First total syntheses of the pro-resolving lipid mediators 7(*S*),13(*R*),20(*S*)-Resolvin T1 and 7(*S*),13(*R*)-Resolvin T4

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Abstract

The first total syntheses of the pro-resolving lipid mediators 7(*S*),13(*R*),20(*S*)-Resolvin T1 [7(*S*),13(*R*),20(*S*)-RvT1] and 7(*S*),13(*R*)-Resolvin T4 [7(*S*),13(*R*)-RvT4], derived from n-3 docosapentaenoic acid (n-3 DPA), are described. 7(*S*),13(*R*),20(*S*)-RvT1 was prepared from 7(*S*),13(*R*)-RvT4 via an enzymatic lipoxidase reaction. 7(*S*),13(*R*)-RvT4 was obtained by total synthesis where the chiral centers at C7 and C13 where introduced by a Noyori transfer hydrogenation and a chiral pool strategy respectively. Wittig reactions, Sonogashira coupling and Boland Zn(Cu/Ag) reduction were the key steps in the synthesis.

Graphical Abstract
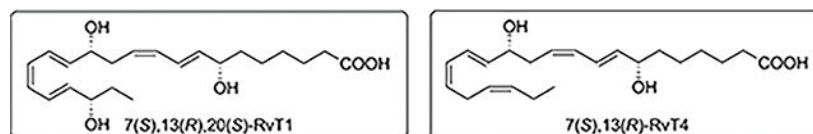
Keywords

7(*S*),13(*R*),20(*S*)-RvT1; 7(*S*),13(*R*)-RvT4; Noyori transfer hydrogenation; Lipoxidase

Inflammation is an immediate response to tissue injury and/or infection.[1] The self-resolving acute inflammation is a protective mechanism, especially against infections, and it involves the biosynthesis of the specialized pro-resolving mediators (SPMs) which include the lipoxins,[2] resolvins,[3] maresins,[4] protectins[5] and their sulfide-conjugates.[6–9] They are formed from poly-unsaturated fatty acids by lipoxidase (LOX), cytochrome P-450 monooxygenase and/or cyclooxygenase (COX) enzymes.[3] In the situation that acute inflammation cannot be resolved chronic inflammatory diseases can develop including cancer, and autoimmune and neurological diseases.[10–12]

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

New SPMs derived from n-3 docosapentaenoic acid (n-3 DPA) have been identified.[13–15] Recently Dalli, Chiang and Serhan discovered the 13-series Resolvin (RvT1, RvT2, RvT3 and RvT4) that are produced from n-3 DPA via an endothelial COX-2 mechanism combined with 5-lipoxidase from adjacent neutrophils to give the RvT1-RvT4.[16] It should be noticed that neither eicosapentaenoic nor docosahexaenoic acid are substrates for this pathway. The RvT1, RvT2, RvT3 and RvT4 are formed during the early phase of bacterial infection. The RvTs protected animals against lethal doses of E-coli and therefore they could become an alternative to antibiotics.[16]

The proposed biosynthesis of RvT1-RvT4 is outlined in Figure 1.[16,17] Dalli and collaborators showed that n-3 DPA is converted via endothelial COX-2 to the 13(R)-hydroperoxy-docosapentaenoic acid that after reduction gives 13(R)-hydroxy-docosapentaenoic acid. The synthesis of this precursor has been recently described by Hansen and collaborators.[17] 13(R)-hydroxy-docosapentaenoic acid is converted to 7-hydroperoxy13(R)-hydroxy-docosapentaenoic acid that after reduction of the hydroperoxy-group gives RvT4. Enzymatic lipoxidase reaction transforms RvT4 into RvT1. [18]O_2 incorporation experiments confirmed that the hydroxyl groups at C-7 and C-20 are derived from enzymatic lipoxidase reaction. The 7-hydroperoxy-13(R)-hydroxy-docosapentaenoic acid can form an allylic epoxide intermediate that gives rise to RvT2 and RvT3 as shown in Figure 1. It is worthwhile to note that due to the change in priority of the groups surrounding chiral center C13 in RvT2 and RvT3, according to the Cahn, Ingold, Prelog rules of nomenclature, this center has now to be assigned as S.

In order to explore the potent biological activities of these novel 13-series resolvins and due to the low abundance from natural sources they need to be prepared by total organic synthesis. Since lipoxidases in neutrophils introduce the hydroperoxy-groups with the (S)-chirality in poly-unsaturated fatty acids herein we describe the total synthesis of 7(S),13(R),20(S)-RvT1 [(7S,8E,10Z,13R,14E,16Z,18E,20S)-7,13,20-trihydroxy-8,10,14,16,18-docosapentaenoic acid (**1**)] and 7(S),13(R)-RvT4 [(7S,8E,10Z,13R,14E,16Z,19Z)-7,13-dihydroxy-8,10,14,16,19-docosapentaenoic acid (**2**)].

