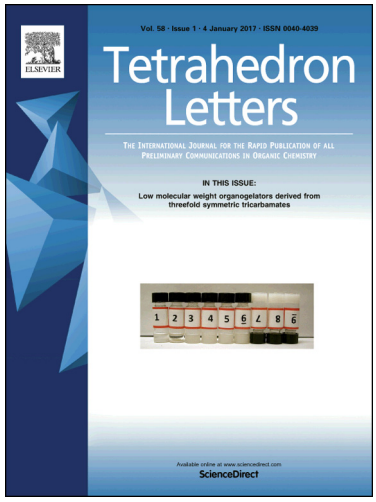

First total synthesis of pro-resolving and tissue-regenerative resolvin sulfido-conjugates

Ana R. Rodriguez, Bernd W. Spur

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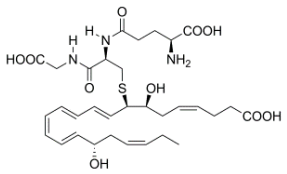

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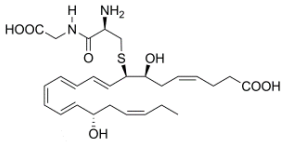

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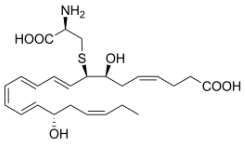

7S,8R,17S-RCTR3

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First total synthesis of pro-resolving and tissue-regenerative resolvin sulfido-conjugates

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ABSTRACT

The first total synthesis of the pro-resolving and tissue-regenerative resolvin sulfido-conjugates: 7*S*,8*R*,17*S*-RCTR1, 7*S*,8*R*,17*S*-RCTR2 and 7*S*,8*R*,17*S*-RCTR3, derived from docosahexaenoic acid, has been achieved. Two synthetic approaches are described. Chiral centers 7*S* and 8*R* were introduced in both approaches via a chiral pool strategy starting from 2-deoxy-D-ribose. The 17*S* chiral center was introduced either by a chiral pool strategy or by an enzymatic hydroxylation with lipoxidase. Wittig reactions, selective epoxide formation and epoxide opening with glutathione, L-cysteinylglycine and L-cysteine respectively, were the key steps in the synthesis.

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Inflammation is a response to tissue damage and/ or infection. If acute inflammation is self-limited and achieves resolution this is a protective mechanism,[1,2] but uncontrolled inflammation is the underlining course of chronic diseases. It is known that ω-3 polyunsaturated fatty acids found in fish-oil, mainly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have anti-inflammatory and anti-infective activities in humans.[3-6] The pioneering work by Serhan and co-workers have identified in self-resolving exudates during the resolution phase of inflammation powerful lipid mediators derived from ω-3 polyunsaturated fatty acids that are produced by lipoxygenase enzymes.[7-12] Those products are among the so called specialized pro-resolving mediators (SPMs) and they include the resolvins, protectins and maresins.

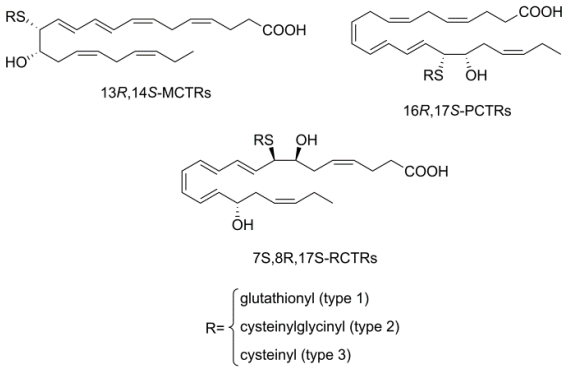


Figure 1. Structures of the maresin, protectin and resolvin sulfido-conjugates.

Recently, Serhan and co-workers investigated self-resolving exudates in E. coli infected mice, human spleen and blood of sepsis patients, and discovered the novel anti-inflammatory, pro-resolving and tissue regenerative sulfido-conjugates of maresin (MCTRs), protectin (PCTRs) and resolvin (RCTRs) (Figure 1).[13,14] These compounds promote pathogen clearance, wound healing, tissue repair and regeneration. The rapidly increasing bacterial resistance towards currently used antibiotics requires new approaches to combat infections. These novel SPMs could provide a different way to treat infections utilizing the immune system.

The proposed biosynthesis of the resolvin sulfido-conjugates by Serhan and co-workers is based on the identified precursor and its products formed as shown in Figure 2.[14] DHA undergoes two subsequent enzymatic lipoxygenations in C-17 and C-7 followed by an enzymatic conversion to an allylic epoxide to produce (4*Z*,7*S*,8*S*,9*E*,11*E*,13*Z*,15*E*,17*S*,19*Z*)-7,8-epoxy-17-hydroperoxy-4,9,11,13,15,19-docosahexaenoic acid. This product is converted enzymatically by a glutathione *S*-transferase to give the 7*S*,8*R*,17*S*-resolvin glutathione conjugate in tissue regeneration (RCTR1). Similar to the maresin and protectin sulfido-conjugates, the epoxide opening by the thiopeptides follows an S_N2 mechanism comparable to the peptido-leukotrienes.[15-20] RCTR1 is further metabolized by a γ-glutamyl transpeptidase to RCTR2 and finally by a dipeptidase to RCTR3.[14]

