE3 was significantly less potent than the parent RvE3. For the first time, we found that the 17-hydroxy group of RvE3 is very important for anti-inflammatory activity.

Polyunsaturated fatty acids act as lipid mediators that regulate various physiological functions. Leukotrienes and prostaglandins, which are metabolites of arachidonic acid, a ω-6 fatty acid, are known to induce inflammation.[1] On the other hand, in recent years, the outstanding contributions of Serhan and co-workers have demonstrated that resolvins (Rvs) produced from ω-3 fatty acids suppress neutrophil migration and promote macrophage phagocytosis to resolve inflammation.[1] Because of their highly potent anti-inflammatory effects, Rvs are attracting attention as prototypes for new anti-inflammatory drugs. Rvs are classified into E-, D-, and T-series according to their parent ω-3 fatty acids: EPA, DHA, and docosapentaenoic acid (DPA), respectively.[1,2] Although Rvs exhibit exciting physiological activities, only a few structure-activity relationship (SAR) studies have been performed. We are engaged in synthetic studies of the resolvin E-series (Figure 1) and their derivatives to develop drug leads and biological tools for investigating the signaling pathways related to Rvs. For example, we recently designed and synthesized cyclopropane derivatives of RvE2 that were successfully identified to be stable equivalents of RvE2.[3]

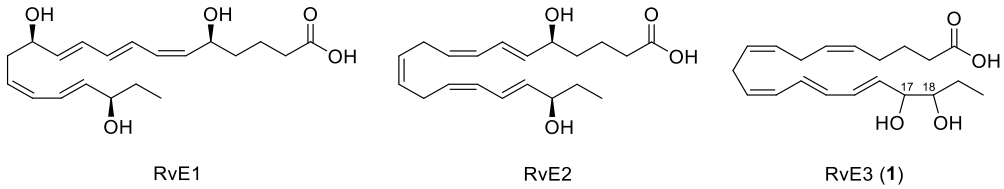



**Figure 1.** Chemical structures of resolvin E-series.

In 2012, Arita and co-workers found remarkably potent anti-inflammatory active metabolites, two isomers of 17,18-dihydroxyeicosapentaenoic acids (17,18-diHEPE), which are named resolvin E3 (RvE3, **1**), derived from EPA via the 12/15-lipoxygenase pathway in eosinophils.[4a] Although the stereochemistry of C17 and C18 was not determined at that time, the anti-inflammatory activity of RvE3s was $10^4$-fold more potent than that of dexamethasone, a clinically effective steroidal anti-inflammatory drug, a mouse model of inflammation.[4a] Comparison of the natural RvE3s with the four stereoisomers, i.e., 17*S*,18*S*-, 17*R*,18*S*-, 17*S*,18*R*-, and 17*R*,18*R*-diHEPE, synthesized by Inoue and co-workers,[4b] confirmed that the natural RvE3s were 17*R*,18*S*- and 17*R*,18*R*-isomers (Figure 2).[4c] Arita and Inoue et al. also reported that unnatural 17*S*,18*R*-diHEPE exhibited a potent anti-inflammatory effect equivalent to that of natural RvE3 in vivo.[4c] These findings suggest that the two hydroxy groups of RvE3 may be key substituents for the potent anti-inflammatory effect.

In this study, we designed 17-deoxy-RvE3 (**1b**) and 18-deoxy-RvE3 (**1c**) based on (17*R*,18*R*)-RvE3 (**1a**), which exhibited the most potent anti-inflammatory activity among the four isomers of RvE3 synthesized by Inoue and co-workers,[4b] and planned to synthesize **1b** and **1c** to confirm the importance of the hydroxy groups at C17 and C18 for the anti-inflammatory effect of RvE3 (Figure 2). Before the synthesis of **1b** and **1c**, we tried to establish a total synthetic route of

(17*R*,18*R*)-RvE3 (**1a**),[5] which could be effectively applied to the synthesis of the deoxy derivatives **1b** and **1c**.

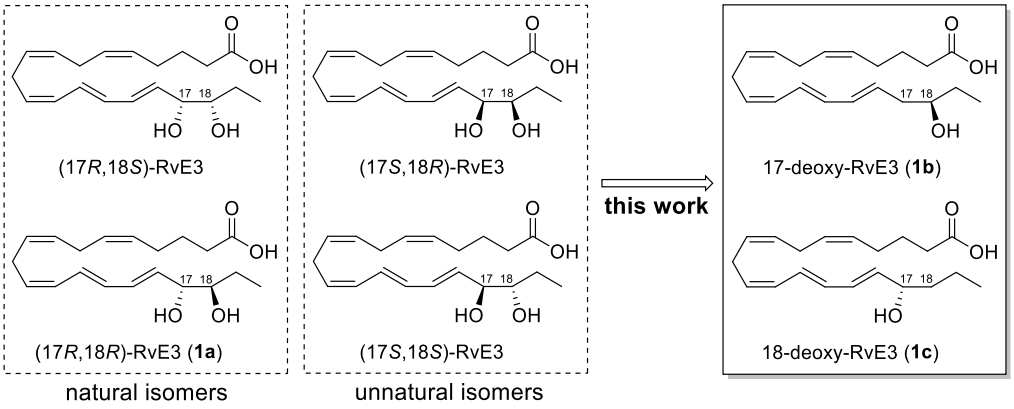
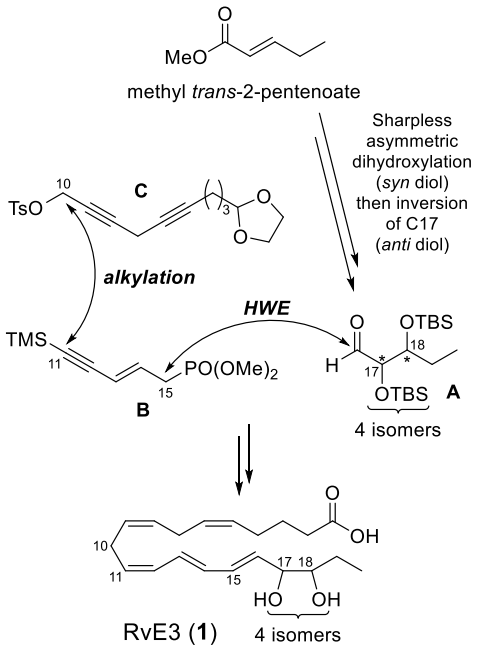



**Figure 2.** Design of deoxy-RvE3s

Inoue et al. synthesized all predicted stereoisomeric structures of RvE3 to determine the

absolute configuration of RvE3 (Scheme 1). Two *syn* diol derivative **A** were prepared by using Sharpless asymmetric dihydroxylation with methyl *trans*-2-pentenoate as a starting material. The other two *anti* diol derivatives **A** were prepared by steric inversion of the carboxy-α position of *syn* diol derivatives. The four intermediates **A**, **B**, and **C** were derivatized into the corresponding RvE3 isomers using Horner-Wadsworth-Emmons (HWE) reaction and alkylation as key reactions. This synthetic route was very effective to confirm the stereochemistry of the natural RvE3.

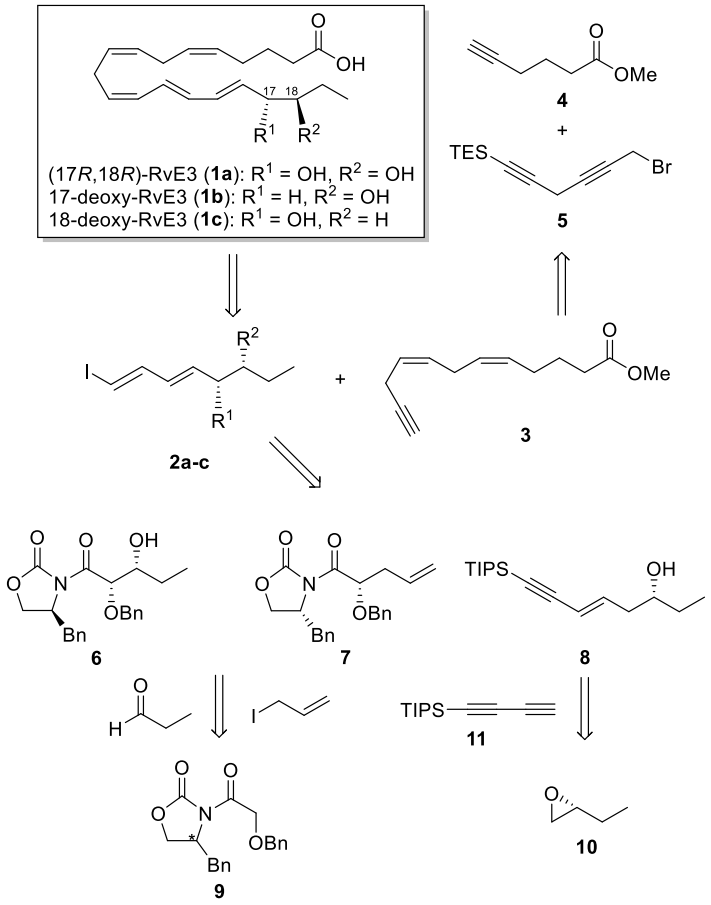
**Scheme 1. Synthesis of four RvE3 isomers by Inoue**




We planned to develop a new synthetic method capable of providing both of RvE3 and the

deoxy derivatives. Scheme 2 illustrates the retrosynthetic analysis of (17*R*,18*R*)-RvE3 (**1a**), 17-deoxy-RvE3 (**1b**) and 18-deoxy-RvE3 (**1c**) by a common route via intermediates **2a-c** and **3**. The three target compounds **1a-c** would be synthesized via Sonogashira coupling with dienyl iodide **2a-c** and alkyne **3**. We envisioned that alkylation of alkyne **4** with diyne **5** would give **3**, and **2a-c** would be obtained from **6**, **8**, and **7**, respectively. Known compound **9**[6] would be converted into **6** and **7** via its diastereoselective aldol reaction or alkylation, respectively. Enyne **8** would be obtained from optically active **10** via epoxy ring-opening substitution with diyne **11**. In this synthetic route, if the key intermediate **2** was prepared, RvE3 and deoxy-RvE3s would be synthesized in three more steps. Thus, this synthetic route is a highly convergent one.