As shown in the retrosynthetic scheme (Figure 2) 7(S),13(R),20(S)-RvT1 (**1**) was synthesized from 7(S),13(R)-RvT4 (**2**) by enzymatic reaction with lipoxidase. Compound **2** was prepared by Sonogashira coupling of the key intermediates **3** and **4**. The chiral center in **4** was generated by a Noyori Ru transfer hydrogenation. Intermediate **3** was synthesized from **5** and **6** via a Wittig reaction whereas the chiral center in **6** was obtained from optical pure glycidol derivative **7**.

The C1–C9 fragment **4** was prepared in nine steps as outlined in Scheme 1. Pimelic acid was converted into its half ester **10** in two steps. Esterification at room temperature produced the diester **9** in quantitative yield.[18] Enzymatic cleavage of **9** with porcine pancreatic lipase (PPL, Sigma) gave half ester **10** in 92% yield.[19] Compound **10** was converted into the acid chloride **11** with oxalyl chloride in the presence of catalytic DMF in CH_2Cl_2.[20] Crude compound **11** was reacted with bis(trimethylsilyl)acetylene in the presence of $AlCl_3$ to afford ketone **12** in 65% yield over two steps. Asymmetric reduction of the ketone **12** in H_2O/ethyl acetate in the presence of a catalytic amount of the phase transfer catalyst

cetyltrimethylammonium bromide (CTABr) using the Noyori RuCl[(*S,S*)-TsDPEN](*p*-cymene) precatalyst (0.04 equiv) with sodium formate as a reducing agent, produced the chiral intermediate **13** with >94% ee as determined by chiral HPLC [Chiracel OD, hexane/*i*-PrOH 90:10, 0.6 mL/min, 210 nm, t_R = 8.0 min (*R*-isomer) and t_R = 8.5 min (*S*-isomer, **13**)].[21,22] Protection of **13** with TBSCl in the presence of imidazole and 4-DMAP in CH_2Cl_2 gave the silyl ether **14** in 93% yield. TMS desilylation of **14** with 1.2 equiv of K_2CO_3 in the presence of Na_2SO_4 in CH_3OH gave cleanly the terminal acetylene **15**. Hydrostannylation of **15** with 1.2 equiv tributyltin hydride in benzene at 80 °C in the presence of 10% of AIBN produced the *trans*-vinyl tin compound **16**. The excess of tributyltin hydride was removed in high vacuo. The key intermediate **4** was obtained from **16** by reaction with iodine in CH_2Cl_2 at 0 °C in 83% yield over two steps.

The C10-C22 intermediate **3** was obtained from commercial R(−)-TBS-glycidol (**7**) in seven steps (Scheme 2). Reaction of **7** with 2 equiv lithium trimethylsilylacetylene in the presence of $BF_3 \cdot Et_2O$ gave the alcohol **17** in 90% yield that was converted to the di-TBS derivative **18** with 1.6 equiv TBSCl in CH_2Cl_2 in 89% yield.[23] Selective deprotection of the primary TBS-ether was accomplished with 10-camphorsulfonic acid (CSA) in CH_2Cl_2/CH_3OH at 0 °C to give **19** in 64% isolated yield. Dess-Martin periodinane oxidation of **19** in CH_2Cl_2 produced the aldehyde **20**.[24] Crude **20** was reacted with 1 equiv of (Triphenylphosphoranylidene)acetaldehyde in CH_3CN at 30 °C for 15 h to give the α,β-unsaturated aldehyde **6** in 58% yield over two steps.[25] Wittig reaction of **6** with 4 equiv of the ylide generated from the crystalline phosphonium salt **5**[26,27] and *n*-BuLi in THF gave **21** in 82% yield. The geometry of the 14*E*,16*Z*-diene unit in **21** was confirmed by the ^{1}H-^{1}H coupling constants ($J_{14,15}$ = 15.3 Hz and $J_{16,17}$ = 11.1 Hz).[28] Removal of the TMSgroup with K_2CO_3 in CH_3OH gave the key intermediate **3** in quantitative yield.[29]

The skeleton of 7(*S*),13(*R*)-RvT4 was assembled from the key intermediates **3** and **4** as outlined in Scheme 3. Pd^0/Cu^I Sonogashira coupling of **3** with **4** produced compound **22**. The synthesis was completed via deprotection of the TBS groups of compound **22** with catalytic HCl, generated in situ from acetyl chloride in absolute CH_3OH at 0 °C to rt, to give **23**. Boland Zn(Cu/Ag) reduction[30] of **23** in CH_3OH/H_2O at 40–45 °C (7 h) produced crude 7(*S*),13(*R*)-RvT4 methyl ester (**24**) that was purified by HPLC [Zorbax SB-C18 250 × 21.2 mm, 235 nm, CH_3OH/H_2O 76/24] to give **24** in 87% yield. The geometry of the 8*E*,10*Z*-diene unit in **24** was confirmed by the ^{1}H-^{1}H coupling constants ($J_{8,9}$ = 15.3 Hz and $J_{10,11}$ = 11.1 Hz).[28] Mild alkaline hydrolysis of **24** with 1 N LiOH in CH_3OH/H_2O at 0 °C to rt gave after HPLC purification [Zorbax SB-C18 250 × 21.2 mm, 235 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 70/30] and desalting 7(*S*),13(*R*)-RvT4 (**2**) in 80% yield. The ^{1}H NMR, ^{13}C NMR, UV, and HPLC/UV/MS analysis were consistent with the structure of **2**.[28]