Based on the reported biological properties and due to the limited availability from natural sources these SPMs have to be prepared by total synthesis to make them available for further biological and pharmacological evaluation. We have reported the first total synthesis of the maresin and protectin sulfido-conjugates (MCTR1, MCTR2, MCTR3, PCTR1, PCTR2 and PCTR3).[15,16] A synthesis of PCTR1 was later reported by Hansen and co-workers.[17]

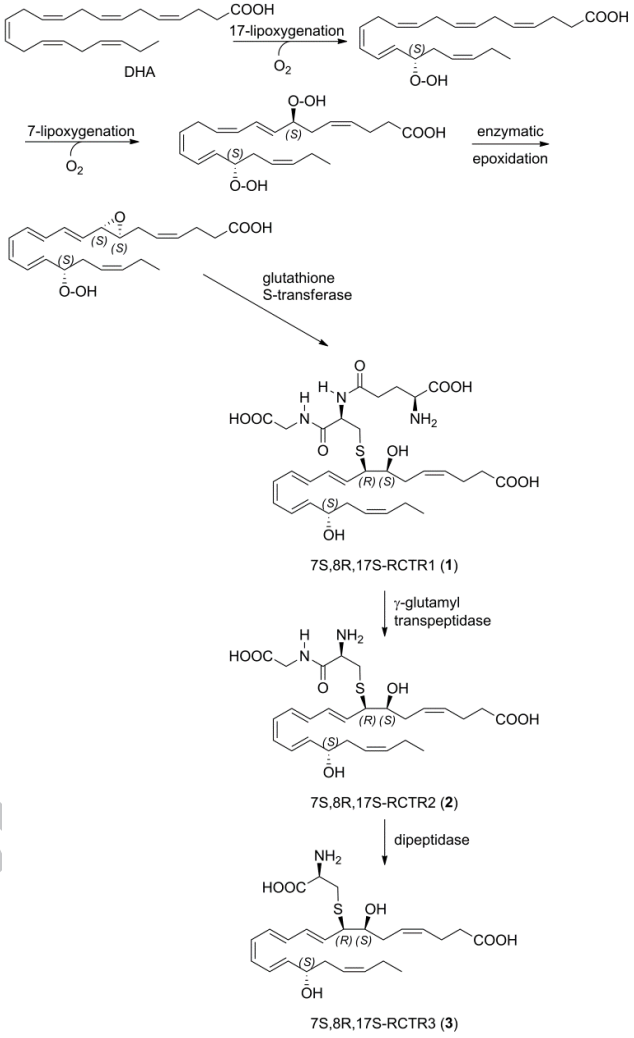


Figure 2. Proposed biosynthesis of 7*S*,8*R*,17*S*-RCTR1 (**1**), 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**) from DHA.[14]

In this letter we wish to report the first total synthesis of the resolvin sulfido-conjugated mediators 7*S*,8*R*,17*S*-RCTR1 [(4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,15*E*,17*S*,19*Z*)-8-glutathionyl-7,17-dihydroxy-4,9,11,13,15,19-docosahexaenoic acid (**1**)], 7*S*,8*R*,17*S*-RCTR2 [(4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,15*E*,17*S*,19*Z*)-8-cysteinylglycinyl-7,17-dihydroxy-4,9,11,13,15,19-docosahexaenoic acid (**2**)] and 7*S*,8*R*,17*S*-RCTR3 [(4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,15*E*,17*S*,19*Z*)-8-cysteinyl-7,17-dihydroxy-4,9,11,13,15,19-docosahexaenoic acid (**3**)]. As shown in the retrosynthetic scheme (Figure 3) compounds **1**, **2**, **3** have been prepared via two different strategies. The chiral epoxy esters **4** and **5** were the key intermediate in each synthesis. The peptide moiety of these sulfido-conjugates was introduced by epoxide opening with glutathione, L-cysteinylglycine and L-cysteine. Chiral centers at C7 and C8 were generated in both approaches from epoxide **6** using a chiral pool strategy starting from 2-deoxy-D-ribose. The introduction of the chiral center at C17 was what differentiated both approaches. One used an enzymatic reaction with lipoxidase once the skeleton of the molecule was already built and the other used the chiral synthon **8** prepared from D-(-)-arabinose.

