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Synthesis of resolvin E3 *via* palladium-catalyzed addition of AcOH to vinyl epoxy alcohols†

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(18*R*)- and (18*S*)-stereoisomers of resolvin E3 (RvE3), potent anti-inflammatory mediators, were synthesized stereo- and enantioselectively through the Wittig reaction of the carbonate of 6*R*,7*R*- and 6*R*,7*S*-dihydroxynona-2*E*,4*E*-dienal, a C12–C20 part, with the phosphonium salt corresponding to the C1–C11 part. The stereoisomeric carbonate was prepared by the Swern oxidation of 3-(AcO)-6*R*,7*R*- or 3-(AcO)-6*R*,7*S*-(dihydroxy-carbonate)-4-nonen-1-ol followed by the spontaneous elimination of the AcO group in one pot. The (6*R*,7*R*)-(dihydroxy-carbonate)-alcohol for (18*R*)-RvE3 was, in turn, provided by stereoselective epoxidation of 9-(TBS-oxy)nona-4*Z*,6*E*-dien-3*R*-ol with *m*-CPBA and the subsequent Pd-catalyzed addition of AcOH to the resulting *syn* vinyl epoxy alcohol followed by carbonate formation of the *vic*-*syn*-diol and TBS desilylation. The Mitsunobu inversion of the *syn* vinyl epoxy alcohol gave the *anti* isomer, which was converted to 3-(AcO)-6*R*,7*S*-(dihydroxy-carbonate)-4-nonen-1-ol, the intermediate to (18*S*)-RvE3, by the same set of reactions.

Introduction

Resolvin E3 (RvE3), a metabolite of eicosapentaenoic acid (EPA) by lipoxygenase and CYPs, brings inflammatory cells to a rest level at a late stage of inflammation.[1] Unlike other *vic*-diol metabolites[2–4] such as those delineated in Fig. 1, RvE3 is a mixture of (17*R*,18*R*)- and (17*R*,18*S*)-diols. The isomers, abbreviated as (18*R*)- and (18*S*)-RvE3, were synthesized by enzymatic oxidation of (18*R*)- and (18*S*)-HEPE using soybean lipoxygenase.[1,5] However, the reported procedure implies that the method is limited to produce a minute quantity of these compounds, whereas RvE3 has been commercially not supplied. To date, only one organic synthesis has been reported.[6] The strategy involves extended H.W.E. olefination of bis-TBS ether of α,β-dihydroxy aldehyde, the Cu-assisted coupling of the resulting dienyl acetylene with the remaining propargyl tosylate and the Lindlar semi-hydrogenation. Although the synthesis is efficient, we considered that development of another method would be supplementary to the above synthesis and supportive of biological studies of RvE3, especially the structure–activity relationship.

We have chosen a strategy that consisted of the Wittig reaction of dihydroxy dienal derivative **3** with a ylide derived from **4** and a base to give **5**, possessing the full structure of (18*R*)-RvE3 (Scheme 1A), and envisioned that enal **1**, a precursor of the key intermediate **3**, would be prepared by the Pd-catalyzed addition of AcOH to vinyl epoxide **6** (R^3 = H)[7,8] followed by hydrolysis of acetate **7** (R^3 = H) and subsequent oxidation (Scheme 1B). The Mitsunobu inversion at an appropriate step was expected to produce the stereochemistry of (18*S*)-RvE3. As mentioned later, aldehyde **2** rationally emerged as the second precursor of **3**, and a similar Pd-catalyzed reaction of **6** (R^3 = $(CH_2)_2$OTBS) followed by oxidation of the $(CH_2)_2$OTBS group in **7** and the elimination of the AcO group was surely expected to afford acetoxy aldehyde **2**. We conjectured high regioselectivity in the Pd-catalyzed reaction based on the previous fact that the repulsion between the acetate anion (AcO^-) and the oxy anion

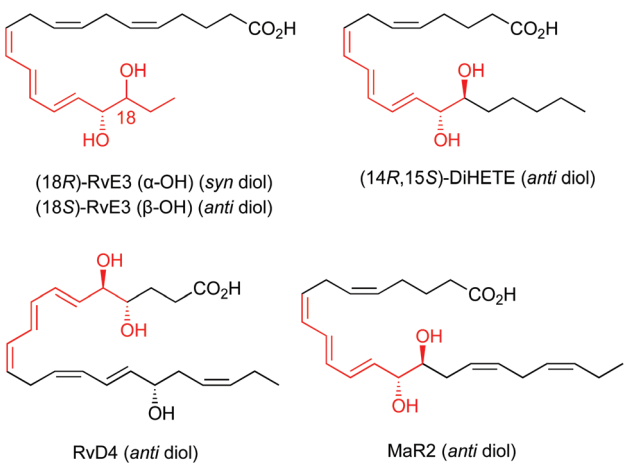

Fig. 1 Metabolites possessing diol and conjugated triene moieties.

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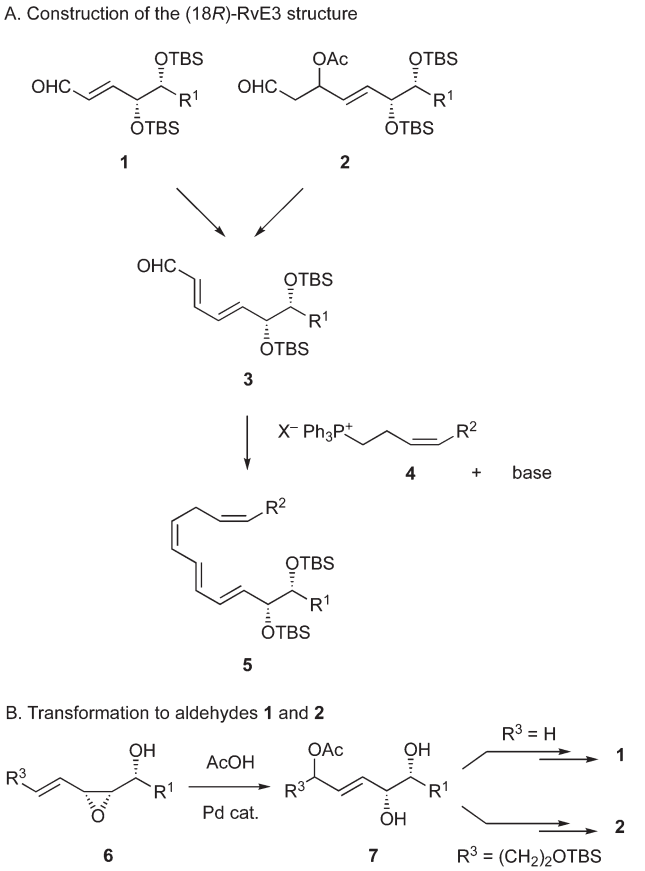
†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C spectra of all new compounds. See DOI: 10.1039/c8ob03196g

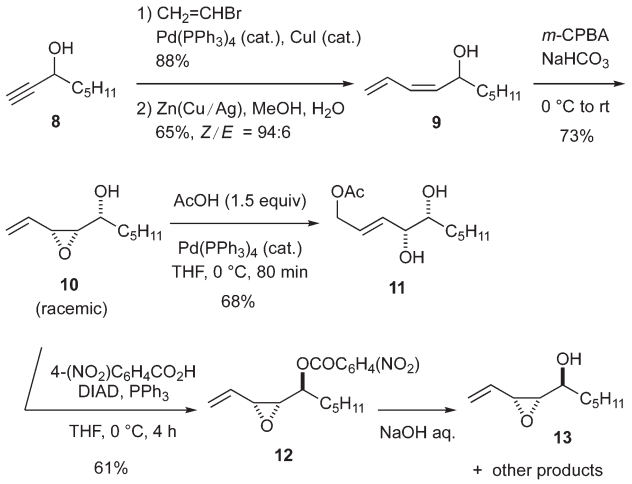


Scheme 1 A strategy for the construction of the core structure for (18*R*)-RvE3.

in the π-allyl Pd intermediate provoked the regioselectivity.[7,8] Herein, we report a full account of this study.