For the synthesis of 7(*S*),13(*R*),20(*S*)-RvT1 (**1**) we considered to use the enzymatic hydroxylation of 7(*S*),13(*R*)-RvT4 (**2**) (Scheme 4). This type of approach was successfully employed in the total syntheses of RCTRs,[31] lipoxins and other lipid mediators.[32–36] The reaction had to be optimized with respect to enzyme, pH and buffer. Compound **2** was reacted in borate buffer pH 10.7, with lipoxidase Type I-B to give after reduction with tris(2-

carboxyethyl)phosphine hydrochloride (TCEP-HCl) directly 7(S),13(R),20(S)-RvT1 (**1**).[37] Purification by HPLC and desalting gave pure **1**. The geometry of the 14E,16Z,18E-triene unit in **1** was confirmed by the ^{1}H-^{1}H coupling constants ($J_{14,15}$ = 15.3 Hz, $J_{16,17}$ ~ 10.8 Hz and $J_{18,19}$ = 15.3 Hz).[28,38,39] The ^{1}H NMR, ^{13}C NMR, UV, and HPLC/UV/MS analysis were consistent with the structure of **1**.[28]

In summary, the total syntheses of 7(S),13(R),20(S)-RvT1 and 7(S),13(R)-RvT4 have been achieved, making these pro-resolving lipid mediators from n-3 DPA available for further biological testing. The syntheses of RvT2 and RvT3, will be reported in due course.