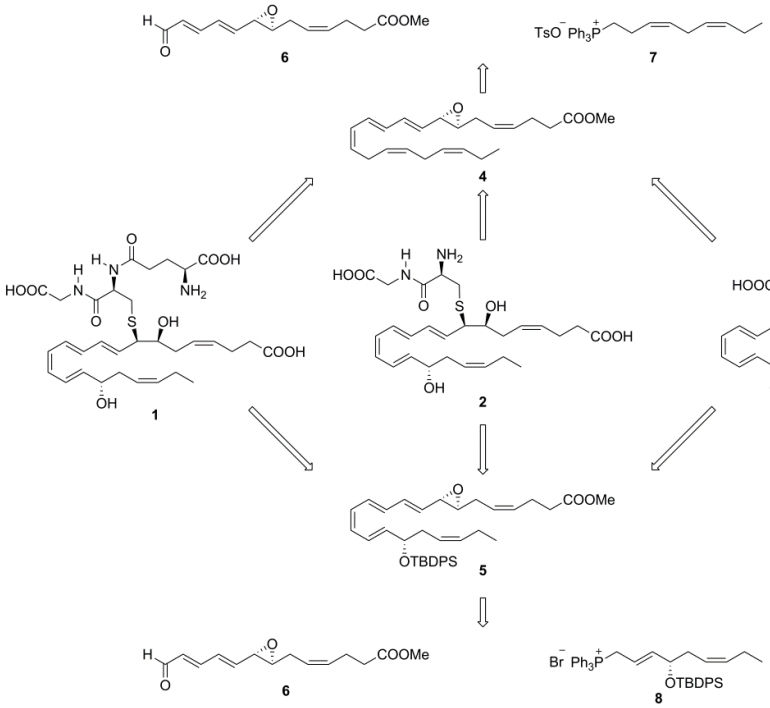
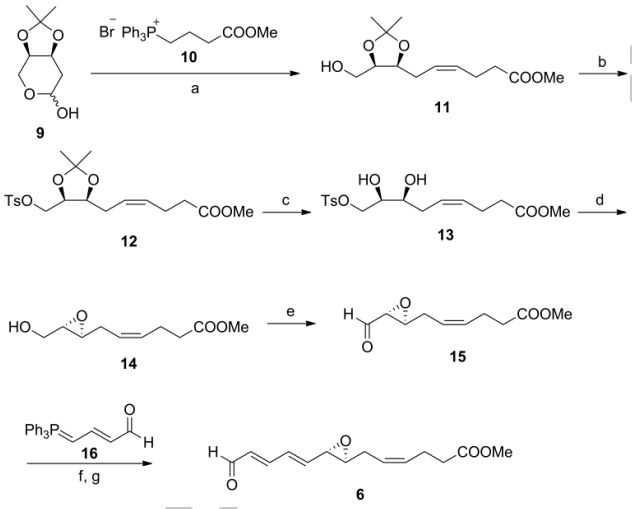


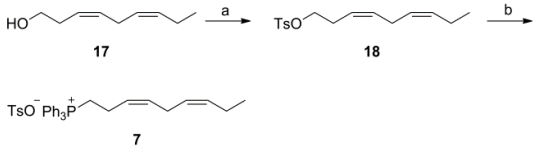
Figure 3. Two retrosynthetic approaches to 7*S*,8*R*,17*S*-RCTR1 (**1**), 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**).



Scheme 1. *Reagents and conditions:* (a) **10**, KHMDS, THF, -78 °C to -15 °C, 58%; (b) TsCl, pyridine, 0 °C to rt, 82%; (c) CH_3COCl, CH_3OH, 0 °C to rt, 95%; (d) NaOMe, Na_2SO_4, CH_3OH, rt, 52%; (e) Dess-Martin, $NaHCO_3$, CH_2Cl_2, rt; (f) **16**, CH_2Cl_2, rt; (g) cat. I_2, benzene, rt, 34% (over three steps).

The synthesis of the C1-C13 key intermediate **6** was achieved in 7 steps starting from the readily available 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**9**)[21] (Scheme 1). *Cis*-selective Wittig reaction of **9** with 2 equiv of the phosphorane generated from (Methoxycarbonylpropyl)triphenylphosphonium bromide (**10**) and KHMDS in THF gave the isopropylidene ester **11**.[22] The free primary hydroxy-group was converted to the tosylate with tosyl chloride in pyridine in good yield. Cleavage of the isopropylidene protective group in **12** with HCl generated in situ from acetyl chloride in CH_3OH at 0 ºC to rt gave **13** in 95% yield. Treatment of the tosylate **13** with 5 equiv of NaOMe in CH_3OH in the presence of Na_2SO_4 at rt afforded the desired chiral epoxy alcohol **14** in 52% isolated yield. In this reaction a terminal epoxide is first formed that undergoes epoxide transposition under the basic condition similar as described by Rokach.[23,24] The epoxy alcohol **14** was cleanly transformed into the epoxy aldehyde **15** using Dess-Martin oxidation in CH_2Cl_2.[25] Four-carbon homologation of aldehyde **15** with recrystallized (2*E*)-4-triphenylphosphoranylidene-2-butenal (**16**) [26,27] in CH_2Cl_2 at rt for 18 h followed by treatment with catalytic iodine in benzene afforded the *E*,*E*-dienal **6**.