Results and discussion

Preparation of epoxide **6** (R^3 = H, R^1 = C_5H_{11}), the Pd-catalyzed transformation and the Mitsunobu inversion were first studied using racemic epoxide **10** possessing the C_5H_{11} group as R^1 as summarized in Scheme 2. The previous synthesis of *Z*-dienyl alcohols by the Ni-catalyzed coupling of *Z*-Br-allylic alcohols with lithium borates[9] required a volatile vinyl boronate ester, and thus, the Sonogashira coupling[10] of propargylic alcohol **8** with vinyl bromide followed by the Boland hydrogenation[11] using Zn (activated by $Cu(OAc)_2$ and $AgNO_3$) was examined. The coupling reaction and the hydrogenation proceeded cleanly to give **9**, although the *Z* purity was 85–97%. Epoxidation of **9** of 94% *Z* purity with *m*-CPBA at 0 °C to rt afforded vinyl epoxide **10**. The stereochemistry of **10** was assigned as depicted based on the literature results.[12] The Pd-catalyzed reaction of **10** with AcOH at 0 °C for 80 min afforded *syn* diol acetate **11** in 68% yield after chromatography, which separated the stereoisomer of **11** (structure not shown) derived from the minor isomer of **9**. The Mitsunobu inversion of **10**

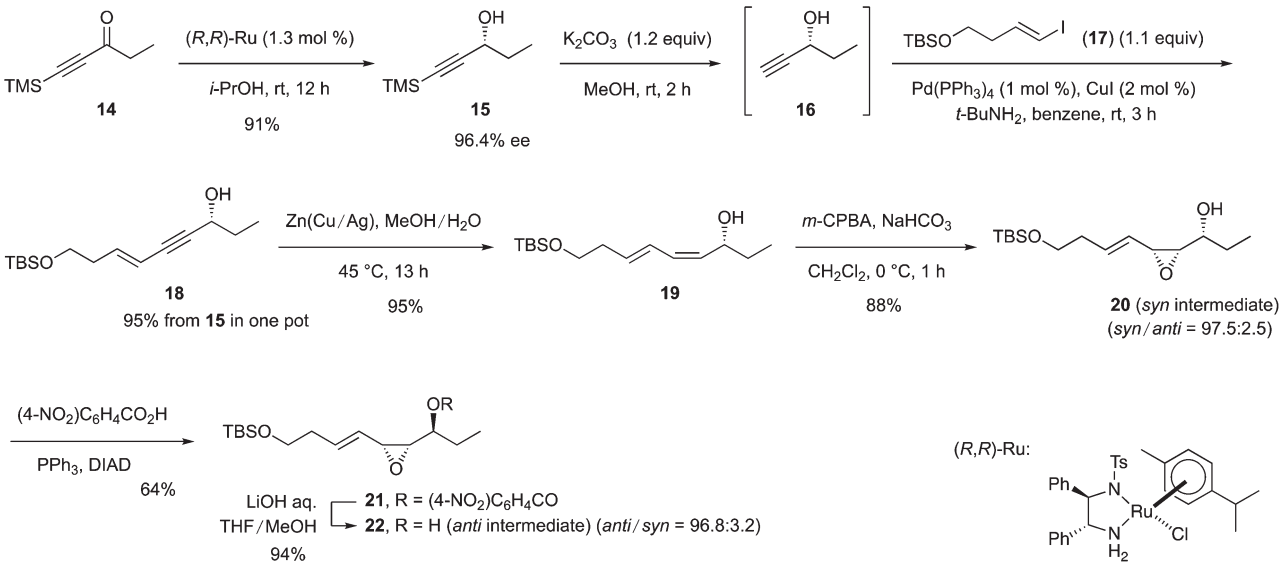


Scheme 2 Inspection of steps for the synthesis of enal **1**.

with 4-$(NO_2)C_6H_4CO_2H$ afforded ester **12** stereoselectively in a moderate yield (61%); however, hydrolysis of the ester gave a mixture of **13** and unidentified byproduct(s), which were inseparable by chromatography. In conclusion of the preliminary study, the transformation of **8** to **11** was easily operated and the diastereomer caused by the *E* isomer of **9** and/or diastereomer of **10** could be separated. However, the hydrolysis after the Mitsunobu inversion did not proceed cleanly. We attributed the result to the high reactivity of the terminal vinyl epoxide, and hence postulated that a substituent on the vinyl group, *i.e.*, R^3 of **6** in Scheme 1, would block the side reaction during the hydrolysis. With these tactics in mind, we next examined the synthesis of RvE3.

A $(CH_2)_2$OTBS group in epoxide **20** was chosen as R^3 in **6** for the synthesis of (18*R*)-RvE3, and the synthesis of **20** was succeeded through a sequence of reactions summarized in Scheme 3. Propargylic alcohol **15** was prepared according to the literature procedure.[13] Thus, the addition of lithium TMS-acetylide to propionaldehyde followed by the PCC oxidation gave ketone **14** in 67% yield over two steps, and the asymmetric transfer hydrogenation[14] of **14** afforded **15** in 91% yield with 96.4% ee as determined by chiral HPLC analysis. Attempted desilylation of **15** with K_2CO_3 in MeOH appeared to produce **16** from TLC analysis (R_f of **15** and **16**: 0.44 and 0.26 (hexane/EtOAc 6 : 1), respectively). However, **16** could not be isolated because of its volatile property (bp *ca.* 124 °C for the racemate).[15] So, the desilylation and the subsequent coupling with iodide **17**[16] were carried out in a one-pot manner to produce **18** in 95% yield from **15**. The semi-hydrogenation of **18** with a standard excess of Zn(Cu/Ag) (20 equiv.) at 45 °C produced **19** exclusively in 95% yield. The epoxidation with *m*-CPBA[12] at 0 °C gave **20** in a good yield with 97.5% *syn* purity.

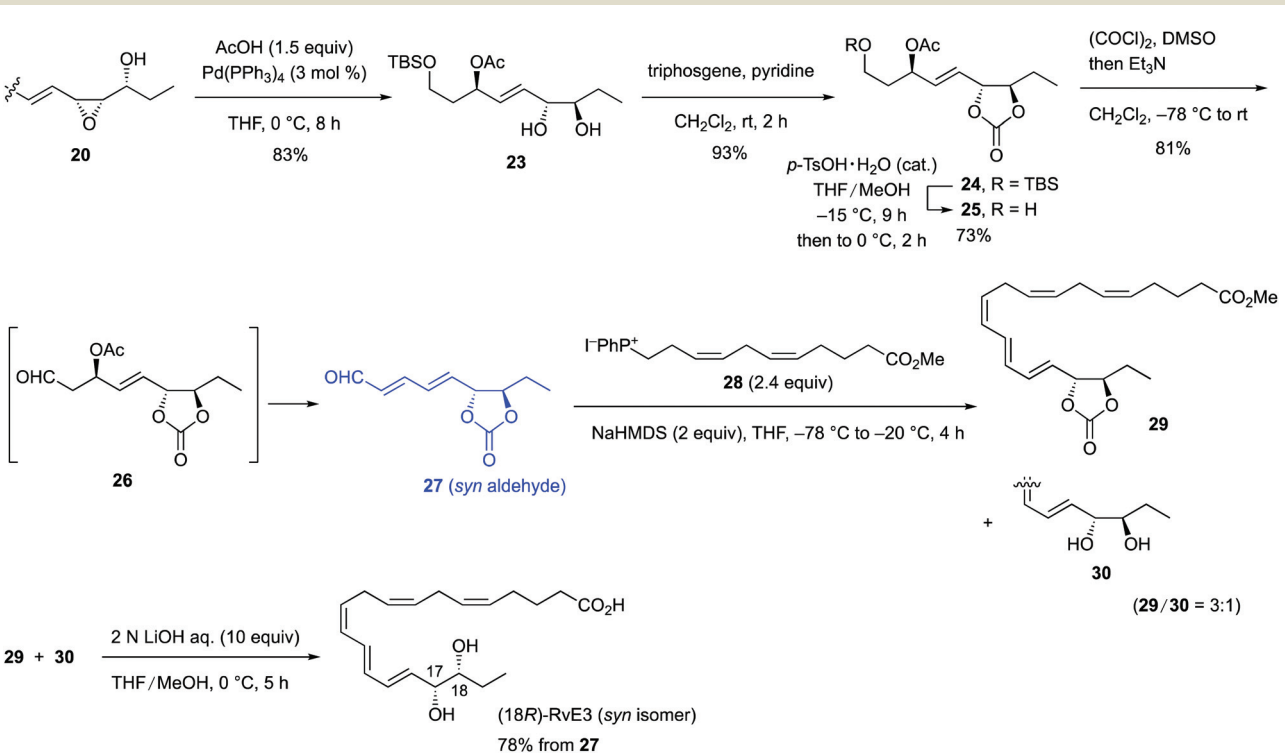
The Mitsunobu inversion of **20** produced **21** in a yield similar to that of the preliminary epoxide **12**. The hydrolysis proceeded cleanly to afford epoxy alcohol **22** in a high yield. The alcohol was the intermediate for the synthesis of (18*S*)-RvE3.