Acknowledgments

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28. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **10**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.6 (s, 3H), 2.4–2.3 (t, J = 7.5 Hz, 2H), 2.3–2.2 (t, J = 7.5 Hz, 2H), 1.7–1.5 (m, 4H), 1.4–1.3 (m, 2H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 179.43, 174.12, 51.53, 33.77, 33.74, 28.44, 24.48, 24.23. Compound **11**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.6 (s, 3H), 2.9–2.8 (t, J = 7.2 Hz, 2H), 2.3 (t, J = 7.5 Hz, 2H), 1.8–1.5 (m, 4H), 1.4–1.3 (m, 2H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 173.73, 173.62, 51.50, 46.77, 33.57, 27.78, 24.63, 24.27. Compound **12**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.6 (s, 3H), 2.6–2.5 (t, J = 7.3 Hz, 2H), 2.3 (t, J = 7.3 Hz, 2H), 1.7–1.5 (m, 4H), 1.4–1.2 (m, 2H), 0.2 (s, 9H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 187.60, 173.96, 101.93, 97.73, 51.47, 44.96, 33.77, 28.33, 24.56, 23.45, –0.79 (3C). Compound **13**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.4–4.3 (t, J = 6.6 Hz, 1H), 3.6 (s, 3H), 2.3 (t, J = 7.5 Hz, 2H), 1.9 (s, 1H), 1.7–1.6 (m, 4H), 1.5–1.3 (m, 4H), 0.14 (s, 9H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 174.18, 106.72, 89.37, 62.71, 51.46, 37.38, 33.91, 28.67, 24.75, 24.70, –0.15 (3C); $[\alpha]_D^{20}$ = –0.5 (c 0.63, CHCl$_3$). Compound **14**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.3 (t, J = 6.6 Hz, 1H), 3.6 (s, 3H), 2.3 (t, J = 7.5 Hz, 2H), 1.7–1.6 (m, 4H), 1.5–1.3 (m, 4H), 0.87 (s, 9H), 0.12 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 174.21, 107.78, 88.41, 63.24, 51.44, 38.21, 33.99, 28.72, 25.80 (3C), 24.87, 24.84, 18.27, –0.18 (3C), –4.48, – 4.95; $[\alpha]_D^{20}$ = –37 (c 0.58, CHCl$_3$). Compound **15**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.3 (td, J = 6.6, 2.1 Hz, 1H), 3.6 (s, 3H), 2.4–2.3 (d, J = 2.1 Hz, 1H), 2.3 (t, J = 7.5 Hz, 2H), 1.7–1.5 (m, 4H), 1.5–1.2 (m, 4H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 174.18, 85.58, 71.96, 62.61, 51.45, 38.30, 33.98, 28.75, 25.75 (3C), 24.85, 24.72, 18.20, –4.59, –5.09; $[\alpha]_D^{20}$ = –36 (c 0.52, CHCl$_3$). Compound **4**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 6.5 (dd, J = 14.4, 6.0 Hz, 1H), 6.2–6.1 (dd, J = 14.4, 1.2 Hz, 1H), 4.2–4.0 (m, 1H), 3.6 (s, 3H), 2.3 (t, J = 7.5 Hz, 2H), 1.7– 1.2 (m, 8H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 174.17, 149.22, 75.58, 75.02, 51.47, 37.28, 33.99, 29.04, 25.80 (3C), 24.85, 24.48, 18.19, –4.53, –4.90; $[\alpha]_D^{20}$ = –18.5 (c 0.35, CHCl$_3$). Compound **18**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.9–3.7 (m, 1H), 3.6–3.4 (2 dd, J = 10.2, 5.4 Hz and J = 10.2, 6.3 Hz, 2H ABsystem), 2.5 (dd, J = 16.8, 5.4 Hz, 1H ABsystem), 2.3–2.2 (dd, J = 16.8, 6.6 Hz, 1H ABsystem), 0.88 (s, 18H), 0.12 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 104.71, 85.78, 72.08, 66.67, 25.96 (3C), 25.84 (3C), 25.76, 18.37, 18.13, 0.07 (3C), – 4.46, – 4.61, – 5.34, – 5.40; $[\alpha]_D^{20}$ = +9.7 (c 0.23, CHCl$_3$). Compound **19**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.9–3.8 (m, 1H), 3.7–3.6 (dd, J = 11.1, 3.9 Hz, 1H ABsystem), 3.6–3.5 (dd, J = 11.1, 4.8 Hz, 1H ABsystem), 2.5–2.4 (dd, J = 16.8, 6.9 Hz, 1H ABsystem), 2.4–2.3 (dd, J = 16.8, 6.3 Hz, 1H ABsystem), 0.88 (s, 9H), 0.11 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 103.31, 86.73, 71.47, 65.87, 25.76 (3C), 25.35, 18.03, –0.02 (3C), –4.52, –4.77. Compound **20**: [1]C NMR (CDCl$_3$, 300 MHz): δ 9.6 (d, J = 1.2 Hz 1H), 4.1 (ddd, J = 7.8, 5.1, 1.2 Hz, 1H), 2.7–2.6 (dd, J = 16.8, 5.1 Hz, 1H ABsystem), 2.6–2.4 (dd, J = 16.8, 7.8 Hz, 1H ABsystem), 0.94 (s, 9H), 0.15 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 202.10, 101.85, 87.36, 76.08, 25.70 (3C), 24.47, 18.21, 1.01, –0.09 (3C), – 4.75. Compound **6**: [1]C NMR (CDCl$_3$, 300 MHz): δ 9.6 (d, J = 7.8 Hz, 1H), 6.9 (dd, J = 15.6, 4.2 Hz, 1H), 6.3 (ddd, J = 15.6, 7.8, 1.8 Hz, 1H), 4.5 (dddd, J = 7.5, 6.3, 4.2, 1.8 Hz, 1H), 2.5 (dd, J = 16.5, 6.3 Hz, 1H ABsystem), 2.4 (dd, J = 16.5, 7.5 Hz, 1H ABsystem), 0.89 (s, 9H), 0.13 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 193.45, 157.82, 131.23, 102.05, 87.77, 70.49, 28.93, 25.70 (3C), 18.13, –0.06 (3C), –4.80, –4.87. Compound **21**: [1]C NMR (CDCl$_3$, 300 MHz): δ 6.5 (dd, J = 15.3, 11.1 Hz, 1H), 6.0– 5.9 (t, J = 11.1 Hz, 1H), 5.7 (dd, J = 15.3, 6.0 Hz, 1H), 5.5–5.2 (m, 3H), 4.4–4.2 (m, 1H), 3.0–2.8 (m, 2H), 2.5–2.4 (dd, J = 16.8, 6.9 Hz, 1H ABsystem), 2.4–2.3 (dd, J = 16.8, 6.3 Hz, 1H ABsystem), 2.1–2.0 (m, 2H), 1.0–0.9 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 135.34, 132.37, 130.32, 127.70, 126.60, 124.86, 104.17, 86.20, 71.92, 30.04, 25.96, 25.83 (3C), 20.55, 18.25, 14.22, 0.05 (3C), – 4.52, –4.71. Compound **3**: [1]C NMR (CDCl$_3$, 300 MHz): δ 6.6– 6.5 (ddt, J = 15.3, 11.1, 1.2 Hz, 1H), 6.0 (t, J = 11.1 Hz, 1H), 5.8–5.7 (dd, J = 15.3, 5.7 Hz, 1H), 5.5–5.2 (m, 3H), 4.4–4.3 (m, 1H), 3.0– 2.8 (m, 2H), 2.4 (ddd, J = 16.5, 6.0, 2.7 Hz, 1H ABsystem), 2.3 (ddd, J = 16.5, 6.9, 2.7 Hz, 1H ABsystem), 2.1–2.0 (m, 2H), 2.0– 1.9 (t, J = 2.7