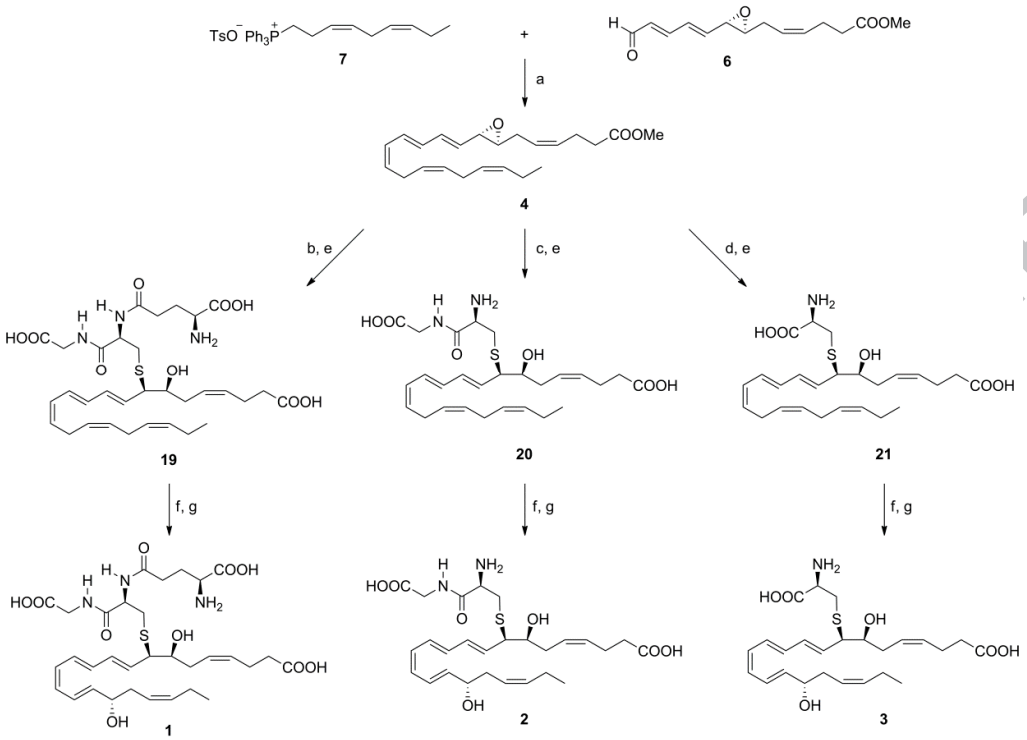
The required phosphonium salt **7** was prepared in 2 steps from the easily available (*Z*,*Z*)-3,6-nonadien-1-ol (**17**) (Scheme 2).[28] **17** was converted to the tosylate **18** with excess tosyl chloride in high yield and then reacted with 3 equiv triphenylphosphine in a small amount of acetonitrile under reflux to give the crystalline phosphonium tosylate **7** as described by Taber and collaborator.[29]



Scheme 2. *Reagents and conditions:* (a) TsCl, pyridine, CH_2Cl_2, 0 °C to rt, 78%; (b) Ph_3P, CH_3CN, reflux, 80%.

Wittig reaction of **6** with the ylide prepared in situ from the phosphonium tosylate **7**[29] with n-BuLi at –78 ºC in THF afforded the key epoxy ester **4** in 64% isolated yield (Scheme 3). Compound **4** was characterized by ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and UV.[30] The conversion of epoxy ester **4** to (4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,16*Z*,19*Z*)-8-glutathionyl-7-hydroxy-4,9,11,13,16,19-docosahexaenoic acid (**19**) was achieved in two steps as described in Scheme 3.[15,16] Reaction of **4** with 3 equiv of glutathione in CH_3OH/triethylamine/H_2O gave the intermediate monomethyl ester that was hydrolyzed with 1 N LiOH in H_2O for

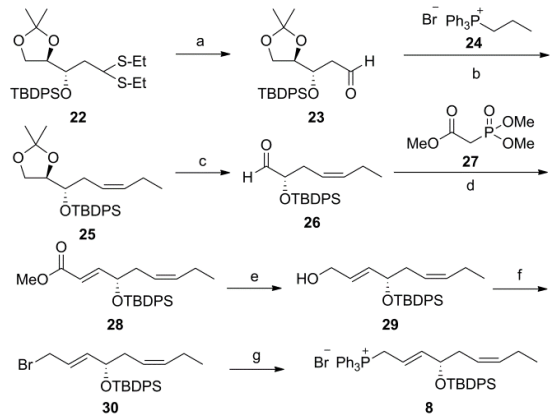
30 min affording crude **19**. Compound **19** was purified by HPLC [Zorbax SB-C18 250 × 21.2 mm, 280 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 64/36]. The fraction containing **19** was desalted using a reversed phase C–18 cartridge to give pure **19**.



Scheme 3. *Reagents and conditions:* (a) n-BuLi, THF, –78 °C to –30 °C, 64%; (b) Glutathione, Et_3N, H_2O, CH_3OH, rt; (c) L-Cysteinylglycine, Et_3N, H_2O, CH_3OH, rt; (d) L-Cysteine methyl ester hydrochloride, Et_3N, H_2O, CH_3OH, rt; (e) 1 N LiOH, H_2O, 0 °C to rt, 29% **19**, 51% **20** and 31% **21** (over two steps after HPLC purification and desalting); (f) lipoxidase from soybean, 0.1 M Phosphate buffer pH 8.5, rt; (g) TCEP-HCl, rt, 23% **1**, 52% **2** and 56% **3** (over two steps after HPLC purification and desalting).