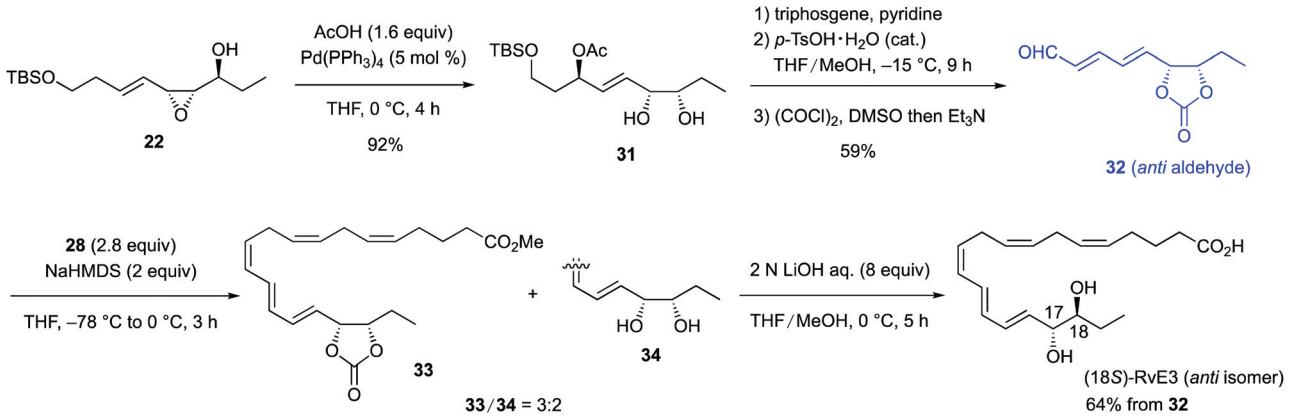
Scheme 3 Synthesis of two epoxy intermediates.

The Pd-catalyzed reaction of **20** with AcOH at 0 °C for 8 h afforded **23** in a good yield with high regio- and stereoselectivity as confirmed by clean ^{1}H and ^{13}C NMR spectroscopy (Scheme 4).

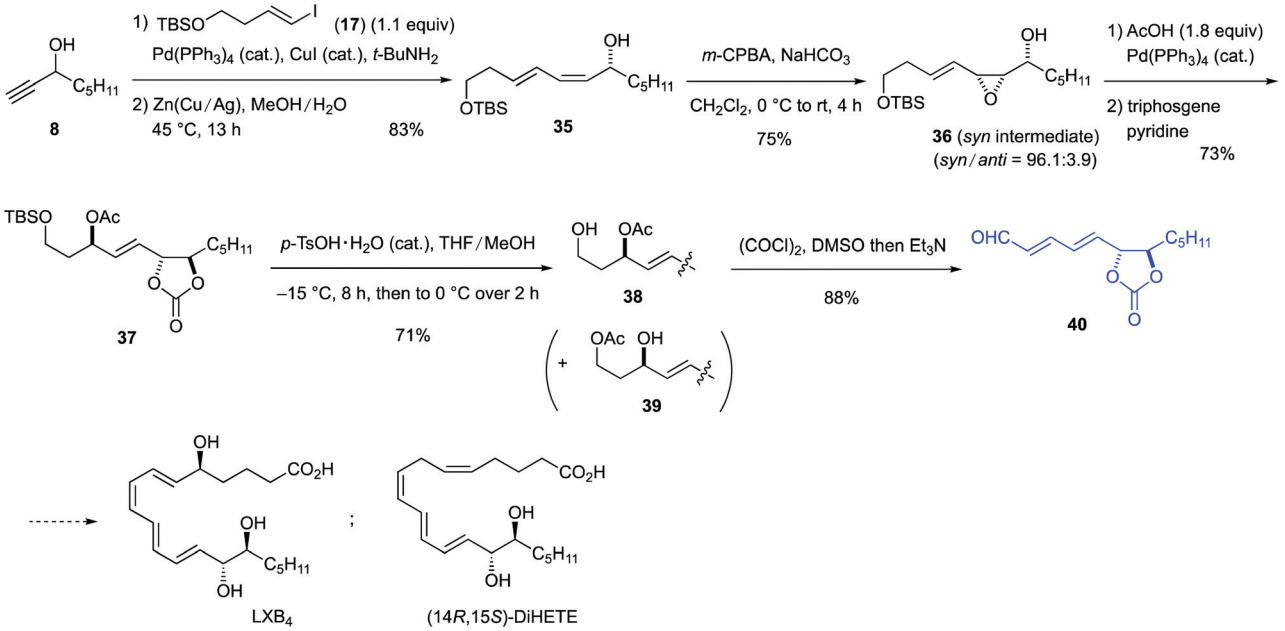
The stereochemistry was assigned as indicated by analogy to the similar case published previously,[7] and the assignment was consistent with the well-established overall retention. The diol part in **23** was protected as the carbonate, and the TBS deprotection was performed using *p*-TsOH·H_2O (5 mol%) at −15 °C.[17] The Swern oxidation of the resulting alcohol **25** gave acetoxy aldehyde **26**, which was confirmed by TLC, and this aldehyde, without isolation, was collapsed moderately fast to the key aldehyde **27** in 81% yield (R_f values of **25**, **26** and **27** = 0.09, 0.20 and 0.25 (hexane/EtOAc = 1 : 1)). Phosphonium salt



Scheme 4 Synthesis of (18*R*)-RvE3.



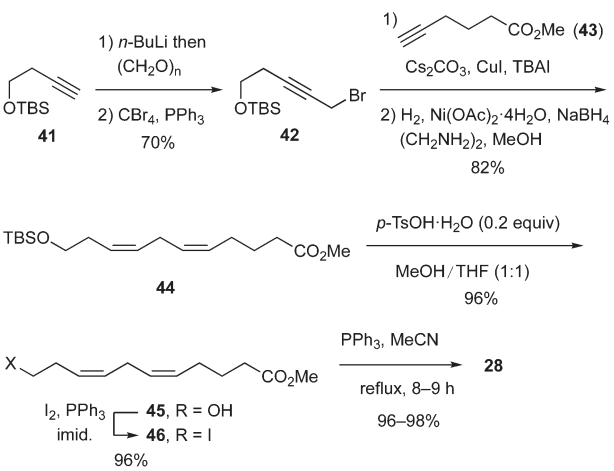
Scheme 5 Synthesis of (18*R*)-RvE3.



Scheme 6 Synthesis of the intermediate for the ω-6 metabolites.

28 was prepared by the method summarized in the latter scheme (Scheme 7) and converted to the ylide using NaHMDS at −78 °C. The Wittig olefination of **27** with the ylide (2 equiv.) at −78 °C and then at temperatures gradually warming to −20 °C over 4 h afforded a mixture of carbonate **29** and diol **30** in a ratio of 3 : 1. The formation of diol **30** was reproduced several times. Without separation, the mixture was subjected to hydrolysis with LiOH in aqueous THF/MeOH to afford (18*R*)-RvE3 in 78% yield from **27**. The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 6. The structure was also confirmed by the ^{13}C–APT NMR spectrum.

Next, the *anti* epoxy alcohol **22** underwent the Pd-catalyzed reaction with AcOH to afford **31** in 92% yield exclusively, and the subsequent three-step transformation produced the key aldehyde **32** in 59% yield. The Wittig olefination of **32** with **28**/NaHMDS gave a mixture of carbonate **33** and diol **34** in 3 : 2



Scheme 7 Preparation of phosphonium salt.

ratio as observed in the Wittig reaction of the *syn* aldehyde **27**. The mixture was then hydrolyzed with aqueous LiOH to furnish (18*S*)-RvE3 in 64%.

The ^{1}H and ^{13}C NMR spectra were consistent with those reported in ref. 6, and the ^{13}C–APT NMR spectrum supported the structure.

In addition, alcohol **35** was prepared from **8**[18] and iodide **17** in two steps, and converted to **37** *via* the epoxidation and the Pd-catalyzed reaction (Scheme 6). These steps proceeded regio- and stereoselectively as well. The TBS desilylation of **37** with *p*-TsOH·H_2O at low temperatures afforded **38**, whereas desilylation at higher temperatures or by other methods competed with the migration of the AcO group to **39**.[17] Finally, the Swern oxidation of **38** produced aldehyde **40**, which has been and would be an intermediate[19] for the synthesis of lipoxin B_4 and (14*R*,15*S*)-diHETE, respectively.