Hz, 1H), 1.0–0.9 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 134.97, 132.37, 130.46, 127.64, 126.56, 125.10, 81.29, 71.63, 69.97, 28.59, 25.98, 25.80 (3C), 20.55, 18.23, 14.22, –4.56, –4.80. Compound **22**: ^{1}C NMR (CDCl$_3$, 300 MHz): δ 6.6–6.5 (br dd, J = 15.0, 11.1 Hz, 1H), 6.1–5.9 (m, 2H), 5.8–5.7 (dd, J = 15.0, 5.7 Hz, 1H), 5.6–5.5 (m, 1H), 5.5–5.2 (m, 3H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.8 (m, 2H), 2.5 (ddd, J = 16.5, 6.9, 2.1 Hz, 1H ABsystem), 2.4 (ddd, J = 16.5, 6.3, 2.1 Hz, 1H ABsystem), 2.3–2.2 (t, J = 7.5 Hz, 2H), 2.1–2.0 (m, 2H), 1.7–1.2 (m, 8H), 1.0–0.9 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). Compound **23**: ^{1}C NMR (CDCl$_3$, 300 MHz): δ 6.6 (ddt, J = 15.3, 11.1, 1.2 Hz, 1H), 6.1–6.0 (dd, J = 15.9, 6.3 Hz, 1H), 6.0 (t, J = 11.1 Hz, 1H), 5.8–5.7 (dd, J = 15.3, 6.6 Hz, 1H), 5.7–5.6 (m, 1H), 5.5–5.2 (m, 3H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.8 (m, 2H), 2.6 (ddd, J = 16.8, 5.4, 2.1 Hz, 1H ABsystem), 2.5 (ddd, J = 16.8, 6.3, 2.1 Hz, 1H ABsystem), 2.3 (t, J = 7.5 Hz, 2H), 2.2–2.0 (m, 2H), 1.7–1.2 (m, 8H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 174.19, 145.16, 133.79, 132.48, 131.41, 127.53, 126.42, 126.37, 109.94, 86.39, 80.94, 72.17, 70.72, 51.48, 36.65, 33.94, 28.92, 28.70, 25.99, 24.86, 24.77, 20.56, 14.22. 7(S),13(R)-RvT4 methyl ester (24): ^{1}C NMR (CD$_3$OD, 300 MHz): δ 6.6–6.4 (2 dd, J = 15.3, 11.1Hz, 2H), 6.2–6.0 (t, J = 11.1 Hz, 1H), 6.0–5.9 (t, J = 11.1 Hz, 1H), 5.7–5.6 (m, 2H), 5.5–5.2 (m, 4H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.9 (m, 2H), 2.5–2.4 (m, 2H), 2.3 (t, J = 7.5 Hz, 2H), 2.2–2.0 (m, 2H), 1.7–1.3 (m, 8H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD$_3$OD, 75.5 MHz): δ 175.97, 138.02, 136.97, 133.13, 131.11, 131.08, 129.12, 128.13, 127.79, 126.55, 126.48, 73.22, 73.04, 51.97, 38.19, 36.80, 34.74, 30.11, 26.83, 26.22, 25.98, 21.47, 14.63. 7(S),13(R)-RvT4 (2): ^{1}C NMR (CD$_3$OD, 300 MHz): δ 6.6–6.4 (2 dd, J = 15.3, 11.1 Hz, 2H), 6.2–6.0 (t, J = 11.1 Hz, 1H), 6.0–5.9 (t, J = 11.1 Hz, 1H), 5.7–5.6 (2 dd, J = 15.3, 6.3 Hz and J = 15.3, 7.2 Hz, 2H), 5.5–5.2 (m, 4H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.0–2.9 (m, 2H), 2.5–2.3 (m, 2H), 2.3–2.2 (t, J = 7.5 Hz, 2H), 2.2–2.0 (m, 2H), 1.7–1.3 (m, 8H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD$_3$OD, 75.5 MHz): δ 178.81, 138.07, 136.97, 133.12, 131.11 (2C), 129.13, 128.08, 127.79, 126.50 (2C), 73.24, 73.05, 38.29, 36.80, 35.86, 30.30, 26.83, 26.43, 26.32, 21.47, 14.63; UV (CD$_3$OD) λ_{max} 239 nm. HPLC/UV: Zorbax SB-C18, 1.8 μm, 50 × 2.1 mm, 237 nm, CD$_3$OD/CD$_3$OD (0.1% formic acid) 50:50–70:30, 0.2 mL/min, tR = 17.3 min; HPLC/MS (m/z): 361.2 [M-H] –. 7(S),13(R),20(S)-RvT1 (1): ^{1}C NMR (CD$_3$OD, 300 MHz): δ 6.8– 6.6 (m, 2H), 6.5 (dd, J = 15.3, 11.1 Hz, 1H), 6.2–6.0 (t, J = 11.1 Hz, 1H), 6.0–5.9 (m, 2H), 5.8–5.6 (3 dd, J = 15.3, 6.3 Hz, J = 15.3, 6.6 Hz and J = 15.3, 6.9 Hz, 3H), 5.5–5.4 (dt, J = 10.8, 7.5 Hz, 1H), 4.3–4.1 (m, 1H), 4.1–4.0 (m, 2H), 2.5–2.4 (m, 2H), 2.2 (t, J = 7.5 Hz, 2H), 1.7–1.3 (m, 10H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD$_3$OD, 75.5 MHz): δ C1 not observed, 138.42, 138.00, 137.74, 131.19, 130.11, 129.81, 127.95, 126.60, 126.53 (2C), 74.63, 73.27, 72.96, 38.19, 36.87, 36.70, 31.08, 30.32, 26.75, 26.27, 10.15. UV (EtOH) λ_{max} 238, 260, 270, 280 nm. HPLC/UV: Zorbax SB-C18, 1.8 μm, 50 × 2.1 mm, 269 nm, CD$_3$OD/CD$_3$OD (0.1% formic acid) 50:50–70:30, 0.2 mL/min, t$_R$ = 12.4 min; HPLC/MS (m/z): 377.2 [M-H] –.