Using the same conditions as described for **19**, compound **4** was reacted with L-cysteinylglycine to obtain after mild hydrolysis (4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,16*Z*,19*Z*)-8-cysteinylglycinyl-7-hydroxy-4,9,11,13,16,19-docosahexaenoic acid (**20**) (Scheme 3). Compound **20** was purified by HPLC [Zorbax SB-C18 250 × 21.2 mm, 280 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 65/35]. Compound **4** was reacted with L-cysteine methyl ester hydrochloride to give after mild hydrolysis (4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,16*Z*,19*Z*)-8-cysteinyl-7-hydroxy-4,9,11,13,16,19-docosahexaenoic acid (**21**) using the same steps as described for **19**. Compound **21** was purified by HPLC [Zorbax SB-C18 250 × 21.2 mm, 280 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 67/33]. The ^1H NMR, COSY, UV, and HPLC/UV/MS analysis were consistent with the structures of **19**, **20** and **21**.[30]

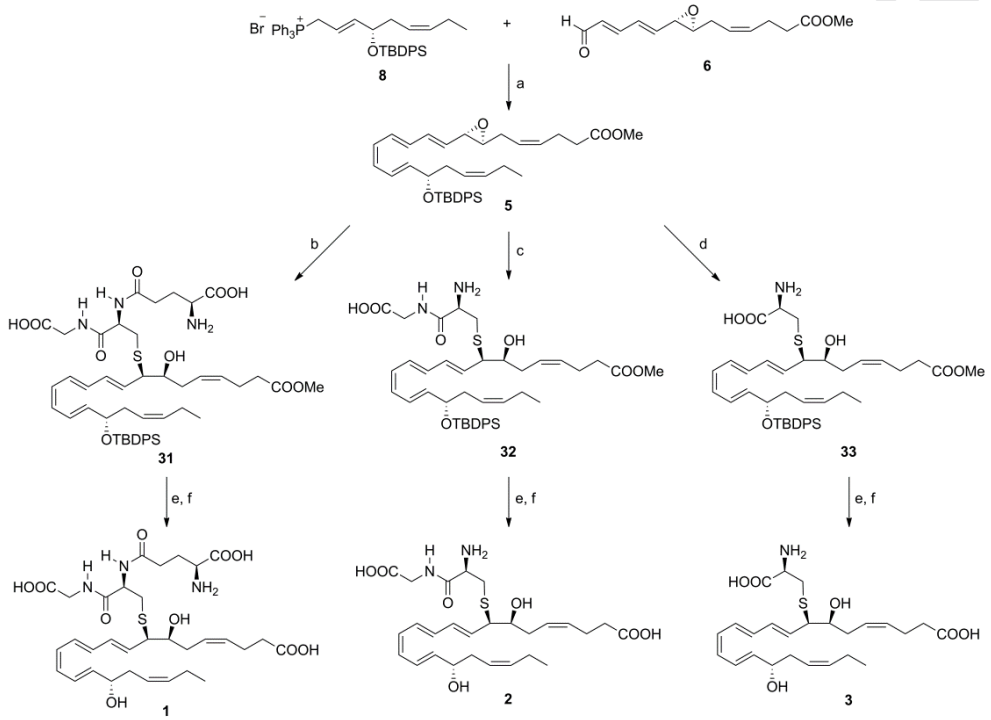
The introduction of the 17*S*-hydroxy group was achieved by an enzymatic reaction with lipoxidase from soybean followed by reduction of the intermediate 17*S*-hydroperoxide. The same enzyme was previously used in the synthesis of Lipoxin A, B and the peptido-lipoxins.[31-37] The standard conditions for this transformation, borate buffer pH 9, lipoxidase and sodium borohydride reduction resulted in a slow and incomplete reaction of **19** to 7*S*,8*R*,17*S*-RCTR1 (**1**). The best results were obtained using phosphate buffer pH 8.5, Fluka lipoxidase and the water soluble reducing agent tris(2-carboxyethyl)phosphine hydrochloride (TCEP-HCl).[38] Compound **19** was cleanly converted to 7*S*,8*R*,17*S*-RCTR1 (**1**) as evidenced by the bathochromic shift from 281 nm to 308 nm,[32] and the HPLC/UV/MS analysis of crude **1**. Purification by HPLC [Zorbax SB-C18 250 × 21.2 mm, 309 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 57/43] and desalting gave pure 7*S*,8*R*,17*S*-RCTR1 (**1**). Compounds **20** and **21** were converted to 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**)[39] respectively using similar conditions. ^1H NMR, COSY, UV, and HPLC/UV/MS analyses were consistent with the structures of **1**, **2** and **3**.[30]



Scheme 4. *Reagents and conditions:* (a) H_5IO_6, Et_2O, THF, 0 °C to rt, 84%; (b) **24**, n-BuLi, THF, –78 °C to 0 °C, 81%; (c) H_5IO_6, Et_2O, THF, rt, 76%; (d) **27**, NaHMDS, THF, –78 °C to rt, 85%; (e) DIBAL-H, CH_2Cl_2, –78 °C to –20 °C, 88%; (f) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt; (g) Ph_3P, CH_2Cl_2, 0 °C to rt, 87% (over two steps).