Phosphonium salt **28** used for the Wittig reactions with aldehydes **27** and **32** (Schemes 4 and 5) was prepared by a method summarized in Scheme 7 with modification of the literature methods. The experimental procedure is presented in the ESI.†

Conclusions

We have developed a method for the synthesis of (18*R*)- and (18*S*)-RvE3 through the stereoselective epoxidation of dienyl alcohol **19**, the subsequent Pd-catalyzed additions of AcOH to vinyl epoxy alcohols **20** and **22**, and the Wittig reactions of **27** and **32** with **28**. The total yields of (18*R*)- and (18*S*)-RvE3 from propionaldehyde through ketone **14** were 17% and 10% over 13 and 15 steps, respectively, which are better than the previous yields of 3.8% and 6.2% over 12 and 17 steps. Furthermore, the Pd-catalyzed addition of AcOH to **20** and **22** proceeded regio- and stereoselectively to produce the triol mono-acetates **23** and **31**, respectively (Schemes 4 and 5). We hope that the present method will be utilized for the synthesis of metabolites possessing a similar structure.

Experimental

General methods

The ^{1}H (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectroscopic data were recorded in $CDCl_3$ or CD_3OD with Me_4Si (δ = 0 ppm), the centerline of the $CDCl_3$ triplet (δ = 77.1 ppm) or residual protonated solvent as an internal standard. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet) and m (multiplet). Coupling constants (J) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by minus (for C and CH_2) and plus (for CH and CH_3) signs of the attached proton test (APT) experiment. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer. The solvents that were distilled prior to use are THF (from Na/benzophenone) and CH_2Cl_2 (from CaH_2). After extraction of the products, the extracts were concentrated by using an evaporator and then residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N).

(*R*)-1-(Trimethylsilyl)pent-1-yn-3-ol (14)

The synthesis was carried out according to the published procedure.[13] To a solution of trimethylsilylacetylene (35.5 mL, 251 mmol) in THF (200 mL) was added *n*-BuLi (1.55 M in hexane, 144 mL, 223 mmol) at −78 °C dropwise. After 30 min of stirring at −78 °C, propionaldehyde (14.4 mL, 201 mmol) was added. The solution was stirred at rt for 4 h and diluted with saturated NH_4Cl and hexane. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give racemic alcohol *rac*-**15** (27.9 g, 89%).

A mixture of alcohol *rac*-**15** (5.02 g, 32.1 mmol), PCC (8.28 g, 38.4 mmol) and Celite (16.5 g) in CH_2Cl_2 (70 mL) was stirred at rt for 8 h and diluted with hexane. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **14** (3.74 g, 76%): liquid; R_f = 0.70 (hexane/EtOAc 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 9 H), 1.13 (t, J = 7.4 Hz, 3 H), 2.58 (q, J = 7.4 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −0.7 (+), 7.9 (+), 38.6 (−), 97.6 (−), 101.8 (−), 188.4 (−). The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 13.

A mixture of RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (201 mg, 0.316 mmol) and KOH (*ca.* 120 mg, 2.14 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 45 min. The mixture was washed with H_2O several times and the CH_2Cl_2 solution was transferred to another flask with CH_2Cl_2. The solution was dried over CaH_2 and the supernatant was concentrated to afford a purple solid. The solid was diluted with *i*-PrOH (24 mL) and ketone **14** (3.67 g, 23.8 mmol) in *i*-PrOH (24 mL) was added. After being stirred at rt for 12 h, the mixture was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **15** (3.39 g, 91%): 96.4% ee by HPLC analysis (Chiralpak AD-H, hexane/*i*-PrOH = 99 : 1, 1.0 mL min^{-1}, 35 °C, t_R/min = 9.0 (*S*-isomer, minor), 9.4 (*R*-isomer, major)); liquid; R_f = 0.44 (hexane/EtOAc 6 : 1); $[\alpha]_D^{21}$ +6.4 (*c* 2.1, $CHCl_3$); lit.[13] $[\alpha]_D^{24}$ +6.12 (*c* 2.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.01 (t, J = 7.4 Hz, 3 H), 1.67–1.76 (m, 2 H), 1.76–1.82 (m, 1 H), 4.31 (q, J = 6.1 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −0.1 (+), 9.5 (+), 30.8 (−), 64.1 (+), 89.4 (−), 106.7 (−). The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 13.

(*E*)-*tert*-Butyl[(4-iodobut-3-en-1-yl)oxy]dimethylsilane (17)

A solution of 3-butyn-1-ol (1.86 g, 26.5 mmol), TBSCl (8.04 g, 29.3 mmol) and imidazole (2.18 g, 32.0 mmol) in DMF (27 mL) was stirred at rt for 13 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give silyl ether **41**

(4.55 g, 93%): liquid; R_f = 0.52 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.96 (t, J = 2.8 Hz, 1 H), 2.40 (dt, J = 2.8, 7.2 HZ, 2 H), 3.74 (t, J = 7.2 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.2 (+), 18.4 (−), 22.9 (−), 26.0 (+), 61.8 (−), 69.4 (−), 81.6 (−). The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 20.

To a solution of Cp_2ZrCl_2 (1.90 g, 6.51 mmol) in THF (30 mL) was added DIBAL (1.03 M in hexane, 5.80 mL, 5.97 mmol) at rt dropwise. After 1 h of stirring at rt, silyl ether **41** (1.00 g, 5.43 mmol) in THF (12 mL) was added at 0 °C. The mixture was stirred at rt for 2 h and then cooled to −78 °C. A solution of I_2 (2.05 g, 8.08 mmol) in THF (12 mL) was added to the mixture. After 2 h of stirring at 0 °C, the resulting mixture was poured onto a mixture of H_2O (1.5 mL, 83.3 mmol), NaF (3.42 g, 81.4 mmol) and Celite (6.84 g). The resulting mixture was stirred at rt for 1 h and filtered through a pad of Celite with hexane. The filtrate was washed successively with aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give iodide **17** (1.36 g, 80%): liquid; R_f = 0.60 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 2.26 (dq, J = 1.3, 6.4 Hz, 2 H), 3.64 (t, J = 6.4 Hz, 2 H), 6.07 (dt, J = 14.4, 1.3 Hz, 1 H), 6.53 (dt, J = 14.4, 7.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.2 (+), 18.4 (−), 26.0 (+), 39.4 (−), 61.7 (−), 76.5 (+), 143.4 (+). The ^{1}H and ^{13}C NMR spectra were identical to those reported.[20]

(*R*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]non-6-en-4-yn-3-ol (18)

A mixture of alcohol **15** (1.17 g, 7.47 mmol) and K_2CO_3 (1.25 g, 9.01 mmol) in MeOH (8 mL) was stirred at rt for 2 h and complete conversion to **16** was confirmed by TLC (R_f of **16** and **15** = 0.26 and 0.44, respectively (hexane/EtOAc 6 : 1)). Without isolation of **16**, the mixture was cooled to 0 °C, and iodide **17** (2.58 g, 8.25 mmol) in benzene (15 mL), *t*-$BuNH_2$ (4 mL, 37.7 mmol), $Pd(PPh_3)_4$ (86.8 mg, 0.0751 mmol) and CuI (28.5 mg, 0.150 mmol) were sequentially added. The mixture was stirred at rt for 3 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give enyne **18** (1.90 g, 95%): liquid; R_f = 0.42 (hexane/EtOAc 6 : 1); $[\alpha]_D^{21}$ +1.4 (c 1.2, $CHCl_3$); IR (neat) 3351, 1255, 1098, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.01 (t, J = 7.4 Hz, 3 H), 1.68–1.79 (m, 3 H), 2.32 (dq, J = 1.2, 6.8 Hz, 2 H), 3.65 (t, J = 6.8 Hz, 2 H), 4.42 (dq, J = 1.6, 6.8 Hz, 1 H), 5.55 (dq, J = 16.0, 1.6 Hz, 1 H), 6.14 (dt, J = 16.0, 7.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.2 (+), 9.5 (+), 18.4 (−), 26.0 (+), 31.0 (−), 36.7 (−), 62.3 (−), 64.2 (−), 83.5 (−), 88.8 (−), 110.9 (+), 141.5 (+); HRMS (FAB^+) calcd for $C_{15}H_{28}O_2SiNa$ [$(M + Na)^+$] 291.1756, found 291.1757.