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37. To compound 2 (2.8 mg, 7.7×10^{-3} mmol) in 0.01 M solution of borate buffer pH 10.7 (10 ml) was added lipoxidase Type I-B from soybean (Sigma cat. # L7395–15MU, EC No. 232–853-1, 158000 U/mg) (9 mg) at rt and stirred for 1 h 45 min. The reaction was monitored by UV showing λ_{max} at 271 nm. The solution was purged with argon and TCEP-HCl (4.6 mg, 0.016 mmol) was added. After stirring for 1 min the reaction mixture was passed through a reversed phase C–18 cartridge, washed with H$_2$O and compound 1 eluted with CH$_3$OH/H$_2$O (8/2). Purification by HPLC [Zorbax SB-C18 250 × 21.2 mm, CH$_3$OH/H$_2$O (0.1% NH$_4$OAc, pH 5.6, 0.05% EDTA disodium) 60/40] and desalting gave pure 7(S),13(R),20(S)-RvT1 (**1**) (0.64 mg, 22%).

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Highlights

- First total syntheses 7(S),13(R),20(S)-Resolvin T1 and 7(S),13(R)-Resolvin T4 have been achieved.

- RvT1 is synthesized from RvT4 via an enzymatic hydroxylation with lipoxidase.

- RvT4 chiral centers at C7 and C13 were introduced by a Noyori transfer hydrogenation and a chiral pool strategy respectively.

- Wittig reactions, Sonogashira coupling and Boland Zn(Cu/Ag) reduction were the key steps.
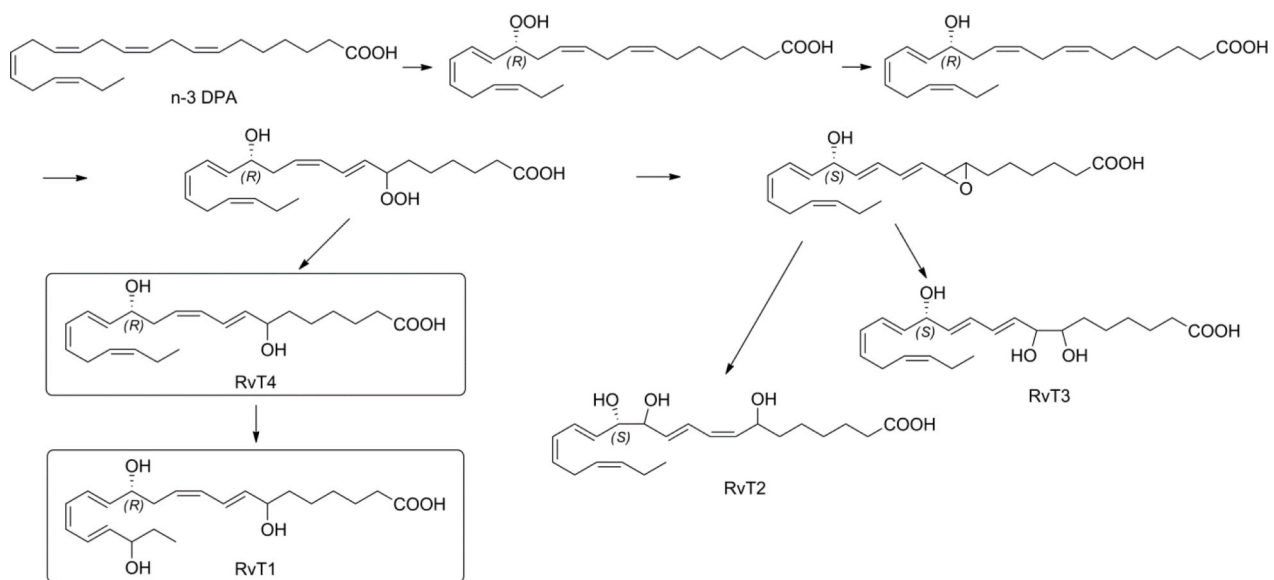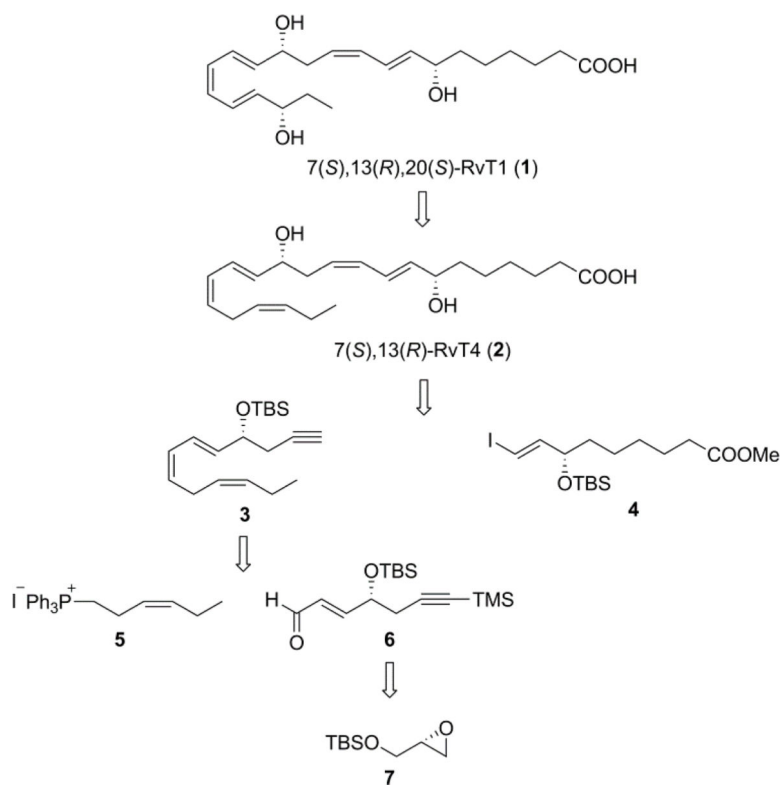
Figure 1.
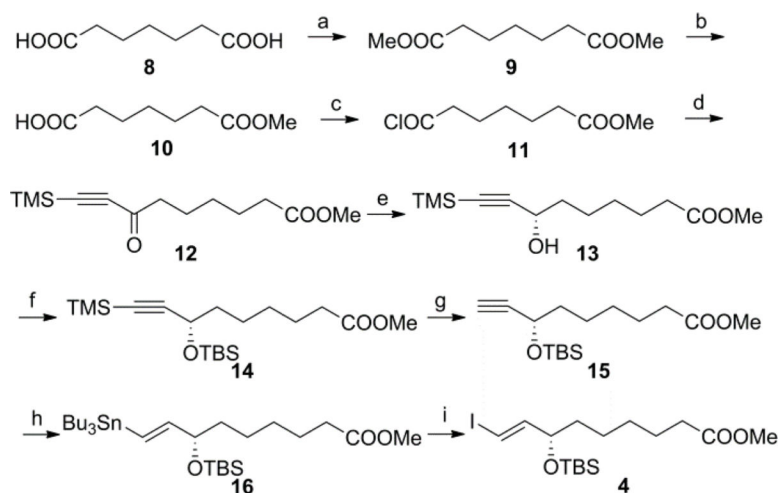Proposed biosynthesis of RvT1, RvT2, RvT3 and RvT4.