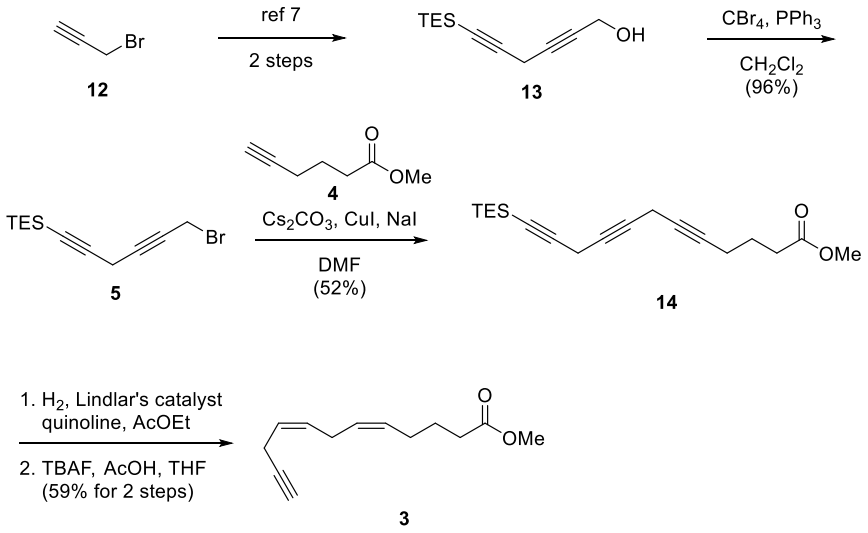
**Scheme 2. Retrosynthetic analysis of 1a-c**




First, the common intermediate alkyne **3** was prepared from 3-bromo-1-propyne (**12**) as

shown in Scheme 3. After converting **12** to diyne **13** in known two-step reactions,[7] bromine was substituted for the hydroxy group of **13** to give bromide **5**. Alkylation of **5** with methyl 5-hexynoate (**4**) gave triyne **14**. Although partial reduction using $Ni(OAc)_2$, $NaBH_4$ and ethylenediamine under hydrogen atmosphere produced not only the desired compound but also its over-reduction products, hydrogenation of **14** using Lindlar's catalyst regioselectively provided the partial reduction product and subsequent removal of the silyl group under mild basic conditions successfully afforded the desired alkyne **3**.[8]

**Scheme 3. Preparation of alkyne 3**

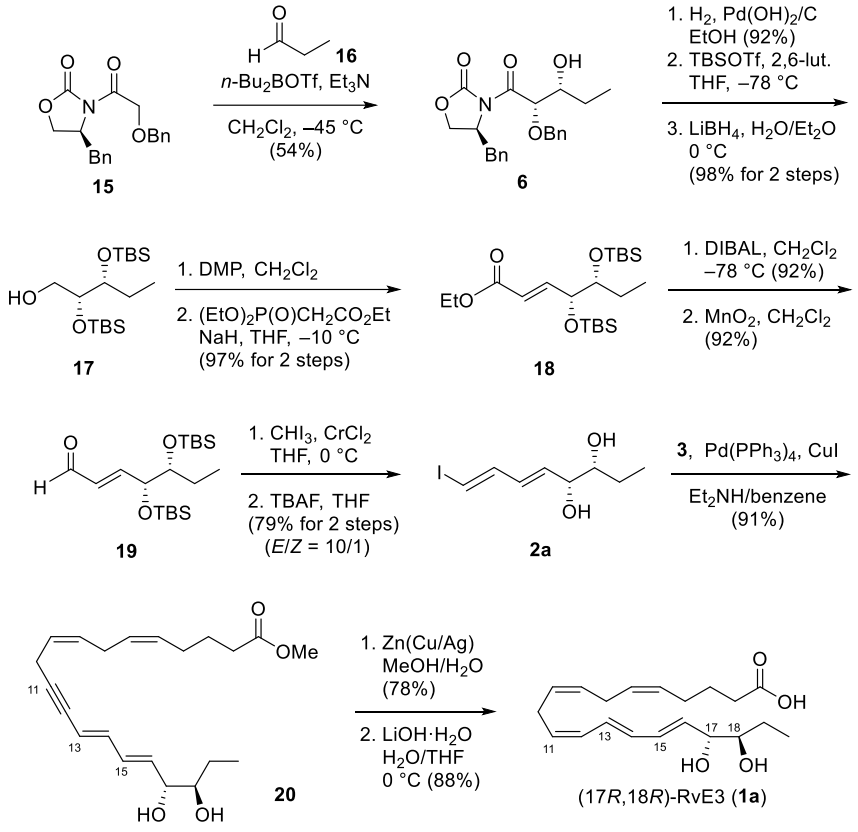



Scheme 4 shows the synthesis of the natural RvE3 (17*R*,18*R*-diHEPE, **1a**). Evans aldol reaction with known oxazolidinone **15**[6] and propanal (**16**) was carried out in the presence of *n*-$Bu_2BOTf$ and $Et_2NH$ to furnish *syn*-aldol adduct **6** in high stereoselectivity (*syn*:*anti* = 98:2).[9] Manipulation of the protecting groups of **6** and the subsequent reductive removal of the oxazolidinone auxiliary gave primary alcohol **17**.[10] Dess–Martin oxidation of **17**[11] followed by Horner-Wadsworth-Emmons reaction afforded ester **18**. Reduction of the ester group of **18** with DIBAL and subsequent oxidation using $MnO_2$ of the resultant allyl alcohol provided enal **19** in excellent yield. Although Takai reaction[12] of **19** with excess $CHI_3$ (3 eq.) and $CrCl_2$ (12 eq.) and subsequent treatment with TBAF afforded diol **2a** in 52-54% yield in poor stereoselectivity (*E*:*Z* = 1.4-2.5 : 1), both of the yield and selectivity of this reaction were improved to 79% and *E*:*Z* = 10 : 1 by using much excess $CHI_3$ (7 eq.) and $CrCl_2$ (17 eq.). Sonogashira coupling of ester **3** and **2a** with $Pd(PPh_3)_4$, CuI, and $Et_2NH$ proceeded successfully to give tetraene **20** in 91% yield. Partial reduction of the alkyne moiety of **20** was carried out with Zn(Cu/Ag)[13] in dark conditions to provide the desired conjugated (11*Z*,13*E*,15*E*)-triene as a major diastereomer although a trace of the undesired (11*E*,13*E*,15*E*)-triene was produced.

Finally, **1a** was synthesized by basic hydrolysis of the methyl ester moiety of the (11*Z*,13*E*,15*E*)-triene.[14] The spectra data of synthesized **1a** were in accordance with those previously reported by Inoue et al.[4b] The overall yield of the synthesis of RvE3 by Inoue et al. was 3.8% over 12 steps, and our overall yield from **15** was improved to 19.7% over 13 steps. However, it should be considered that Inoue's synthesis was carried out for the purpose of structure determination and our synthesis was for derivative preparation.

Thus, we established a synthetic route of (17*R*,18*R*)-RvE3 (**1a**), which could be applicable to the synthesis of the desired deoxy derivatives of RvE3.