In our second approach the 17*S*-hydroxy group was introduced using the chiral phosphonium salt **8**. As shown in Scheme 4 compound **8** was prepared starting from compound **22** readily available from D-(-)-arabinose in four steps.[40-42] Cleavage of the dithioacetal group in **22** using the Rokach protocol,[43,44] with periodic acid dihydrate in THF/Ether for 5 min produced the aldehyde **23** after filtration through celite. Wittig reaction of **23** with the ylide prepared from n-propyl triphenylphosphonium bromide (**24**) and n-BuLi in THF at -78 ºC gave intermediate **25**. Deprotection of the isopropylidene group and oxidative diol cleavage of **25** occurs smoothly with periodic acid dihydrate in THF/Ether at rt for 18 h to give the aldehyde **26**.[45] Horner–Wadsworth–Emmons reaction of **26** with **27** gave the α,β-unsaturated ester **28**. Compound **28** was reduced to the allyl alcohol **29** by DIBAL-H in CH_2Cl_2 and converted to the labile bromide **30** with CBr_4/triphenylphosphine in CH_2Cl_2. Reaction of compound **30** with 5 equiv triphenylphosphine in CH_2Cl_2 followed by flash chromatography gave the crystalline phosphonium bromide **8**.

The phosphorane of **8** was generated with 1.0 equiv n-BuLi in THF at -100 ºC[46-48] and reacted with 1 equiv of aldehyde **6** to give the protected RCTR precursor **5** and its 13*E*-isomer in a 1:1 ratio in only moderate yield (Scheme 5). The use of different bases and temperatures resulted in lower yields. **5** could be easily separated from the 13*E*-isomer by straight phase HPLC [Altex Ultrasphere-Si 250 × 10 mm, 325 nm, Hexane/Et_3N 99/1]. Compound **5** was characterized by ^1H NMR, ^{13}C NMR, COSY, HSQC, and UV.[30]



Scheme 5. *Reagents and conditions:* (a) n-BuLi, THF, –100 °C to –40 °C, 24% (after HPLC purification); (b) Glutathione, Et_3N, H_2O, CH_3OH, rt; (c) L-Cysteinylglycine, Et_3N, H_2O, CH_3OH, rt; (d) L-Cysteine, Et_3N, H_2O, CH_3OH, rt; (e) TBAF, CH_3COOH, THF, 0 °C to rt; (f) 1 N LiOH, H_2O, 0 °C to rt, 61% **1**, 60% **2**, 64% **3** (over three steps).

The conversion of **5** to 7*S*,8*R*,17*S*-RCTR1 (**1**), 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**) required reaction with glutathione, L-cysteinylglycine and L-cysteine respectively followed by TBDPS cleavage and ester hydrolysis. Reaction of **5** with 10 equiv of glutathione in CH_3OH/triethylamine/H_2O gave the intermediate monomethyl ester **31** that was purified by reversed phase C–18 cartridge to remove excess glutathione. The TBDPS-group was cleaved using excess TBAF/acetic acid (1:1)[46] followed by mild hydrolysis of the methyl ester with 1N LiOH in H_2O to give after HPLC purification and desalting 7*S*,8*R*,17*S*-RCTR1 (**1**). Compounds **2** and **3** were prepared from **5** similar as described for **1**. Co-injections of 7*S*,8*R*,17*S*-RCTR1 (**1**), 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**) prepared from both routes were analyzed by HPLC/UV/MS and found to be identical.

In summary we have developed two synthetic routes for the synthesis of 7*S*,8*R*,17*S*-RCTR1 (**1**), 7*S*,8*R*,17*S*-RCTR2 (**2**) and 7*S*,8*R*,17*S*-RCTR3 (**3**)[30] that makes these pro-resolving and tissue regenerative resolvin sulfido-conjugates available for further biological and pharmacological testing. The synthesis of other specialized pro-resolving mediators (SPMs) will be reported in due course.