(*R*)-1-[(2*S*,3*R*)-3-[(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-1-en-1-yl]oxiran-2-yl]propan-1-ol (20)

A suspension of Zn powder (5.31 g, 80.8 mmol) in H_2O (50 mL) was gently bubbled with nitrogen gas for 20 min and $Cu(OAc)_2$ (733 mg, 4.04 mmol) was added. After being stirred for 20 min, $AgNO_3$ (687 mg, 4.05 mmol) was added. The suspension was stirred for further 30 min. The resulting suspension was filtered by suction and the remaining solid was washed with H_2O, MeOH, acetone and Et_2O, twice respectively. The solid was suspended with H_2O (20 mL) and a solution of enyne **18** (1.07 g, 3.98 mmol) in MeOH (20 mL) was added. After being stirred at 45 °C for 13 h, the mixture was filtered through a pad of Celite. The filtrate was concentrated to leave a residue, which was diluted with EtOAc. The solution was washed with saturated $NaHCO_3$. After drying with $MgSO_4$ and concentration, the residue was purified by chromatography on silica gel (hexane/EtOAc) to give diene **19** (1.02 g, 95%): liquid; R_f = 0.43 (hexane/EtOAc 4 : 1); $[\alpha]_D^{22}$ −34 (c 1.2, $CHCl_3$); IR (neat) 3358, 1255, 1102, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 0.91 (t, J = 7.6 Hz, 3 H), 1.42–1.56 (m, 2 H), 1.58–1.70 (m, 1 H), 2.32 (dq, J = 1.2, 6.8 Hz, 2 H), 3.66 (t, J = 6.8 Hz, 2 H), 4.50 (ddt, J = 5.6, 2.4, 6.4 Hz, 1 H), 5.29 (t, J = 10.0 Hz, 1 H), 5.74 (dt, J = 15.6, 6.8 Hz, 1 H), 6.04 (t, J = 11.2 Hz, 1 H), 6.38 (dd, J = 15.2, 11.2, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.2 (+), 9.7 (+), 18.4 (−), 26.0 (+), 30.4 (−), 36.5 (−), 62.7 (−), 69.3 (+), 127.0 (+), 130.5 (+), 131.9 (+), 133.3 (+).

To an ice-cold mixture of diene **19** (1.11 g, 4.10 mmol) and $NaHCO_3$ (762 mg, 9.07 mmol) in CH_2Cl_2 (21 mL) was added *m*-CPBA (70% purity, 1.21 g, 4.92 mmol). After 1 h of stirring at 0 °C, Me_2S (0.15 mL, 2.05 mmol) was added to the mixture. The mixture was stirred at 0 °C for 1 h, diluted with saturated $NaHCO_3$ and extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc with Et_3N (trace)) to give epoxide **20** (1.04 g, 88%, 97.5% *syn* over *anti* by ^{1}H NMR spectroscopy): liquid; R_f = 0.32 (hexane/EtOAc 4 : 1); $[\alpha]_D^{24}$ −19 (c 1.1, $CHCl_3$); IR (neat) 3440, 1255, 1100, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 0.95 (t, J = 7.6 Hz, 3 H), 1.48–1.67 (m, 2 H), 2.20 (s, 1 H), 2.30 (q, J = 6.4 Hz, 2 H), 3.02 (dd, J = 7.6, 4.6 Hz, 2 H), 3.45 (dt, J = 5.8, 7.6 Hz, 1 H), 3.51 (dd, J = 8.0, 4.6 Hz, 1 H), 3.65 (t, J = 6.4 Hz. 2 H), 5.38 (ddt, J = 15.6, 8.0, 1.4 Hz, 1 H), 5.96 (dt, J = 15.6, 7.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.3 (+), 9.5 (+), 18.4 (−), 25.9 (+), 26.7 (−), 36.1 (−), 58.0 (+), 62.2 (+), 62.5 (−), 71.1 (+), 125.7 (+), 135.2 (+); HRMS (FAB^+) calcd for $C_{15}H_{31}O_3Si$ [$(M + H)^+$] 287.2042, found 287.2047.

(*S*)-1-[(2*S*,3*R*)-3-[(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-1-en-1-yl]oxiran-2-yl]propan-1-ol (22)

To an ice-cold solution of epoxide **20** (969 mg, 3.38 mmol, *syn*/*anti* = 97.5 : 2.5), 4-nitrobenzoic acid (845 mg, 5.06 mmol) and PPh_3 (1.34 g, 5.11 mmol) in THF (11 mL) was added DIAD (1.0 mL, 5.14 mmol). The solution was stirred at 0 °C for 80 min and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc with Et_3N (trace)) to give ester **21** (947 mg,

64%): liquid; R_f = 0.69 (hexane/EtOAc 4 : 1); $[\alpha]_D^{23}$ +71 (*c* 1.0, $CHCl_3$); IR (neat) 1729, 1530, 1271, 1101, 837, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.018 (s, 3 H), 0.022 (s, 3 H), 0.86 (s, 9 H), 1.06 (t, *J* = 7.4 Hz, 3 H), 1.86–2.05 (m, 2 H), 2.30 (tq, *J* = 1.6, 6.8 Hz, 2 H), 3.24 (dd, *J* = 8.0, 3.8 Hz, 1 H), 3.48 (dd, *J* = 7.6, 3.8 Hz, 1 H), 3.61 (dt, *J* = 1.6, 6.8 Hz, 2 H), 4.92 (dt, *J* = 5.2, 7.6 Hz, 1 H), 5.50 (ddt, *J* = 15.6, 7.6, 1.6 Hz, 1 H), 5.96 (dt, *J* = 15.6, 6.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ −5.3 (+), 9.2 (+), 18.3 (−), 25.91 (−), 25.94 (+), 36.1 (−), 57.1 (+), 58.5 (+), 62.6 (−), 73.6 (+), 123.6 (+), 125.0 (+), 130.8 (+), 135.2 (+), 135.5 (−), 150.6 (−), 163.6 (−).

To an ice-cold solution of ester **21** (641 mg, 1.47 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was added 2 N LiOH (2.0 mL, 4.00 mmol). The mixture was stirred at 0 °C for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc with Et_3N (trace)) to give epoxide **22** (394 mg, 94%, 96.8% *anti* over *syn* by ^1H NMR spectroscopy): liquid; R_f = 0.43 (hexane/EtOAc 4 : 1); $[\alpha]_D^{25}$ −6.8 (*c* 1.2, $CHCl_3$); IR (neat) 3440, 1255, 1101, 968, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 1.58–1.81 (m, 3 H), 2.32 (dq, *J* = 1.0, 6.8 Hz, 2 H), 3.01 (dd, *J* = 4.0, 7.2 Hz, 1 H), 3.45 (dd, *J* = 4.0 8.0 Hz, 1 H), 3.50–3.58 (m, 1 H), 3.67 (t, *J* = 6.8 Hz, 2 H), 5.54 (ddt, *J* = 15.6, 8.0, 1.4 Hz, 1 H), 5.99 (dt, *J* = 15.6, 6.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ −5.2 (+), 9.5 (+), 18.4 (−), 26.0 (+), 27.9 (−), 36.2 (−), 56.9 (+), 60.6 (+), 62.5 (−), 70.4 (+), 125.6 (+), 135.3 (+); HRMS (FAB^+) calcd for $C_{15}H_{31}O_3Si$ $[(M + H)^+]$ 287.2042, found 287.2042.

(3*R*,6*R*,7*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dihydroxynon-4-en-3-yl acetate (23)

To an ice-cold solution of $Pd(PPh_3)_4$ (102 mg, 0.088 mmol) and AcOH (0.25 mL, 4.37 mmol) in THF (8 mL) was added a solution of epoxide **20** (847 mg, 2.96 mmol) in THF (8 mL). After 8 h of stirring at 0 °C, H_2O_2 (35 wt/v%, 1.0 mL, 10.3 mmol) was added to the mixture. The mixture was stirred at 0 °C for 2 h, diluted with saturated $NaHCO_3$ and extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give diol **23** (845 mg, 83%): liquid; R_f = 0.14 (hexane/EtOAc 2 : 1); $[\alpha]_D^{25}$ +28 (*c* 1.1, $CHCl_3$); IR (neat) 3422, 1740, 1254, 1099, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 1.35–1.49 (m, 1 H), 1.50–1.66 (m, 1 H), 1.75–1.92 (m, 2 H), 2.05 (s, 3 H), 2.17–2.27 (m, 2 H), 3.35–3.42 (m, 1 H), 3.65 (t, *J* = 6.0 Hz. 2 H), 3.92–3.99 (m, 1 H), 5.39 (dt, *J* = 7.6, 5.6 Hz, 1 H), 5.72 (dd, *J* = 15.6, 5.6 Hz, 1 H), 5.76 (dd, *J* = 15.6, 5.6 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.4 (+), 10.0 (+), 18.3 (−), 21.3 (+), 25.8 (−), 25.9 (+), 37.3 (−), 59.0 (−), 71.3 (+), 74.9 (+), 75.8 (+), 131.1 (+), 132.0 (+), 170.5 (−); HRMS (FAB^+) calcd for $C_{17}H_{35}O_5Si$ $[(M + H)^+]$ 347.2254, found 347.2259.