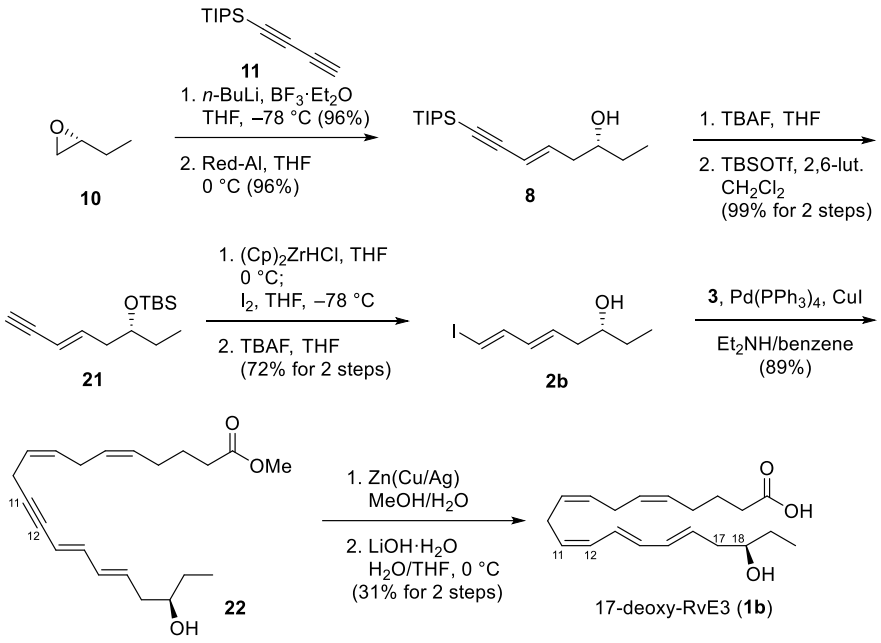
**Scheme 4. Synthesis of (17*R*,18*R*)-RvE3 (1a)**




The synthesis of 17-deoxy-RvE3 (**1b**) was started from (*R*)-1,2-epoxybutane (**10**) (Scheme

5). A regioselective epoxide ring-opening reaction of **10** by a nucleophilic attack with diyne **11** using BuLi and $BF_3 \cdot Et_2O$[15] and subsequent regio- and stereoselective partial reduction with Red-Al[16] gave homoallyl alcohol **8** in excellent yield. Manipulation of the protecting groups of **8** converted it to terminal alkyne **21**. Dienyl iodide **2b** was obtained by stereoselective hydroiodination of **21** with Schwartz reagent,[17] followed by removal of the TBS group. According to the synthetic route for (17*R*,18*R*)-RvE3 (**1a**) described above, the synthesis of 17-deoxy-RvE3 (**1b**) was accomplished by Sonogashira coupling with **2b** and **3** producing **22**, followed by its partial reduction and hydrolysis of the terminal ester. Unlike the cases of RvE3 and 18-deoxy-RvE3, *Z*-isomer at C11-C12 was produced by partial reduction of **22**. However, fortunately it was possible to separate the isomer mixture in the final stage to provide the desired 17-deoxy-RvE3 (**1b**) in a pure form.

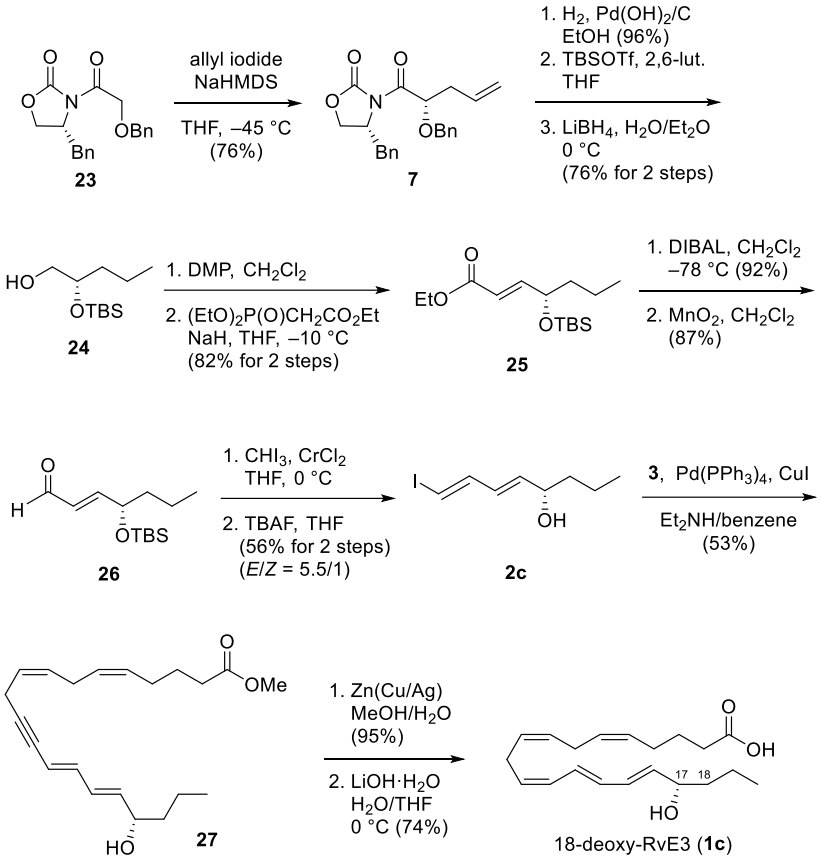
**Scheme 5. Synthesis of 17-deoxy-RvE3 (1b)**




The synthesis of 18-deoxy-RvE3 (**1c**) commenced with known compound **23** (Scheme 6).

Compound **7** was obtained from **23** by stereoselective allylation,[18] and 18-deoxy-RvE3 (**1c**) was synthesized from **7** according to the established synthetic route for (17*R*,18*R*)-RvE3 (**1a**).

**Scheme 6. Synthesis of 18-deoxy-RvE3 (1c)**




We evaluated the anti-inflammatory activity of 17-deoxy-RvE3 (**1b**) and 18-deoxy-RvE3

(**1c**) in comparison with that of parent (17*R*,18*R*)-RvE3 (**1a**) in vivo using a mouse model of bacteria-induced peritonitis,[19] and the results are summarized in Figure 3. Intraperitoneal injection of heat-killed *Propionibacterium acnes* (*P. acnes*), a Gram-positive bacterium, induced acute inflammation of the peritoneum, which resulted in a definite increase in the number of polymorphonuclear leukocytes (PMNs) in peritoneal exudates collected after 24 h. Intraperitoneal administration of (17*R*,18*R*)-RvE3 (**1a**) at a dose of 300 ng 12 h after injecting the heat-killed *P. acnes* significantly suppressed the induced inflammation (suppressed the increase in PMNs by 33%) at 24 h. On the other hand, administering 300 ng of 17-deoxy-RvE3 (**1b**) did not significantly decrease the PMN number. However, 18-deoxy-RvE3 (**1c**) exhibited a significant anti-inflammatory effect, not only at a 300 ng dose (approximately 50% suppression) but also at a 300 pg dose (approximately 50% suppression) and even at a 300 fg dose (more than 30% suppression), which corresponds to a $1/10^6$ dose of the active dose of parent (17*R*,18*R*)-RevE3 (**1a**) at 300 ng in this evaluation system.

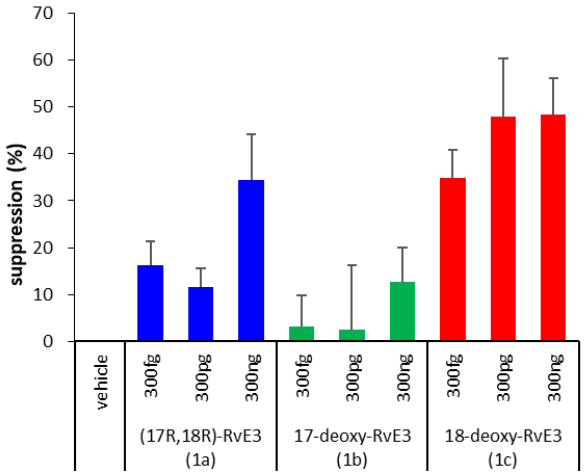



**Figure 3.** Anti-inflammatory activity of (17*R*,18*R*)-RvE3 (**1a**), 17-deoxy-RvE3 (**1b**), and 18-deoxy-RvE3 (**1c**). The numbers of polymorphonuclear leukocytes (PMNs) in peritoneal exudates were counted by flow cytometry and indicated. Results are the mean plusminus s.d. (n = 3–5).

In conclusion, we designed 17-deoxy-RvE3 (**1b**) and 18-deoxy-RvE3 (**1c**) to clarify the importance of the hydroxy groups at C17 and C18 for the anti-inflammatory effects of RvE3s. First,

we established a synthetic route for the natural (17*R*,18*R*)-RvE3 (**1a**) that was applicable to the synthesis of the two deoxy derivatives, was established. The synthesis of 17-deoxy-RvE3 and 18-deoxy-RvE3 was subsequently achieved. Evaluation of the anti-inflammatory activity revealed that 18-deoxy-RvE3 (**1c**) had remarkably more potent activity than the parent RvE3 (**1a**), while 17-deoxy-RvE3 (**1b**) was much less active in the evaluation system, suggesting that the hydroxy group at C17 of RvE3s is essential for the anti-inflammatory activity.[20] To the best of our knowledge, this is the first report of a deoxy-Rv with more potent anti-inflammatory activity than the parent natural Rv. The results may provide insight for simplification of molecular structures of polyunsaturated lipid mediators, which can make the synthesis easily.