Figure 2.
Retrosynthetic approach to 7(S),13(R),20(S)-RvT1 and 7(S),13(R)-RvT4.

Scheme 1.

Reagents and conditions: (a) TMSCl, 2,2-dimethoxypropane, CH_3OH, rt, quantitative; (b) PPL, 0.05M phosphate buffer pH 7, 1 N NaOH, 92%; (c) $(COCl)_2$, cat. DMF, CH_2Cl_2, rt; (d) bis(trimethylsilyl)acetylene, $AlCl_3$, CH_2Cl_2, 0 °C, 65% (over two steps); (e) RuCl[(*S,S*)-TsDPEN](p-cymene), CTABr, NaCOOH, H_2O, EtOAc, rt, 97%; (f) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, 0 °C to rt, 93%; (g) K_2CO_3, Na_2SO_4, CH_3OH, rt, 98%; (h) $(Bu)_3SnH$, AIBN, benzene, reflux; (i) I_2, CH_2Cl_2, 0 °C, 83% (over two steps).
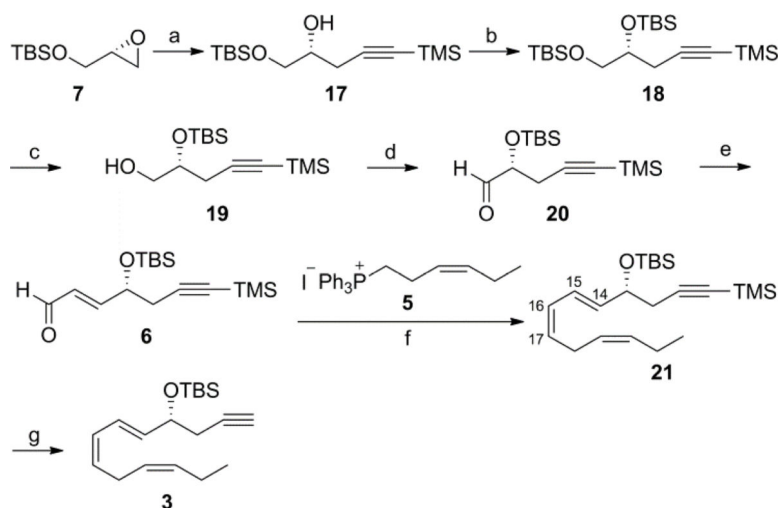
Scheme 2.