(2*E*,4*E*)-5-[(4*R*,5*R*)-5-Ethyl-2-oxo-1,3-dioxolan-4-yl]penta-2,4-dienal (27)

A mixture of diol **23** (1.88 g, 5.41 mmol), triphosgene (803 mg, 2.70 mmol) and pyridine (2.60 mL, 32.3 mmol) in CH_2Cl_2 (27 mL) was stirred at rt for 2 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give carbonate **24** (1.88 g, 93%): liquid; R_f = 0.61 (hexane/EtOAc 2 : 1); $[\alpha]_D^{23}$ +49 (*c* 1.1, $CHCl_3$); IR (neat) 1810, 1742, 1235, 1098, 838, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 1.70–1.91 (m, 4 H), 2.05 (s, 3 H), 3.59–3.69 (m, 2 H), 4.25 (dt, *J* = 5.6, 7.2 Hz, 1 H), 4.64 (t, *J* = 7.2 Hz, 1 H), 5.42 (dt, *J* = 6.0, 6.4 Hz, 1 H), 5.72 (ddd, *J* = 15.6, 5.6, 1.2 Hz, 1 H), 5.89 (ddd, *J* = 15.6, 6.4, 0.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ −5.4 (+), 8.9 (+), 18.2 (−), 21.1 (+), 25.9 (+), 26.1 (−), 37.0 (−), 58.6 (−), 70.4 (+), 81.4 (+), 83.1 (+), 126.1 (+), 135.6 (+), 154.2 (−), 170.0 (−).

A solution of carbonate **24** (189 mg, 0.507 mmol) and *p*-TsOH·H_2O (4.9 mg, 0.0255 mmol) in THF (1.3 mL) and MeOH (1.3 mL) was stirred at −15 °C for 9 h and then at temperatures raised to 0 °C over 2 h. The solution was diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **25** (96 mg, 73%): liquid; R_f = 0.09 (hexane/EtOAc 1 : 1); $[\alpha]_D^{25}$ +74 (*c* 1.1, $CHCl_3$); IR (neat) 3490, 1801, 1736, 1241, 1046, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.4 Hz, 3 H), 1.73–1.94 (m, 4 H), 1.99 (br s, 1 H), 2.10 (s, 3 H), 3.58–3.74 (m, 2 H), 4.26 (dt, *J* = 6.0, 7.2 Hz, 1 H), 4.67 (t, *J* = 7.2 Hz, 1 H), 5.51 (dt, *J* = 8.0, 6.0 Hz, 1 H), 5.76 (ddd, *J* = 15.2, 7.2, 0.8 Hz, 1 H), 5.92 (ddd, *J* = 15.2, 6.0, 0.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 8.8 (+), 21.1 (+), 26.0 (−), 36.9 (−), 58.0 (−), 70.2 (+), 81.4 (+), 83.1 (+), 126.0 (+), 135.3 (+), 154.3 (−), 170.7 (−).

To a solution of $(COCl)_2$ (0.075 mL, 0.874 mmol) in CH_2Cl_2 (0.7 mL) was added DMSO (0.090 mL, 1.27 mmol) at −78 °C. After 20 min of stirring at −78 °C, a solution of alcohol **25** (109 mg, 0.422 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min and then Et_3N (0.35 mL, 2.48 mmol) was added. After being stirred at −78 °C for 10 min, the ice bath was removed. The mixture was stirred at rt for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give aldehyde **27** (67.0 mg, 81%): liquid; R_f = 0.25 (hexane/EtOAc 1 : 1); $[\alpha]_D^{23}$ +74 (*c* 1.1, $CHCl_3$); IR (neat) 1803, 1683, 1045, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.6 Hz, 3 H), 1.78–1.88 (m, 2 H), 4.32 (dt, *J* = 5.6, 6.8 Hz, 1 H), 4.81 (t, *J* = 6.8 Hz, 1 H), 6.17 (dd, *J* = 15.2, 6.8 Hz, 1 H), 6.26 (dd, *J* = 15.2, 7.6 Hz, 1 H), 6.64 (dd, *J* = 15.2, 10.8 Hz, 1 H), 7.10 (dd, *J* = 15.2, 10.8 Hz, 1 H), 9.62 (d, *J* = 7.6 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$)

δ 8.9 (+), 26.2 (−), 80.7 (+), 82.8 (+), 132.4 (+), 134.3 (+), 135.5 (+), 148.3 (+), 153.9 (−), 193.2 (+); HRMS (FAB^+) calcd for $C_{10}H_{13}O_4$ [$(M + H)^+$] 197.0814, found 197.0813. Cf. β-Acetoxyaldehyde **26** from **25**: R_f = 0.20 (hexane/EtOAc 1 : 1).

(3*R*,6*R*,7*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dihydroxynon-4-en-3-yl acetate (31)

To an ice-cold solution of $Pd(PPh_3)_4$ (61 mg, 0.0528 mmol) and AcOH (0.090 mL, 1.57 mmol) in THF (2.6 mL) was added a solution of epoxide **22** (272 mg, 0.949 mmol) in THF (2.6 mL). After 4 h of stirring at 0 °C, H_2O_2 (35 wt/v%, 0.50 mL, 5.15 mmol) was added to the resulting mixture. The mixture was stirred at 0 °C for 1 h, diluted with saturated $NaHCO_3$ and extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated, which was purified by chromatography on silica gel (hexane/EtOAc) to give diol **31** (302 mg, 92%): liquid; R_f = 0.19 (hexane/EtOAc 2 : 1); $[\alpha]_D^{22}$ +23 (*c* 1.0, $CHCl_3$); IR (neat) 3430, 1740, 1254, 1098, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 0.98 (t, *J* = 7.6 Hz, 3 H), 1.33–1.53 (m, 2 H), 1.76–1.93 (m, 2 H), 1.94 (s, 1 H), 2.05 (s, 3 H), 2.05–2.13 (m, 1 H), 3.55–3.62 (m, 1 H), 3.65 (t, *J* = 5.6 Hz. 2 H), 4.09–4.14 (m, 1 H), 5.38 (dt, *J* = 7.6, 5.2 Hz, 1 H), 5.73 (dd, *J* = 15.6, 5.2 Hz, 1 H), 5.77 (dd, *J* = 15.6, 5.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ −5.4 (+), 10.3 (+), 18.3 (−), 21.3 (+), 25.1 (−), 25.9 (+), 37.3 (−), 59.0 (−), 71.4 (+), 74.7 (+), 75.6 (+), 130.4 (+), 131.4 (+), 170.6 (−); HRMS (FAB^+) calcd for $C_{17}H_{35}O_5Si$ [$(M + H)^+$] 347.2254, found 347.2251.

(2*E*,4*E*)-5-[(4*R*,5*S*)-5-Ethyl-2-oxo-1,3-dioxolan-4-yl]penta-2,4-dienal (32)

A mixture of diol **31** (251 mg, 0.723 mmol), triphosgene (107 mg, 0.362 mmol) and pyridine (0.35 mL, 4.34 mmol) in CH_2Cl_2 (4.5 mL) was stirred at rt for 1 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give the corresponding carbonate (234 mg, 87%): liquid; R_f = 0.62 (hexane/EtOAc 2 : 1); $[\alpha]_D^{20}$ +15 (*c* 1.1, $CHCl_3$); IR (neat) 1806, 1740, 1236, 1096, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 1.51–1.94 (m, 4 H), 2.06 (s, 3 H), 3.59–3.71 (m, 2 H), 4.61 (ddd, *J* = 9.2, 7.6, 4.8 Hz, 1 H), 5.09 (t, *J* = 7.6 Hz, 1 H), 5.42 (dt, *J* = 6.8, 6.4 Hz, 1 H), 5.72 (ddd, *J* = 15.6, 7.6, 0.8 Hz, 1 H), 5.87 (ddd, *J* = 15.6, 6.8, 0.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ −5.4 (+), 9.9 (+), 18.3 (−), 21.2 (+), 23.4 (−), 25.9 (+), 37.1 (−), 58.7 (−), 70.7 (+), 79.2 (+), 81.4 (+), 123.8 (+), 135.7 (+), 154.4 (−), 170.1 (−).