## EXPERIMENTAL SECTION

NMR spectra were measured on JEOL ECX400P (400 MHz), JEOL ECS400 (400 MHz) and JEOL ECA500 (500 MHz). Chemical shifts were reported in the δ scale relative to tetramethylsilane (TMS) as 0.00 ppm for $^{1}$H ($CDCl_3$) and residual $CHCl_3$ (7.26 ppm for $^{1}$H and 77.00 ppm for $^{13}$C), $CH_3OH$ (3.30 ppm for $^{1}$H and 49.00 ppm for $^{13}$C) as internal reference. Optical rotations were measured on JASCO DIP-1030. Mass spectra (MS) were measured on JEOL JMS-HX110, JEOL JMS-T100GCV, JEOL JMS-T100LCP, JEOL JMS-700TZ. Silica gel column chromatography and flash column chromatography was carried out with Wakogel 60N (Wako Pure Chemical Industries, Ltd., neutral, 63-212 μm) and silica gel (Kishida Chemical Co., Ltd., neutral, 32-63 μm), respectively. Elemental analysis (EA) was measured on J-SCIENCE LAB Co. MICRO CORDER JM10. All reactions were carried out under an argon atmosphere using flame-dried or oven-dried glassware, unless otherwise noted, and monitored with analytical TLC (Merck Ltd., TLC Silica gel 60 $F_{254}$). HPLC analyses were carried using JASCO PU-2087 Plus (pump), JASCO PU-2089 Plus (pump), JASCO CO-2065 Plus (column oven), JASCO MD-2018 Plus (detector), JASCO LC-Net II/ADC (systemcontroller) with Mightysil RP-18 GP 250-4.6 (5 μm, KANTO CHEMICAL CO., INC.; column for determination of purity) and Mightysil RP-18 GP 250-20 (5 μm, KANTO CHEMICAL CO., INC.; column for purification).

**(6-Bromohexa-1,4-diyn-1-yl)triethylsilane (5).** To a stirred solution of **13** (2.1 g, 10.0 mmol) in $CH_2Cl_2$ (50 mL) was added $PPh_3$ (3.93 g, 15.0 mmol) and $CBr_4$ (4.3 g, 13.0 mmol) at 0 °C under dark. The mixture was stirred at the same temperature for 2 h, quenched by addition of $Na_2S_2O_3$ aq and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:100) to give **5** (2.6 g, 9.6 mmol, 96%) as a pale yellow oil. TLC $R_f$ = 0.5 (AcOEt-hexane = 1:100); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.92 (t, *J* = 2.4 Hz, 2H), 3.30 (t, *J* = 2.4 Hz, 2H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.59

(q, $J$ = 8.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 99.8, 83.1, 81.1, 75.6, 14.8, 11.2, 7.4, 4.2; LRMS (EI) *m/z* 270 ($M^+$); HRMS (EI) calcd for $C_{12}H_{19}BrSi$: 270.0440 ($M^+$), found: 270.0444.

**Methyl 12-(triethylsilyl)dodeca-5,8,11-triynoate (14).** To a stirred solution of CuI (1.20 g, 6.29 mmol), $Cs_2CO_3$ (1.88 g, 5.76 mmol) and NaI (0.94 g, 6.29 mmol) in DMF (10 mL) was added **4** (0.73 g, 5.76 mmol) in DMF (9 mL) at room temperature. The mixture was stirred at the same temperature for 25 min and added the solution of **5** (1.42 g, 5.24 mmol) in DMF (7 mL). The reaction mixture was stirred overnight. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:30) to give **14** (0.86 g, 2.73 mmol, 52%) as a yellow oil. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:10); $^{1}H$ NMR (400MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.22 (t, $J$ = 2.0 Hz, 2H), 3.14 (tt, $J$ = 2.4, 2.0 Hz, 2H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.24 (tt, $J$ = 6.8, 2.4 Hz, 2H), 1.82 (tt, $J$ = 7.2, 6.8 Hz, 2H), 0.98 (t, $J$ = 8.0 Hz, 9H), 0.59 (q, $J$ = 8.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 100.9, 82.4, 79.4, 74.9, 74.7, 74.0, 51.5, 32.8, 23.8, 18.1, 10.9, 9.7, 7.4, 4.3; LRMS (ESI) *m/z* 339.18 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{19}H_{28}O_2NaSi$: 339.1751 [$(M+Na)^+$], found: 339.1755.

**Methyl (5*Z*,8*Z*)-dodeca-5,8-dien-11-ynoate (3).** A solution of **14** (950 mg, 3.0 mmol), quinoline (1.7 mL, 15.0 mmol) and Lindlar catalyst (190 mg, 20% w/w) in AcOEt (20 mL) was stirred at room temperature under $H_2$ atmosphere for 17 h. The mixture was filtrated through Celite pad and the filtrate was concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:40) to give crude diene (805 mg) as a colorless oil. To a stirred solution of crude diene (805 mg) in THF (6.1 mL) was added AcOH (150 μL, 2.68 mmol) and TBAF (1.0 M in THF, 3.2 mL, 3.2 mmol) at room temperature. The mixture was stirred at the same temperature. The reaction mixture was stirred overnight. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt-hexane = 1:40) to give **3** (362 mg, 1.76 mmol, 59% for 2 steps) as a colorless oil. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:10); $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 5.49-5.36 (m, 4H), 3.67 (s, 3H), 2.97 (dd, $J$ = 5.5, 3.0 Hz, 2H), 2.80 (dd, $J$ = 6.0, 5.0 Hz, 2H), 2.33 (t, $J$ = 7.5 Hz, 2H), 2.11 (td, $J$ = 7.0, 5.5 Hz, 2H), 1.97 (t, $J$ = 3.0 Hz, 1H), 1.71 (tt, $J$ = 7.5, 7.0 Hz, 2H); Data for **3** agreed with previous data.[8]

**(4*S*)-4-Benzyl-3-(2*S*,3*R*)-(2-(benzyloxy)-3-hydroxypentanoyl)oxazolidin-2-one (6).** To a stirred solution of **15** (210 mg, 0.66 mmol) in $CH_2Cl_2$ (1 mL) was added *n*-$Bu_2BOTf$ (1.0 M in $CH_2Cl_2$, 0.52 mL, 2.4 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 30 min. After triethylamine (0.36 mL, 2.6 mmol) was added to the reaction mixture, the mixture was stirred at –78 °C for 30 min, 0 °C for 50 min, and was then recooled to –78 °C. After 30 min, propanal (**16**) (0.24 mL, 3.2 mmol) was added. The solution was allowed to stir at –78 °C for 2 h and at –40 °C for 40 min. The reaction was quenched by the addition of 2:1 MeOH/pH 7 phosphate buffer (0.7 mL) and was allowed to warm

to 0 °C. A solution of 0.6 mL 30% $H_2O_2$ in 0.8 mL MeOH was added. After concentration in vacuo to remove the organic solvents, extracted with 50% EtOAc/hexane. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 3:1) to give **6** (140 mg, 0.37 mmol, 54%) as a white amorphous. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:1); $[\alpha]^{25}_D$ +2.6 (*c* 1.39, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42-7.21 (m, 10H), 5.16 (d, *J* = 2.0 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.72-4.67 (m, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.25 (dd, *J* = 9.2, 7.6 Hz, 1H), 4.20 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.83-3.76 (m, 1H), 3.30 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.77 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.15 (d, *J* = 10.0 Hz, 1H), 1.67-1.63 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 170.8, 153.4, 137.0, 135.0, 129.4, 129.0, 128.5, 128.4, 128.2, 127.4, 79.0, 73.9, 72.9, 67.0, 55.6, 37.7, 27.2, 10.0; LRMS (ESI) *m/z* 406.16 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{22}H_{25}O_5NNa$: 406.1625 [(M+Na)$^+$], found: 406.1624.; Data for **6** agreed with its enantiomer.[9]

**(2*R*,3*R*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)pentan-1-ol (17).** A solution of **6** (50 mg, 0.13 mmol), $Pd(OH)_2$ (13 mg, 0.018 mmol) in EtOH (0.5 mL) was stirred at room temperature under $H_2$ atmosphere for 3 h. The mixture was filtrated through Celite pad and the filtrate was concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:2) to give deprotected diol (35 mg, 0.12 mmol, 91%) as a colorless oil. To a stirred solution of deprotected diol (1.69 g, 5.76 mmol) in THF (19 mL) was added 2,6-lutidine (4.6 mL, 40.3 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 30 min. After *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.0 mL, 25.9 mmol) was added to the reaction mixture, the mixture was stirred at –78 °C for 30 min. The reaction mixture was warmed to room temperature for 1 h. The resulting solution was quenched by addition of MeOH and extracted with $Et_2O$. The combined organic extracts were washed with 1M HCl aq., sat. $NaHCO_3$ aq., brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:40) to give crude product diTBS ether (3.0 g) as a white amorphous. To a crude product diTBS ether in $Et_2O$ (60 mL) was added $H_2O$ (0.5 mL, 28.8 mmol) and $LiBH_4$ (250 mg, 11.5 mmol) at 0 °C. After the reaction mixture was stirres at 0 °C for 30min and at room temperature for 40 min. The resulting solution was quenched by addition of 1M NaOH aq. and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:40) to give **17** (2.0 g, 5.74 mmol, 98% for 2 steps) as a white amorphous. TLC $R_f$ = 0.7 (AcOEt-hexane = 1:3); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.80-3.72 (m, 2H), 3.61-3.54 (m, 2H), 2.35 (dd, *J* = 6.8, 5.2 Hz, 1H), 1.79-1.69 (m, 1H), 1.42-1.31 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H) 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); Data for **17** agreed with previous data.[10]