Reagents and conditions: (a) Trimethylsilylacetylene, *n*-BuLi, BF$_3$·Et$_2$0, THF, –78 °C, 90%; (b) TBSCl, imidazole, 4-DMAP, CH$_2$Cl$_2$, 0 °C to rt, 89%; (c) CSA, CH$_2$Cl$_2$/CH$_3$OH 1/1, 0 °C, 64%; (d) Dess-Martin periodinane, CH$_2$Cl$_2$, rt; (e) (Triphenylphosphoranylidene)acetaldehyde, CH$_3$CN, 30 °C, 58% (over two steps); (f) **5**, *n*-BuLi, THF, –78 °C to 0 °C, 82%; (g) K$_2$CO$_3$, CH$_3$OH, rt, quantitative.
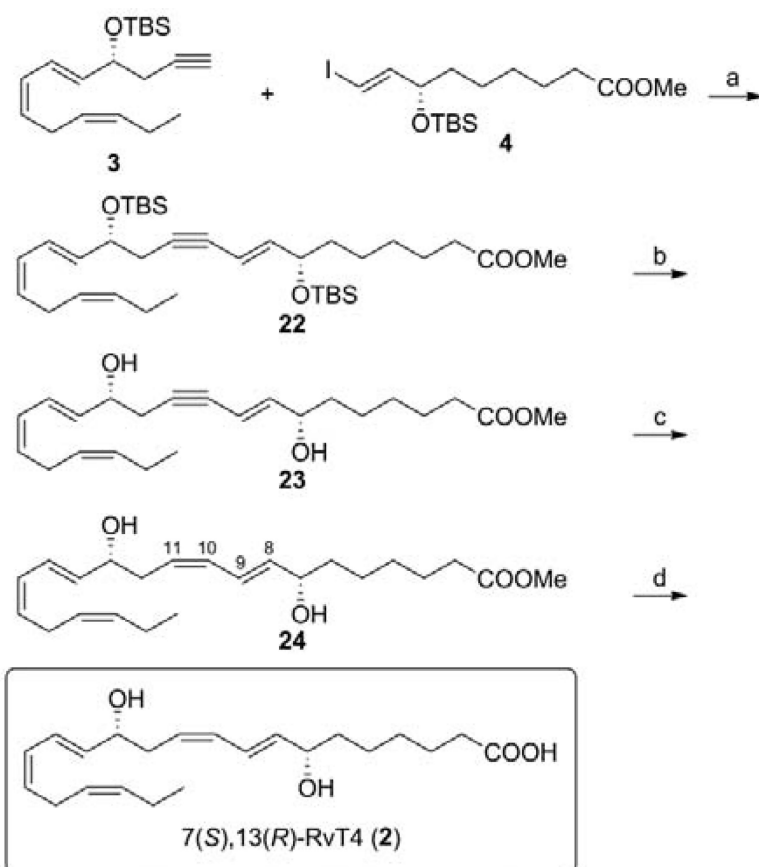
Scheme 3.

Reagents and conditions: (a) Pd(PPh$_3$)$_4$, CuI, piperidine, benzene, rt; (b) CH$_3$COCl, CH$_3$OH, 0 °C to rt, 31% (over two steps); (c) Zn(Cu/Ag), CH$_3$OH, H$_2$O, 40–45 °C, 87%; (d) 1 N LiOH, CH$_3$OH/H$_2$O 1/1, 0 °C to rt, 80%.

7(S),13(R)-RvT4 (**2**)

a, b

15 14
16
17 19
18

7(S),13(R),20(S)-RvT1 (**1**)
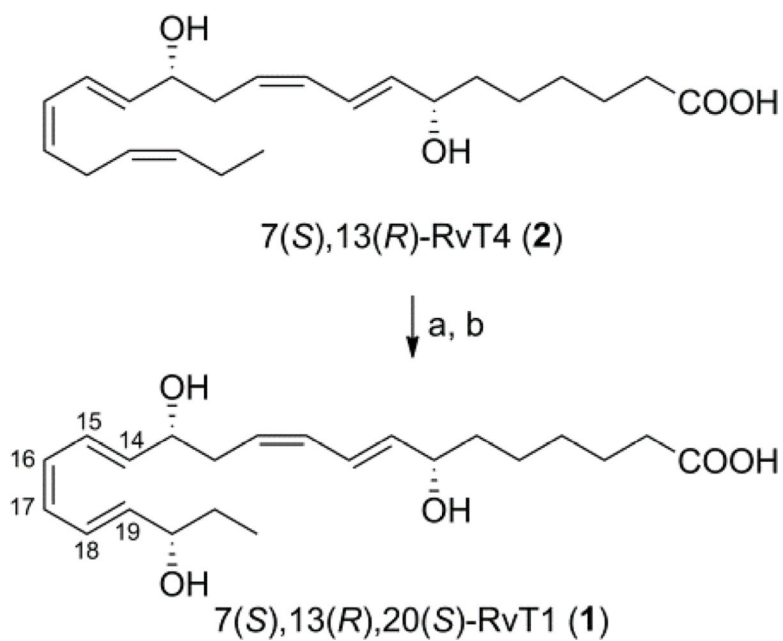
Scheme 4.
Reagents and conditions: (a) lipoxidase type I-B from soybean, 0.01 M borate buffer pH 10.7, rt; (b) TCEP-HCl, rt, 22% (over two steps after HPLC purification and desalting).