A solution of the above carbonate (222 mg, 0.595 mmol) and *p*-TsOH·H_2O (6 mg, 0.032 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was stirred at −15 °C for 9 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give the corresponding alcohol (114 mg, 74%): liquid; R_f = 0.23 (hexane/EtOAc 1 : 1); $[\alpha]_D^{21}$ +24 (*c* 1.1, $CHCl_3$); IR (neat) 3480, 1798, 1735, 1242, 1041, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.4 Hz, 3 H), 1.51–1.76 (m, 2 H), 1.79–1.96 (m, 3 H), 2.10 (s, 3 H), 3.58–3.74 (m, 2 H), 4.62 (ddd, *J* = 9.4, 7.4, 4.6 Hz, 1 H), 5.11 (t, *J* = 7.4 Hz, 1 H), 5.47–5.54 (m, 1 H), 5.76 (ddd, *J* = 15.6, 7.4, 1.2 Hz, 1 H), 5.90 (ddd, *J* = 15.6, 6.4, 0.8 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 9.9 (+), 21.1 (+), 23.3 (−), 37.1 (+), 58.2 (−), 70.5 (+), 79.1 (+), 81.4 (+), 123.6 (+), 135.3 (+), 154.4 (−), 170.7 (−).

To a solution of $(COCl)_2$ (0.10 mL, 1.17 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.12 mL, 1.69 mmol) at −78 °C. After 20 min of stirring at −78 °C, a solution of the above alcohol (141 mg, 0.547 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min and then Et_3N (0.46 mL, 3.30 mmol) was added. After being stirred at −78 °C for 10 min, the ice bath was removed and the mixture was stirred at rt further 2 h. The resulting mixture was diluted with saturated NH_4Cl and extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give aldehyde **32** (99 mg, 92%): liquid; R_f = 0.35 (hexane/EtOAc 1 : 1); $[\alpha]_D^{20}$ +4.9 (*c* 1.4, $CHCl_3$); IR (neat) 1801, 1684, 1182, 1038, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3 H), 1.54–1.78 (m, 2 H), 4.70 (ddd, *J* = 9.4, 7.2, 4.6 Hz, 1 H), 5.26 (t, *J* = 7.2 Hz, 1 H), 6.15 (dd, *J* = 15.2, 7.2 Hz, 1 H), 6.25 (dd, *J* = 15.6, 7.6 Hz, 1 H), 6.66 (dd, *J* = 15.6, 10.8 Hz, 1 H), 7.12 (dd, *J* = 15.2, 10.8 Hz, 1 H), 9.62 (d, *J* = 7.6 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 9.9 (+), 23.6 (−), 78.6 (+), 81.3 (+), 132.7 (+), 133.2 (+), 133.9 (+), 148.4 (+), 154.0 (−), 193.3 (+); HRMS (FAB^+) calcd for $C_{10}H_{13}O_4$ [$(M + H)^+$] 197.0814, found 197.0814.

(5*Z*,8*Z*,11*Z*,13*E*,15*E*,17*R*,18*R*)-17,18-Dihydroxyicosa-5,8,11,13,15-pentaenoic acid ((18*R*)-Resolvin E3)

A solution of iodide **46** (399 mg, 1.24 mmol) and PPh_3 (491 mg, 1.87 mmol) in MeCN (6 mL) was heated under reflux for 8 h, cooled to rt, and concentrated. The residue was washed with Et_2O repeatedly to give phosphonium salt **28** (696 mg, 96%), which was used for the next reaction without further purification: viscous liquid; R_f = 0.38 (CH_2Cl_2/MeOH 10 : 1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (quint., *J* = 7.2 Hz, 2 H), 1.95 (q, *J* = 7.2 Hz, 2 H), 2.25 (t, *J* = 7.2 Hz, 2 H), 2.39–2.55 (m, 2 H), 2.55 (t, *J* = 6.5 Hz, 2 H), 3.64 (s, 3 H), 3.81–3.92 (m, 2 H), 5.16–5.44 (m, 3 H), 5.56–5.68 (m, 1 H), 7.66–7.76 (m, 6 H), 7.76–7.92 (m, 9 H).

To a solution of the above phosphonium salt **28** in THF (3 mL) was added NaHMDS (1.0 M in THF, 1.0 mL, 1.00 mmol) at −78 °C. After 30 min of stirring at −78 °C, aldehyde **27** (99 mg, 0.505 mmol) in THF (2 mL) was added dropwise. The mixture was warmed to −20 °C over 4 h and poured onto a mixture of saturated NH_4Cl and EtOAc with vigorous stirring. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was passed through a short column of silica gel (hexane/EtOAc) to give a mixture of carbonate **29** and diol **30**

(3 : 1 by ^{1}H NMR spectroscopy). The Wittig reaction was repeated and the products were purified by chromatography on silica gel (hexane/EtOAc). Carbonate **29**: R_f = 0.75 (hexane/EtOAc 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3 H), 1.64–1.84 (m, 4 H), 2.05–2.16 (m, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.80 (t, J = 5.4 Hz, 2 H), 2.98 (t, J = 7.2 Hz, 2 H), 3.66 (s, 3 H), 4.26 (dt, J = 7.7, 6.5 Hz, 1 H), 4.71 (t, J = 7.7 Hz, 1 H), 5.30–5.47 (m, 4 H), 5.53 (dt, J = 11.0, 7.2 Hz, 1 H), 5.64 (dd, J = 15.0, 7.7 Hz, 1 H), 6.05 (t, J = 11.0 Hz, 1 H), 6.21 (dd, J = 15.0, 10.8 Hz, 1 H), 6.46 (dd, J = 15.0, 10.8 Hz, 1 H), 6.64 (dd, J = 15.0, 11.0 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 9.0 (+), 24.7 (−), 25.6 (−), 26.0 (−), 26.3 (−), 26.5 (−), 33.4 (−), 51.5 (+), 82.5 (+), 83.2 (+), 125.2 (+), 127.1 (+), 128.0 (+), 128.6 (+), 128.9 (+), 129.1 (+), 130.2 (+), 131.5 (+), 132.9 (+), 136.9 (+), 154.4 (−), 174.0 (−). Diol **30**: R_f = 0.49 (hexane/EtOAc 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3 H), 1.36–1.50 (m, 1 H), 1.54–1.66 (m, 1 H), 1.70 (quint., J = 7.4 Hz, 2 H), 2.10 (dt, J = 6.8, 7.4 Hz, 2 H), 2.24–2.33 (m, 1 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.37 (s, 1 H), 2.81 (t, J = 5.6 Hz, 2 H), 2.92–3.00 (m, 2 H), 3.37–3.45 (m, 1 H), 3.67 (s, 3 H), 4.00 (t, J = 6.8 Hz, 1 H), 5.32–5.49 (m, 5 H), 5.70 (dd, J = 15.2, 6.8 Hz, 1 H), 6.04 (t, J = 11.2 Hz, 1 H), 6.21 (dd, J = 14.8, 10.8 Hz, 1 H), 6.39 (dd, J = 15.2, 10.8 Hz, 1 H), 6.55 (dd, J = 14.8, 11.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 10.1 (+), 24.8 (−), 25.7 (−), 25.9 (−), 26.3 (−), 26.7 (−), 33.6 (−), 51.7 (+), 75.7 (+), 76.1 (+), 127.5 (+), 128.5 (+), 128.8 (+), 129.1 (+), 131.1 (+), 132.0 (+), 132.4 (+), 133.0 (+), 174.4 (−).