**(2*E*,4*R*,5*R*)-(Ethyl 4,5-bis((*tert*-butyldimethylsilyl)oxy)hept-2-enoate (18).** To a stirred solution of **17** (400 mg, 1.38 mmol) in $CH_2Cl_2$ (7.6 mL) was added DMP (730 mg, 1.73 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, quenched by addition of $Na_2S_2O_3$ aq. and sat. $NaHCO_3$

aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was concentrated to give crude aldehyde (410 mg) as a pale yellow oil. To a stirred solution of NaH (60% mineral oil, 115 mg, 2.88 mmol) in THF (1.8 mL) was added triethyl phosphonoacetate (0.69 mL, 3.45 mmol) at –10 °C. The resulting solution was stirred at –10 °C for 30 min. After crude aldehyde (410 mg) in THF (2.0 mL) was added to the reaction mixture, the mixture was stirred at -10 °C for 3 h. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with hexane. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:20) to give **18** (500 mg, 1.20 mmol, 97% for 2 steps) as a colorless oil. TLC $R_f$ = 0.6 (AcOEt-hexane = 1:6); $[\alpha]^{25}_D$ +79.9 (*c* 1.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 15.6, 3.2 Hz, 1H), 6.03 (dd, *J* = 15.6, 2.0 Hz, 1H), 4.32 (m, 1H), 4.22-4.15 (m, 2H), 3.57-3.52 (m, 1H), 1.64-1.54 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.20-1.08 (m, 1H), 0.914 (s, 9H), 0.910 (s, 9H) 0.87 (t, *J* = 7.2 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 166.5, 147.9, 120.8, 76.6, 74.5, 60.1, 25.8, 25.7, 24.1, 18.0, 17.9, 14.2, 10.8, –4.4, –4.7, –4.9, –5.0; LRMS (ESI) *m/z* 439.27 [(M+Na)$^+$]; Anal. calcd for $C_{21}H_{44}O_4Si_2$: C, 60.52; H, 10.64. found: C, 60.36; H, 10.70.

**(2*E*,4*R*,5*R*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)hept-2-enal (19).** To a stirred solution of **18** (500 mg, 1.20 mmol) in $CH_2Cl_2$ (12 mL) was added DIBAL (1.0 M toluene solution, 2.4 mL, 2.4 mmol) at –78 °C. The mixture was stirred for 3 h, quenched by addition of sat. Rochelle salt aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:20) to give allyl alcohol (410 mg, 1.10 mmol, 92%) as a colorless oil. A solution of allyl alcohol (90 mg, 0.24 mmol) in $CH_2Cl_2$ (2.4 mL) was added $MnO_2$ (450 mg, 500% w/w) at room temperature for 7 h. The mixture was filtrated through Celite pad. The filtrate was concentrated to give **19** (80 mg, 0.22 mmol, 92%) as a colorless oil. TLC $R_f$ = 0.6 (AcOEt-hexane = 1:6); $[\alpha]^{25}_D$ +119.1 (*c* 1.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 16.0, 3.2 Hz, 1H), 6.35 (ddd, *J* = 16.0, 8.0, 1.6 Hz, 1H), 4.43-4.40 (m, 1H), 3.63-3.58 (m, 1H), 1.65-1.58 (m, 1H), 1.16-1.08 (m, 1H), 0.94-0.87 (m, 21H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 193.5, 157.4, 131.9, 76.5, 74.7, 25.8, 25.7, 24.2, 18.0, 179, 10.8, –4.4, –4.7, –4.9, –5.0; LRMS (ESI) *m/z* 395.24 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{19}H_{40}O_3NaSi_2$: 395.2408 [(M+Na)$^+$], found: 395.2412.

**(4*R*,5*R*,5*E*,7*E*)-8-Iodoocta-5,7-diene-3,4-diol (2a).** To a stirred solution of $CrCl_2$ (320 mg, 2.6 mmol) and $CHI_3$ (410 mg, 1.04 mmol) in THF (4.3 mL) was added **19** (56 mg, 0.15 mmol) at -10 °C. The mixture was stirred at 0 °C for 1 h, quenched by addition of $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was concentrated to give crude vinyl iodide (56 mg, *E*/*Z* = 10/1) as a pale yellow oil. To a stirred solution of crude vinyl iodide (56 mg) in THF (4.3 mL) was added TBAF (1.0 M THF solution, 0.29 mL, 0.29 mmol) at room temperature. The resulting solution was stirred overnight. The resulting

solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:1) to give **2a** (32 mg, 0.12 mmol, 79% for 2 steps, *E*/*Z* = 10/1) as a pale yellow oil. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 14.0, 10.8 Hz, 1H), 6.40 (d, *J* = 14.0 Hz, 1H), 6.26 (dd, *J* = 15.2, 10.8, Hz, 1H), 5.72 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.96 (dd, *J* = 6.4, 6.0 Hz, 1H), 3.43-3.39 (m, 1H), 2.31 (brs, 1H), 2.17 (brs, 1H), 1.62-1.55 (m, 1H), 1.51-1.40 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 144.3, 133.2, 132.1, 80.4, 75.7, 74.9, 25.8, 9.9; LRMS (ESI) *m/z* 290.99 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_8H_{13}O_2INa$: 290.9852 [$(M+Na)^+$], found: 290.9856.

**(5*Z*,8*Z*,13*E*,15*E*,17*R*,18*R*)-Methyl 17,18-dihydroxyicosa-5,8,13,15-tetraen-11-ynoate (20).** To a stirred solution of **3** (21 mg, 102 μmol) and **2a** (32 mg, 120 μmol) in benzene (670 μL) was added $Et_2NH$ (67 μL), CuI (9.5 mg, 50 μmol) and $Pd(PPh_3)_4$ (11.5 mg, 10 μmol) at room temperature. The mixture was stirred at the same temperature for 3 h, quenched by addition of water and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 2:1) to give **20** (32 mg, 92 μmol, 91%) as a yellow oil. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:1); $[\alpha]^{25}_D$ +8.3 (*c* 0.97, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.33 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.74 (dd, *J* = 15.0, 7.0 Hz, 1H), 5.62 (d, *J* = 15.5 Hz, 1H), 5.49-5.38 (m, 4H), 3.99 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.67 (s, 3H), 3.41 (dt, *J* = 9.0, 3.5 Hz, 1H), 3.11 (d, *J* = 3.0 Hz, 2H), 2.81 (dd, *J* = 5.5, 5.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 1H), 2.23 (d, *J* = 4.0 Hz, 1H), 2.11 (td, *J* = 7.5, 6.0 Hz, 2H), 1.70 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.61-1.56 (m, 1H), 1.46-1.40 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ 174.1, 139.7, 133.9, 131.7, 129.8, 129.3, 128.0, 124.0, 112.5, 91.3, 79.3, 75.8, 75.2, 51.5, 33.3, 26.4, 25.8, 25.4, 24.6, 17.9, 9.9; LRMS (ESI) *m/z* 369.20 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{21}H_{30}O_4Na$: 369.2036 [$(M+Na)^+$], found: 369.2039.

**(5*Z*,8*Z*,11*Z*,13*E*,15*E*,17*R*,18*R*)-17,18-Dihydroxyicosa-5,8,11,13,15-pentaenoic acid ((17*R*,18*R*)-RvE3, 1a).** To a stirred solution of Zn powder (300 mg, 4.6 mmol) in $H_2O$ (1.0. mL) was added $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol) at room temperature under dark. The mixture was stirred at the same temperature for 30 min. To the mixture was added $AgNO_3$ (30 mg, 0.18 mmol) and stirred at the same temperature for 45 min. To the reaction mixture was added **20** (10 mg, 29 μmol) in MeOH (1.0 mL), stirred 1 h, filtrated through Celite pad and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (MeOH-$CHCl_3$ = 1:100) to give pentaene (8.4 mg, 23 μmol, 78%) as a yellow oil. To a stirred solution of pentaene (4.8 mg, 14 μmol) in THF (280 μL) was added $LiOH \cdot H_2O$ (1.7 mg, 28 μmol) in $H_2O$ (280 μL) at room temperature. The resulting solution was stirred 20 h. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue

was purified by silica gel column chromatography (MeOH-$CHCl_3$ = 1:20) to give (17*R*,18*R*)-RvE3 (**1a**) (4.3 mg, 12 μmol, 88%) as a colorless oil. TLC $R_f$ = 0.4 (MeOH-$CHCl_3$ = 1:19); $[\alpha]^{25}_D$ +28.0 (*c* 0.18, MeOH); $^1$H NMR (500 MHz, $CD_3OD$) δ 6.57 (dd, *J* = 15.0, 10.5 Hz, 1H), 6.37 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.23 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.03 (dd, *J* = 11.0, 10.5 Hz, 1H), 5.73 (dd, *J* = 15.5, 6.5 Hz, 1H) 5.42-5.36 (m, 5H), 3.96 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.36-3.23 (m, 1H), 2.98 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.84 (dd, *J* = 6.0, 5.0 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.13 (td, *J* = 7.5, 7.0 Hz, 2H), 1.66 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.59-1.54 (m, 1H), 1.38-1.28 (m, 1H), 0.96 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CD_3OD$) δ 177.6, 134.3, 133.7, 133.4, 131.2, 130.2, 129.8, 129.7, 129.6, 129.2, 128.6, 77.3, 76.6, 34.4, 27.6, 27.1, 26.6, 26.5, 26.0, 10.6; LRMS (ESI) *m/z* 333.21 [$(M-H)^-$]; HRMS (ESI) calcd for $C_{20}H_{29}O_4$: 333.2071 [$(M-H)^-$], found: 333.2073 ; HPLC purity 97% ($CH_3CN/H_2O$/AcOH 50:50:0.1, 1.0 mL/min, $t_R$= 11.6 min, detection 270 nm). Data for RvE3 agreed with previous data.[4b]

**(*R*,*E*)-8-(Triisopropylsilyl)oct-5-en-7-yn-3-ol (8).** To a stirred solution of buta-1,3-diyn-1-yltriisopropylsilane (**11**) (900 mg, 4.4 mmol) in THF (15 mL) was added *n*-BuLi (2.6M hexane solution, 1.7 mL, 4.4 mmol) at –78 °C. After 30 min, the reaction mixture was added boron trifluoride diethyl ether complex (370 μL, 2.9 mmol) and (*R*)-1,2-epoxybutane (**10**) (210 mg, 2.9 mmol). The reaction mixture was stirred 1 h, quenched by addition of sat. $NH_4Cl$ aq and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 0:1-1:10) to give diyne (770 mg, 2.8 mmol, 96%) as a brown oil. To a stirred solution of diyne (3.1 g, 11.3 mmol) in THF (150 mL) was added Red-Al (3.3 M toluene solution, 10 mL, 34 mmol) at –20 °C, and the solution was stirred for 2.5 h. After the reaction mixture was warmed at 0 °C, quenched by addition of sat. Rochelle salt aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give **8** (3.0 g, 10.9 mmol, 96%) as a brown oil. TLC $R_f$ = 0.5 (AcOEt-hexane = 1:5); $[\alpha]^{25}_D$ –12.1 (*c* 1.40, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.21 (ddd, *J* = 16.0, 8.0, 8.0 Hz, 1H), 5.62 (dd, *J* = 16.0, 1.2 Hz, 1H), 3.61 (m, 1H), 2.34 (ddd, *J* = 16.0, 4.8, 4.8 Hz), 2.21 (ddd, *J* = 16.0, 4.8, 4.8 Hz), 1.59 (brs, 1H), 1.51 (m, 2H), 1.11-1.04 (m, 21H), 0.97 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.2, 113.0, 105.4, 89.6, 72.2, 40.6, 29.7, 18.6, 11.3, 9.9; LRMS (ESI) *m/z* 281.23 [$(M+H)^+$]; HRMS (ESI) calcd for $C_{17}H_{33}OSi$: 281.2295 [$(M+H)^+$], found: 281.2296.

**(*R*,*E*)-*Tert*-butyldimethyl (oct-5-en-7-yn-3-yloxy) silane (21).** To a stirred solution of **8** (3.0 g, 10.9 mmol) in THF (55 mL) was added TBAF (1.0 M in THF, 16 mL, 16 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 5 h. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give deprotected enyne. To a stirred solution of

deprotected enyne in $CH_2Cl_2$ (105 mL) was added 2,6-lutidine (3.6 mL, 31.5 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 30 min. After *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.6 mL, 24.2 mmol) was added to the reaction mixture, the mixture was stirred at –78 °C for 30 min. The reaction mixture was warmed to room temperature. After the resulting solution was stirred for 1 h, quenched by addition of MeOH and extracted with $Et_2O$. The combined organic extracts were washed with 1M HCl aq., sat. $NaHCO_3$ aq., brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 0:1-1:10) to give **21** (2.6g, 10.9 mmol, 99% for 2 steps) as a pale yellow oil. TLC $R_f$ = 0.9 (AcOEt-hexane = 1:5); $[\alpha]^{25}_D$ +12.1 (*c* 1.88, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.24 (ddd, *J* = 16.4, 8.0, 7.6 Hz, 1H), 5.48 (dd, *J* = 16.4, 2.0 Hz, 1H), 3.64 (tt, *J* = 6.0, 6.0 Hz, 1H), 2.79 (d, *J* = 2.0 Hz, 1H), 2.32-2.19 (m, 2H), 1.51-1.40 (m, 2H), 0.90 (s, 9H), 0.87 (t, *J* = 8.4 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 143.4, 110.5, 82.4, 75.8, 72.7, 40.5, 29.7, 25.8, 18.1, 9.6, –4.5, –4.6; LRMS (EI) *m/z* 237.17 [(M-H)$^-$]; HRMS (EI) calcd for $C_{14}H_{25}OSi$: 237.1675[(M-H)$^-$], found: 237.1675.

**(*R*,5*E*,7*E*)-8-Iodoocta-5,7-dien-3-ol (2b).** To a stirred solution of Schwartz's reagent (180 mg, 0.63 mmol) in THF (1.0 mL) was added **21** (50 mg, 0.21 mmol) at 0 °C. After stirred at room temperature for 30 min, the reaction mixture was cooled to –78 °C. The reaction mixture was added iodide (160 mg, 0.63 mmol) in THF (1.0 mL), and the solution was stirred for 1 h. The resulting solution was quenched by addition of $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 0:1) to give vinyl iodide. To a stirred solution of vinyl iodide in THF (2.1 mL) was added TBAF (1.0 M THF solution, 0.42 mL, 0.42 mmol) at room temperature. After the reaction mixture was stirred overnight, quenched by addition of sat. $NH_4Cl$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:5) to give **2b** (38 mg, 0.15 mmol, 72% for 2 steps) as a yellow oil. TLC $R_f$ = 0.3 (AcOEt-hexane = 1:5); $[\alpha]^{25}_D$ +2.9 (*c* 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 14.4, 10.4 Hz, 1H), 6.24 (d, *J* = 14.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.74 (ddd, *J* = 15.2, 7.6, 7.6 Hz, 1H), 3.60 (m, 1H), 2.28 (m, 1H), 2.15 (ddd, *J* = 14.4, 6.8, 6.8 Hz, 1H), 1.52-1.46 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ 145.0, 133.1, 131.6, 77.7, 72.2, 40.0, 29.7, 9.9; LRMS (ESI) *m/z* 274.90 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_8H_{13}ONaI$: 274.9909 [(M+Na)$^+$], found: 274.9907.

**Methyl (*R*,5*Z*,8*Z*,13*E*,15*E*)-18-hydroxyicosa-5,8,13,15-tetraen-11-ynoate (22).** To a stirred solution of **2b** (50 mg, 0.20 mmol), $Et_2NH$ (120 μL), CuI (19 mg, 0.10 mmol) and $Pd(PPh_3)_4$ (23 mg, 20 μmol) in benzene (0.6 mL) was added **3** (45 mg, 0.22 mmol) in benzene (0.6 mL) at room temperature. The mixture was stirred at the same temperature for 1 h, quenched by addition of water and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give **22** (59

mg, 0.18 mmol, 89%) as a yellow oil. TLC $R_f$ = 0.3 (AcOEt-hexane = 1:3); $[\alpha]^{25}_D$ –9.6 (*c* 0.93, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.15 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.76 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 5.52 (d, *J* = 15.5 Hz, 1H), 5.49-5.35 (m, 4H), 3.67 (s, 3H), 3.61-3.57 (m, 1H), 3.10 (d, *J* = 4.0 Hz, 2H), 2.80 (dd, *J* = 5.5, 5.5 Hz, 2H), 2.34-2.31 (m, 3H), 2.22-2.16 (m, 1H), 2.11 (td, *J* = 7.5, 7.5 Hz, 2H), 1.71 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.56-1.44 (m, 2H), 0.95 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.0, 140.6, 132.7, 132.3, 129.8, 129.3, 128.1, 124.3, 110.4, 90.4, 79.6, 72.4, 51.5, 40.3, 33.4, 29.7, 26.5, 25.5, 24.7, 18.0, 9.9; LRMS (ESI) *m/z* 353.21 $[(M+Na)^+]$; HRMS (ESI) calcd for $C_{21}H_{30}O_3$: 353.2087 $[(M+Na)^+]$, found: 353.2084.