To an ice-cold solution of the above mixture in THF (4 mL) and MeOH (4 mL) was added 2 N LiOH (2.5 mL, 5.00 mmol). The mixture was stirred at 0 °C for 5 h and diluted with McIlvaine's phosphate buffer (pH 5.0). The resulting mixture was extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (Et_2O) to give (18*R*)-resolvin E3 (132 mg, 78% over two steps), which was further purified by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 25 : 75, 25 mL min^{-1}): liquid; R_f = 0.39 (CH_2Cl_2/MeOH 10 : 1); $[\alpha]_D^{22}$ +31 (*c* 0.19, MeOH); lit.[6] $[\alpha]_D^{25}$ +34 (*c* 0.16, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.97 (t, J = 7.4 Hz, 3 H), 1.28–1.42 (m, 1 H), 1.52–1.63 (m, 1 H), 1.67 (quint., J = 7.2 Hz, 2 H), 2.13 (q, J = 7.2 Hz, 2 H), 2.30 (t, J = 7.2 Hz, 2 H), 2.85 (t, J = 5.6 Hz, 2 H), 2.99 (t, J = 5.8 Hz, 2 H), 3.30–3.38 (m, 1 H), 3.97 (t, J = 6.6 Hz, 1 H), 4.89 (br s, 3 H), 5.32–5.46 (m, 5 H), 5.74 (dd, J = 15.0, 6.6 Hz, 1 H), 6.04 (t, J = 11.2, 1 H), 6.24 (dd, J = 14.8, 10.8 Hz, 1 H), 6.38 (dd, J = 15.0, 10.8 Hz, 1 H), 6.58 (dd, J = 14.8, 11.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, CD_3OD) δ 10.6 (+), 26.0 (−), 26.6 (−), 27.1 (−), 27.6 (−), 34.3 (−), 76.6 (+), 77.3 (+), 128.6 (+), 129.2 (+), 129.6 (+), 129.8 (+), 130.1 (+), 131.2 (+), 133.4 (+), 133.7 (+), 134.3 (+), 177.1 (−). The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 6.

(5*Z*,8*Z*,11*Z*,13*E*,15*E*,17*R*,18*S*)-17,18-Dihydroxyicosa-5,8,11,13,15-pentaenoic acid ((18*S*)-Resolvin E3)

A solution of iodide **46** (234 mg, 0.727 mmol) and PPh_3 (279 mg, 1.06 mmol) in MeCN (3.5 mL) was heated under reflux for 9 h, cooled to rt, and concentrated. The residue was washed with Et_2O repeatedly to give phosphonium salt **28** (417 mg, 98%), which was used for the next reaction without further purification.

To a solution of the above phosphonium salt **28** in THF (2 mL) was added NaHMDS (1.0 M in THF, 0.51 mL, 0.510 mmol) at −78 °C. After 30 min of stirring at −78 °C, aldehyde **32** (50 mg, 0.255 mmol) in THF (1.5 mL) was added dropwise. The mixture was warmed to 0 °C over 3 h and poured onto a mixture of saturated NH_4Cl and EtOAc with vigorous stirring. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to leave a residue, which was passed through a short column of silica gel (hexane/EtOAc) to give a mixture of carbonate **33** and diol **34** (3 : 2 by ^{1}H NMR spectroscopy). The Wittig reaction was repeated and the products were purified by chromatography on silica gel (hexane/EtOAc). Carbonate **33**: R_f = 0.74 (hexane/EtOAc 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3 H), 1.53–1.77 (m, 4 H), 2.10 (q, J = 7.2 Hz, 2 H), 2.31 (t, J = 7.4 Hz, 2 H), 2.80 (t, J = 5.8 Hz, 2 H), 2.97 (t, J = 7.4 Hz, 2 H), 3.66 (s, 3 H), 4.61 (ddd, J = 9.2, 7.8, 4.8 Hz, 1 H), 5.15 (t, J = 7.8 Hz, 1 H), 5.32–5.44 (m, 4 H), 5.52 (dt, J = 11.0, 7.4 Hz, 1 H), 5.64 (dd, J = 15.2, 7.8 Hz, 1 H), 6.05 (t, J = 11.0 Hz, 1 H), 6.22 (dd, J = 14.8, 10.8 Hz, 1 H), 6.45 (dd, J = 15.2, 10.8 Hz, 1 H), 6.63 (dd, J = 14.8, 11.0 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 10.0 (+), 23.5 (−), 24.8 (−), 25.7 (−), 26.3 (−), 26.6 (−), 33.5 (−), 51.6 (+), 80.3 (+), 81.6 (+), 122.6 (+), 127.2 (+), 128.1 (+), 128.6 (+), 129.0 (+), 129.2 (+), 130.4 (+), 131.3 (+), 132.9 (+), 136.9 (+), 154.6 (−), 174.1 (−). Diol **34**: R_f = 0.48 (hexane/EtOAc 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.36–1.54 (m, 2 H), 1.70 (quint., J = 7.4 Hz, 2 H), 2.06–2.14 (m, 3 H), 2.27 (br s, 1 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.80 (t, J = 5.6 Hz, 2 H), 2.92–2.99 (m, 2 H), 3.58–3.67 (m, 1 H), 3.66 (s, 3 H), 4.13–4.19 (m, 1 H), 5.32–5.48 (m, 5 H), 5.77 (dd, J = 15.2, 7.0 Hz, 1 H), 6.03 (t, J = 11.2 Hz, 1 H), 6.22 (dd, J = 15.0, 10.8 Hz, 1 H), 6.37 (dd, J = 15.2, 10.8 Hz, 1 H), 6.54 (dd, J = 15.0, 11.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 10.3 (+), 24.8 (−), 25.3 (−), 25.7 (−), 26.3 (−), 26.7 (−), 33.6 (−), 51.7 (+), 75.4 (+), 75.9 (+), 127.5 (+), 128.5 (+), 128.7 (+), 128.8 (+), 129.1 (+), 130.9 (+), 131.0 (+), 132.0 (+), 133.4 (+), 174.3 (−).

To an ice-cold solution of the above mixture in THF (2 mL) and MeOH (2 mL) was added 2 N LiOH (1.0 mL, 2.00 mmol). The mixture was stirred at 0 °C for 5 h and diluted with McIlvaine's phosphate buffer (pH 5.0). The resulting mixture was extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (Et_2O) to give (18*S*)-resolvin E3 (54 mg, 64% over two steps), which was further purified by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 25 : 75, 25 mL min^{-1}): liquid; R_f = 0.44 (CH_2Cl_2/MeOH 10 : 1); $[\alpha]_D^{23}$ +11 (*c* 0.15, MeOH); lit.[6] $[\alpha]_D^{27}$ +7.7 (*c* 0.15, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.30–1.44 (m, 1 H), 1.54–1.64 (m, 1 H), 1.67 (quint., J = 7.2 Hz, 2 H), 2.13 (q, J = 7.2 Hz, 2 H), 2.30 (t, J = 7.2 Hz, 2 H), 2.85 (t, J = 5.6 Hz, 2 H), 2.99 (t, J = 5.8 Hz,

2 H), 3.41 (ddd, J = 9.4, 6.0, 3.8 Hz, 1 H), 3.98 (t, J = 6.0 Hz, 1 H), 4.87 (br s, 3 H), 5.33–5.45 (m, 5 H), 5.81 (dd, J = 15.2, 6.0 Hz, 1 H), 6.04 (t, J = 11.4 Hz, 1 H), 6.25 (dd, J = 14.4, 10.8 Hz, 1 H), 6.36 (dd, J = 15.2, 10.8 Hz, 1 H), 6.58 (dd, J = 14.4, 11.4 Hz, 1 H); ^{13}C–APT NMR (75 MHz, CD_3OD) δ 10.6 (+), 26.0 (−), 26.6 (−), 26.7 (−), 27.1 (−), 27.6 (−), 34.4 (−), 76.5 (+), 77.3 (+), 128.6 (+), 129.0 (+), 129.6 (+), 129.78 (+), 129.81 (+), 130.1 (+), 131.1 (+), 133.4 (+), 133.9 (+), 134.2 (+), 177.6 (−). The ^{1}H and ^{13}C NMR spectra were identical to those reported in ref. 6.

Conflicts of interest

There are no conflicts to declare.

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16 Synthesized by hydrozirconation of the TBS ether **41** (Scheme 7) with $Cp_2Zr(H)Cl$ generated *in situ* followed by iodination in 80% yield (see the ESI†).

17 The reaction conditions for the TBS desilylation of **37** were optimized first (Scheme 6), and then applied to **24** and the carbonate derived from **31**. The use of TBAF (3 equiv.) in THF at 0 °C for 30 min caused the migration of the Ac group in **38** to the *prim*-OH to afford **39** as the sole product. Deprotection with PPTS (1 equiv.) in EtOH at 0 °C took 3 days to afford **38** without migration, whereas the deprotection at rt for 14 h produced a 86 : 14 mixture of **38** and **39**. In contrast, *p*-TsOH·H_2O (5 mol%) in MeOH/THF (1 : 1) at 0 °C for 4 h gave a 90 : 10 mixture. Finally, *p*-TsOH·H_2O at −15 °C for 8 h then to 0 °C over 2 h afforded **38** in 71% yield.

18 Enantioenriched **8** is commercially available.

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