**(*R*,5*Z*,8*Z*,11*Z*,13*E*,15*E*)-18-Hydroxyicosa-5,8,11,13,15-pentaenoic acid (17-deoxy-RvE3, 1b).** To a stirred solution of Zn powder (270 mg, 4.2 mmol) in $H_2O$ (0.9 mL) was added $Cu(OAc)_2 \cdot H_2O$ (27 mg, 0.14 mmol) at room temperature under dark. The mixture was stirred at the same temperature for 30 min. To the mixture was added $AgNO_3$ (27 mg, 0.16 mmol) and stirred at the same temperature for 45 min. To the reaction mixture was added **22** (9.0 mg, 27 μmol) in MeOH (0.9 mL), stirred 1 h, filtrated through Celite pad and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give pentaene (6.0 mg, 18 μmol) as a yellow oil. To a stirred solution of pentaene (6.0 mg, 18 μmol) in MeOH (9.5 mL) and $H_2O$ (9.5 mL) was added 1M LiOH aq. (1.1 mL, 1.1 mmol) in at 0°C. The resulting solution was stirred for 48 h. The resulting solution was quenched by addition of sat. $NaH_2PO_4$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (MeOH-$CHCl_3$ = 1:50). This mixture was further purified with HPLC ($CH_3CN/H_2O$/AcOH 30:70:0.1, 10 mL/min, $t_R$=5.8 min) to give 17-deoxy-RvE3 (**1b**) (2.8 mg, 8.4 μmol, 31% for 2 steps) as a pale yellow oil. TLC $R_f$ = 0.5 (MeOH-$CHCl_3$ = 1:1); $[\alpha]^{25}_D$ –14.4 (*c* 0.46, $CH_3OH$); $^1H$ NMR (500 MHz, $CD_3OD$) δ 6.20-6.17 (m, 2H), 6.10-6.06 (m, 1H), 6.00 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.78-5.72 (m, 1H), 5.42-5.31 (m, 5H), 3.53-3.48 (m, 1H), 2.97 (dd, *J* = 7.5, 7.0 Hz, 2H), 2.84 (ddd, *J* = 7.5, 7.5, 5.5 Hz, 2H), 2.30-2.21 (m, 4H), 2.12 (td, *J* = 7.5, 7.0 Hz, 2H), 1.66 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.54-1.48 (m, 1H), 1.43-1.37 (m, 1H), 0.84 (t, *J* = 7.5Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CD_3OD$) δ 177.5, 134.5, 134.0, 132.3, 130.3, 130.1, 130.0, 129.8, 129.5, 128.7, 127.3, 73.8, 41.4, 34.3, 30.5, 27.6, 27.1, 26.6, 26.0, 10.3; LRMS (ESI) *m/z* 341.21 $[(M+Na)^+]$; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$: 341.2087 $[(M+H)^+]$, found: 341.2091; HPLC purity 97% ($CH_3CN/H_2O$/AcOH 30:70:0.1, 1.0 mL/min, $t_R$= 5.1 min, detection 270 nm).

**(4*R*)-4-Benzyl-3-((2*S*)-2-(benzyloxy)pent-4-enoyl)oxazolidin-2-one (7).** To a stirred solution of NaHMDS (1.9 M toluene solution, 6.3 mL,12 mmol) in THF (52 mL) was added **23** (2.6 g, 8.0 mmol) in THF (20 mL) slowly at –78 °C. Allyl iodide (3.7 mL, 40 mmol) in THF (20 mL) was added to the reaction mixture slowly, the mixture was stirred at –78 °C for 10 min. The reaction mixture was warmed to –45 °C for 1 h, quenched the resulting solution was quenched by addition of sat. $NH_4Cl$ aq.

and extracted with AcOEt-hexane = 1:1. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:8) to give **7** (2.2 g, 6.1 mmol, 76 %) as a yellow oil. TLC $R_f$ = 0.5 (AcOEt-hexane = 1:3); $[\alpha]^{25}_D$ –84.0 (*c* 1.51, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 10H), 6.00-5.89 (m, 1H), 5.20-5.12 (m, 3H), 4.68-4.57 (m, 1H), 4.63 (d, *J* = 13.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.18 (d, *J* = 5.6 Hz, 2H), 3.27 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.68 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.64-2.53 (m, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 172.2, 153.0, 137.5, 135.0, 133.0, 129.0, 128.3, 128.2, 127.8, 127.4, 118.3, 76.7, 72.6, 66.7, 55.0, 38.0, 37.3; LRMS (ESI) *m/z* 388.15 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{22}H_{23}O_4NNa$: 388.1520 [(M+Na)$^+$], found: 388.1515. Data for **7** agreed with enantiomer.[7]

**(2*S*)-2-((*Tert*-butyldimethylsilyl)oxy)pentan-1-ol (24).** A solution of **7** (50 mg, 0.13 mmol), $Pd(OH)_2$ (130 mg, 0.47 mmol) in EtOH (5.2 mL) was stirred at room temperature under $H_2$ atmosphere for 1 h. The mixture was filtrated through Celite pad and the filtrate was concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:5) to give deprotected alcohol (340 mg, 1.24 mmol, 96%) as a colorless oil. To a stirred solution of deprotected alcohol (900 mg, 3.3 mmol) in THF (11 mL) was added 2,6-lutidine (1.3 mL, 11.4 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 30 min. After *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.7 mL, 7.4 mmol) was added to the reaction mixture, the mixture was stirred at –78 °C for 30 min. The reaction mixture was warmed to room temperature for 1 h. The resulting solution was quenched by addition of MeOH and extracted with $Et_2O$. The combined organic extracts were washed with 1M HCl aq., sat. $NaHCO_3$ aq., brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:40) to give crude TBS ether (1.2 g) as a pale yellow oil. To a crude TBS ether in $Et_2O$ (28 mL) was added $H_2O$ (250 μL, 14.0 mmol) and $LiBH_4$ (120 mg, 5.6 mmol) at 0 °C. After the reaction mixture was stirres at 0 °C for 30min and at room temperature for 40 min. The resulting solution was quenched by addition of 1M NaOH aq. and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:40) to give **24** (500 mg, 2.3 mmol, 76% for 2 steps) as a colorless oil. TLC $R_f$ = 0.4 (AcOEt-hexane = 1:3); $[\alpha]^{25}_D$ +9.5 (*c* 1.46, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.74 (ddd, *J* = 11.2, 6.4, 3.6 Hz, 1H), 3.59-3.54 (m, 1H), 3.44 (dt, *J* = 11.2, 6.4 Hz, 1H), 1.93 (dd, *J* = 6.4, 6.0 Hz, 1H), 1.48 (td, *J* = 7.2, 6.4 Hz, 1H), 1.39-1.25 (m, 2H), 0.93-0.90 (m, 12H), 0.08 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 72.7, 66.3, 36.2, 25.8, 18.6, 18.1, 14.2, -4.5, -4.6; LRMS (ESI) *m/z* 241.16 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{11}H_{26}O_2NaSi$: 241.1594 [(M+Na)$^+$], found: 241.1596.

**(2*E*,4*S*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)hept-2-enoate (25).** To a stirred solution of **24** (53 mg, 0.24 mmol) in $CH_2Cl_2$ (1.5 mL) was added DMP (145 mg, 0.69 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, quenched by addition of $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was

concentrated to give crude aldehyde (55 mg) as a pale yellow oil. To a stirred solution of NaH (60% mineral oil, 14 mg, 0.35 mmol) in THF (1.4 mL) was added triethyl phosphonoacetate (84 μL, 0.42 mmol) at –10 °C. The resulting solution was stirred at –10 °C for 30 min. After crude aldehyde (55 mg) in THF (2.0 mL) was added to the reaction mixture, the mixture was stirred at –10 °C for 1.5 h. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with hexane. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:100) to give **25** (42 mg, 0.20 mmol, 82% for 2 steps) as a colorless oil. TLC $R_f$ = 0.6 (AcOEt-hexane = 1:10); $[\alpha]^{25}_D$ –3.5 (*c* 1.31, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 16.0, 4.8 Hz, 1H), 5.96 (dd, *J* = 16.0, 2.0 Hz, 1H), 4.30 (tdd, *J* = 5.5, 4.8, 1.6 Hz, 1H), 4.20 (qd, *J* = 7.4, 2.0 Hz, 1H), 1.67-1.48 (m, 2H), 1.40-1.33 (m, 2H), 1.30 (t, *J* = 7.4 Hz, 3H), 0.93-0.90 (m, 12H), 0.06 (s, 3H), 0.03 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 166.8, 151.1, 119.6, 71.4, 60.3, 39.5, 25.8, 18.2, 18.1, 14.2, 14.1, -4.6, -5.0; LRMS (ESI) *m/z* 309.19 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{15}H_{30}O_3NaSi$: 309.1856 [$(M+Na)^+$], found: 309.1857.

**(2*E*, 4*S*)-4-((*Tert*-butyldimethylsilyl)oxy)hept-2-enal (26).** To a stirred solution of **25** (400 mg, 1.4 mmol) in $CH_2Cl_2$ (14 mL) was added DIBAL (1.0 M toluene solution, 2.1 mL, 2.1 mmol) at –78 °C. The mixture was stirred for 2 h, quenched by addition of sat. Rochelle salt aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:20) to give allyl alcohol (310 mg, 1.3 mmol, 92%) as a colorless oil. A solution of allyl alcohol (110 mg, 0.44 mmol) in $CH_2Cl_2$ (5 mL) was added $MnO_2$ (1.6 g, 1500% w/w) at room temperature for 24 h. The mixture was filtrated through Celite pad. The filtrate was concentrated to give **26** (100 mg, 0.42 mmol, 96%) as a colorless oil. TLC $R_f$ = 0.5 (AcOEt-hexane = 1:10); $[\alpha]^{25}_D$ +11.7 (*c* 1.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 15.6, 4.8 Hz, 1H), 6.26 (ddd, *J* = 15.6, 8.0, 1.6 Hz, 1H), 4.41 (td, *J* = 5.4, 4.8 Hz, 1H), 1.59-1.54 (m, 1H), 1.43-1.34 (m, 2H), 0.95-0.87 (m, 12H), 0.06 (s, 3H), 0.03 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 193.6, 160.3, 130.5, 71.4, 39.3, 25.7, 18.1, 14.0, –4.7, –5.0; LRMS (APCI) *m/z* 243.16 [$(M+H)^+$]; HRMS (APCI) calcd for $C_{13}H_{27}O_2Si$: 243.1775 [$(M+H)^+$], found: 243.1775.

**(4*S*,5*E*,7*E*)-8-Iodoocta-5,7-dien-4-ol (2c).** To a stirred solution of $CrCl_2$ (1.02 g, 8.3 mmol) in THF (8 mL) and $CHI_3$ (1.3 g, 3.3 mmol) was added **26** (90 mg, 0.37 mmol) and at -10 °C. The mixture was stirred at -10 °C for 1 h, quenched by addition of $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. and extracted with ether. The combined organic extracts were washed with brine, dried ($Na_2SO_4$). The residue was concentrated to give crude vinyl iodide (150 mg, *E*/*Z* = 5.5/1) as a yellow oil. To a stirred solution of crude vinyl iodide (150 mg) in THF (3 mL) was added TBAF (1.0 M THF solution, 1.0 mL, 1.0 mmol) at room temperature. The resulting solution was stirred overnight. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with AcOEt. The combined organic extracts were washed

with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:1) to give **2c** (52 mg, 0.21 mmol, 56% for 2 steps, *E*/*Z* = 5.5/1) as a pale yellow oil. TLC $R_f$ = 0.5 (AcOEt-hexane = 1:3); $[\alpha]^{25}_D$ +3.00 (*c* 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.34 (d, *J* = 14.8 Hz, 1H), 6.16 (dd, *J* = 15.6, 10.8, Hz, 1H), 5.73 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.14 (td, *J* = 6.4, 6.4 Hz, 1H), 1.59-1.31 (m, 4H), 0.93 (t, *J* = 7.6 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 144.5, 137.2, 129.8, 79.3, 71.8, 39.2, 18.5, 14.0; LRMS (EI) *m/z* 252.04 ($M^+$); HRMS (EI) calcd for $C_8H_{13}IO$: 252.0011 ($M^+$), found: 252.0013.

**(5*Z*,8*Z*,13*E*,15*E*,17*S*)-Methyl 17-hydroxyicosa-5,8,13,15-tetraen-11-ynoate (27).** To a stirred solution of **2c** (46 mg, 0.18 mmol), $Et_2NH$ (140 μL), CuI (25 mg, 90 μmol) and $Pd(PPh_3)_4$ (21 mg, 18 μmol) in benzene (0.7 mL) was added **3** (41 mg, 0.20 mmol) in benzene (0.7 mL) at room temperature. The mixture was stirred at the same temperature for 1 h, quenched by addition of water and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give **27** (35 mg, 0.11 mmol, 53%) as a yellow oil. TLC $R_f$ = 0.3 (AcOEt-hexane = 1:3); $[\alpha]^{25}_D$ +5.3 (*c* 1.93, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 16.0, 11.2 Hz, 1H), 6.23 (dd, *J* = 15.2, 11.2 Hz, 1H), 5.75 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.59 (d, *J* = 16.0 Hz, 1H), 5.50-5.36 (m, 4H), 4.16 (td, *J* = 6.4, 6.4 Hz, 1H), 3.67 (s, 3H), 3.11 (d, *J* = 2.8 Hz, 2H), 2.80 (dd, *J* = 5.6, 5.2 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.11 (td, *J* = 7.2, 6.8 Hz, 2H), 1.70 (tt, *J* = 7.6, 7.2 Hz, 2H), 1.59-1.33 (m, 4H), 0.92 (t, *J* = 7.6 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) δ 174.1, 140.1, 138.0, 129.8, 129.4, 129.3, 128.1, 124.2, 111.8, 90.9, 79.4, 72.1, 51.5, 39.3, 33.4, 26.5, 25.5, 24.7, 18.5, 18.0, 13.9; LRMS (ESI) *m/z* 353.21 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{21}H_{30}O_3Na$: 353.2087 [$(M+Na)^+$], found: 353.2085.

**(*S*,5*Z*,8*Z*,11*Z*,13*E*,15*E*)-17-Hydroxyicosa-5,8,11,13,15-pentaenoic acid (18-deoxy-RvE3, 1c).** To a stirred solution of Zn powder (240 mg, 3.7 mmol) in $H_2O$ (0.8 mL) was added $Cu(OAc)_2 \cdot H_2O$ (24 mg, 0.12 mmol) at room temperature under dark. The mixture was stirred at the same temperature for 30 min. To the mixture was added $AgNO_3$ (24 mg, 0.14 mmol) and stirred at the same temperature for 45 min. To the reaction mixture was added **27** (7.9 mg, 24 μmol) in MeOH (0.8 mL), stirred 1 h, filtrated through Celite pad and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt-hexane = 1:10) to give pentaene (7.4 mg, 23 μmol, 95%) as a yellow oil. To a stirred solution of pentaene (3.0 mg, 9 μmol) in THF (230 μL) was added $LiOH \cdot H_2O$ (0.8 mg, 18 μmol) in $H_2O$ (230 μL) at room temperature. The resulting solution was stirred 24 h. The resulting solution was quenched by addition of sat. $NH_4Cl$ aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (MeOH-$CHCl_3$ = 1:30) to give 18-deoxy-RvE3 (**1c**) (2.1 mg, 6.6 μmol, 74%) as a colorless oil. TLC $R_f$ = 0.5 (MeOH-$CHCl_3$ = 1:19); $[\alpha]^{25}_D$ +28.0 (*c* 0.18, MeOH); $^1$H NMR (400 MHz, $CD_3OD$) δ 6.55 (dd, *J* = 14.4, 11.6 Hz, 1H), 6.29 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.21 (dd, *J* = 14.4, 11.2

Hz, 1H), 6.02 (dd, *J* = 11.6, 11.2 Hz, 1H), 5.68 (dd, *J* = 14.8, 7.2 Hz, 1H) 5.39-5.35 (m, 5H), 4.08 (td, *J* = 7.0, 6.8 Hz, 1H), 2.98 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.84 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.13 (td, *J* = 7.6, 6.8 Hz, 2H), 1.66 (tt, *J* = 7.6, 7.6 Hz, 2H), 1.51-1.40 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CD_3OD$) δ 177.7, 137.9, 133.8, 131.6, 131.0, 130.2, 129.82, 129.78, 129.6, 128.9, 128.6, 73.0, 40.6, 34.4, 27.6, 27.1, 26.5, 26.0, 19.8, 14.4; LRMS (ESI) *m/z* 341.21 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$: 341.2087 [$(M+Na)^+$], found: 341.2089, HPLC purity 98% ($CH_3CN/H_2O$/AcOH 30:70:0.1, 1.0 mL/min, $t_R$= 7.4 min, detection 270 nm).

**Murine peritonitis evaluation**

Male BALB/c mice (6–7 weeks; Japan SLC, Shizuoka, Japan) were used. Heat-killed *Propionibacterium acnes* (*P. acnes*; 500 μg per mouse) was injected intraperitoneally. At 12 h after *P. acnes* injection, three different doses (300 fg, 300 pg or 300 ng per mouse) of (17*R*,18*R*)-RvE3, 17-deoxy-RvE3, 18-deoxy-RvE3 or vehicle alone was administered intraperitoneally. At 24 h after *P. acnes* injection, peritoneal exudate cells (PECs) were collected and counted. Results were expressed as percentage inhibition of *P. acnes*-induced increase in the number of PECs compared with vehicle alone. All animal procedures were conducted in accordance with the Hokkaido University animal ethics committee.

## ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org

Experimental procedures and $^{1}H$ and $^{13}C$ NMR spectra (PDF)

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**Notes**

The authors declare no competing financial interest.

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