Acknowledgments

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30. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (d, *J* = 7.8 Hz, 2H), 7.4–7.3 (d, *J* = 7.8 Hz, 2H), 5.5–5.3 (m, 2H), 4.2 (q, *J* = 6.0 Hz, 1H), 4.1 (dt, *J* = 7.6, 6.0 Hz, 1H), 4.0 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.9 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.7 (s, 3H), 2.4 (s, 3H), 2.4–2.2 (m, 6H), 1.3 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.39 (C), 145.02 (C), 132.57 (C), 130.41 (CH), 129.89 (2C, CH), 128.03 (2C, CH), 125.76 (CH), 108.76 (C), 76.50 (CH), 74.63 (CH), 67.91 (CH2), 51.59 (CH3), 33.66 (CH2), 27.82 (CH3), 27.01 (CH2), 25.30 (CH3), 22.90 (CH2), 21.65 (CH3). R_f = 0.63 (hexane/EtOAc 6:4). Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (d, *J* = 7.8 Hz, 2H), 7.4–7.3 (d, *J* = 7.8 Hz, 2H), 5.6–5.4 (m, 2H), 4.3 (dd, *J* = 10.5, 3.3 Hz, 1H), 4.1 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.8–3.7 (m, 1H), 3.7–3.5 (m, 1H), 3.7 (s, 3H), 2.6 (d, *J* = 2.1 Hz, 1H), 2.6 (d, *J* = 3.3 Hz, 1H), 2.4 (s, 3H), 2.4–2.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.06 (C), 145.09 (C), 132.50 (C), 131.67 (CH), 129.95 (2C, CH), 128.00 (2C, CH), 126.08 (CH), 72.03 (CH), 71.64 (CH2), 71.05 (CH), 51.77 (CH3), 33.24 (CH2), 30.91 (CH2), 22.46 (CH2), 21.66 (CH3). R_f = 0.20 (hexane/EtOAc 6:4). Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (m, 2H), 3.9 (ddd, *J* = 12.6, 5.4, 2.7 Hz, 1H), 3.7 (s, 3H), 3.7–3.6 (m, 1H), 3.0–2.9 (m, 2H), 2.4–2.3 (m, 6H), 1.7–1.6 (dd, *J* = 6.9, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.46 (C), 130.78 (CH), 124.67 (CH), 61.51 (CH2), 57.78 (CH), 54.98 (CH), 51.61 (CH3), 33.80 (CH2), 29.17 (CH2), 22.84 (CH2). R_f = 0.34 (hexane/EtOAc 1:1). Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.0 (d, *J* = 6.0 Hz, 1H), 5.6–5.3 (m, 2H), 3.7 (s, 3H), 3.3–3.2 (td, *J* = 5.1, 1.8 Hz, 1H), 3.2–3.1 (dd, *J* = 6.0, 1.8 Hz, 1H), 2.5 (ddd, *J* = 5.7, 5.1, 1.8 Hz, 2H), 2.4–2.3 (m, 4H). R_f = 0.49 (hexane/EtOAc 7:3). Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6–9.5 (d, *J* = 7.8 Hz, 1H), 7.1–7.0 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.6 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.2–6.1 (dd, *J* = 15.3, 7.8 Hz, 1H), 6.0–5.9 (dd, *J* = 15.3, 7.5 Hz, 1H), 5.6–5.4 (m, 2H), 3.7 (s, 3H), 3.3–3.2 (dd, *J* = 7.5, 2.1 Hz, 1H), 3.0–2.9 (td, *J* = 5.1, 2.1 Hz, 1H), 2.5–2.3 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.59 (CH), 173.38 (C), 149.97 (CH), 141.08 (CH), 132.19 (CH), 131.19 (CH), 131.00 (CH), 124.14 (CH), 60.55 (CH), 56.71 (CH), 51.62 (CH3), 33.73 (CH2), 29.52 (CH2), 22.85 (CH2). R_f = 0.38 (hexane/EtOAc 7:3). Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8–7.7 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 8.4 Hz, 2H), 5.5–5.3 (m, 2H), 5.3–5.1 (m, 2H), 4.0 (t, *J* = 7.0 Hz, 2H), 2.8–2.7 (br t, *J* = 7.2 Hz, 2H), 2.5–2.3 (m, 2H), 2.4 (s, 3H), 2.1–1.9 (m, 2H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.68 (C), 133.08 (C), 132.31 (CH), 132.00 (CH), 129.77 (2C, CH), 127.86 (2C, CH), 126.33 (CH), 122.92 (CH), 69.59 (CH2), 27.02 (CH2), 25.50 (CH2), 21.60 (CH3), 20.48 (CH2), 14.17 (CH3). R_f = 0.65 (hexane/EtOAc 8:2). Compound **7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.9–7.6 (m, 17H), 7.1–7.0 (d, *J* = 7.8 Hz, 2H), 5.6–5.4 (m, 1H), 5.4–5.2 (m, 2H), 5.2–5.0 (m, 1H), 3.8–3.6 (m, 2H), 2.5–2.4 (br t, *J* = 7.2 Hz, 2H), 2.5–2.3 (m, 2H), 2.3 (s, 3H), 1.9–1.8 (m, 2H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.58 (C), 138.34 (C), 134.84 (d, *J* = 2.9 Hz, 3C, CH), 133.70 (d, *J* = 9.8 Hz, 6C, CH), 132.22 (CH), 130.40 (d, *J* = 12.7 Hz, 6C, CH), 130.28 (CH), 128.24 (2C, CH), 126.64 (d, *J* = 14.4 Hz, CH), 126.29 (CH), 126.21 (2C, CH), 118.51 (d, *J* = 85.3 Hz, 3C, C), 25.40 (CH2), 21.99 (d, *J* = 48.9 Hz, CH2), 21.28 (CH3), 20.47 (CH2), 20.35 (d, *J* = 4.0 Hz, CH2), 14.16 (CH3). R_f = 0.45 (CH_2Cl_2/CH_3OH 9:1). Compound **4**: ^{1}H NMR (C_6D_6, 300 MHz): δ 6.6–6.4 (dd, *J* = 14.4, 11.7 Hz, 1H), 6.4–6.3 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.2–6.0 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.1–6.0 (t, *J* = 11.7 Hz, 1H), 5.5–5.2 (m, 8H), 3.3 (s, 3H), 3.0 (dd, *J* = 7.5, 1.8 Hz, 1H), 3.0–2.8 (br t, *J* = 6.6 Hz, 2H), 2.8–2.7 (br t, *J* = 5.7 Hz, 2H), 2.7–2.6 (td, *J* = 5.1, 1.8 Hz, 1H), 2.3–1.9 (m, 8H), 0.9 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (C_6D_6, 75.5 MHz): δ 172.64 (C), 134.07 (CH), 132.32 (CH), 132.22 (CH), 131.33 (CH), 131.07 (CH), 130.86 (CH), 129.26 (CH), 129.08 (CH), 128.73 (CH), (1CH under the C_6D_6 signals), 127.26 (CH), 125.21 (CH), 60.00 (CH), 57.61 (CH), 50.98 (CH3), 33.84 (CH2), 30.00 (CH2), 26.54 (CH2), 25.90 (CH2), 23.12 (CH2), 20.88 (CH2), 14.40 (CH3). UV (Hexane/Et_3N 9.9/0.1) λ_{max} 270, 280, 292 nm. R_f = 0.83 (hexane/EtOAc/Et_3N 8:2:0.1). Compound **19**: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.6 (dd, *J* = 13.6, 11.1 Hz, 1H), 6.3–6.2 (m, 2H), 6.0 (t, *J* = 11.1 Hz, 1H), 5.7 (dd, *J* = 13.8, 9.9 Hz, 1H), 5.5–5.2 (m, 7H), 4.6–4.5 (dd, *J* = 9.3, 5.1 Hz, 1H), 3.9–3.7 (2d ABsystem, *J* = 17.4 Hz, 2H), 3.7 (m, 1H), 3.7–3.6 (t, *J* = 6.0 Hz, 1H), 3.4 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.1–2.9 (m, 2H), 3.0–2.9 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.9–2.8 (br t, *J* = 6.0 Hz, 2H), 2.7 (dd, *J* = 14.1, 9.3 Hz, 1H), 2.6–2.5 (m, 2H), 2.4–2.0 (m, 10H), 0.95 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH) λ_{max} 272, 281, 292 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 280 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 12.7 min; HPLC/MS (m/z): 648.2 [M-H] $^-$. Compound **20**: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.7–6.5 (dd, *J* = 13.8, 11.1 Hz, 1H), 6.4–6.2 (m, 2H), 6.1–6.0 (t, *J* = 11.1 Hz, 1H), 5.7 (dd, *J* = 14.1, 10.2 Hz, 1H), 5.6–5.2 (m, 7H), 4.0 (d, *J* = 17.1 Hz, 1H), 3.9–3.8 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.8–3.7 (m, 1H), 3.6 (d, *J* = 17.1 Hz, 1H), 3.5–3.4 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.1–2.7 (m, 6H), 2.4–2.2 (m, 6H), 2.1–2.0 (br quint, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH) λ_{max} 272, 281, 292 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 280 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 11.5 min; HPLC/MS (m/z): 519.2 [M-H] $^-$. Compound **21**: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.6 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.4–6.2 (m, 2H), 6.1–6.0 (t, *J* = 10.8 Hz, 1H), 5.7 (dd, *J* = 14.4, 10.2 Hz, 1H), 5.5–5.2 (m, 7H), 3.8 (m, 1H), 3.7–3.6 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.5–3.4 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.1 (dd, *J* = 14.7, 3.3 Hz, 1H), 3.0–2.7 (m, 4H), 2.8–2.7 (dd, *J* = 14.7, 10.2 Hz, 1H), 2.4–2.2 (m, 6H), 2.2–2.0 (br quint, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH) λ_{max} 272, 281, 292 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 280 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 13.9 min; HPLC/MS (m/z): 462.2 [M-H] $^-$. **7*S*,8*R*,17*S*-RCTR1** (**1**): ^{1}H NMR (CD_3OD, 300 MHz): δ 6.9–6.7 (m, 2H), 6.4–6.2 (m,

2H), 6.1–5.9 (m, 2H), 5.8–5.6 (m, 2H), 5.5–5.3 (m, 4H), 4.6–4.5 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.2–4.1 (m, 1H), 3.8–3.7 (2d ABsystem, *J* = 17.4 Hz, 2H), 3.8–3.6 (m, 1H), 3.6 (t, *J* = 6.3 Hz, 1H), 3.4 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.0–2.9 (dd, *J* = 14.1, 4.8 Hz, 1H), 2.8–2.6 (dd, *J* = 14.1, 9.6 Hz, 1H), 2.6–2.5 (m, 2H), 2.4–2.2 (m, 8H), 2.2–2.1 (q, *J* = 6.3 Hz, 2H), 2.1–2.0 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH) λ_{max} 295, 308, 323 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 309 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 9.9 min; HPLC/MS (m/z): 664.2 $[M-H]^-$. **7*S*,8R,17*S*-RCTR2** (**2**): ^1H NMR (CD_3OD, 300 MHz): δ 6.9–6.7 (m, 2H), 6.4–6.2 (m, 2H), 6.1–5.9 (m, 2H), 5.8–5.6 (m, 2H), 5.6–5.3 (m, 4H), 4.2–4.1 (m, 1H), 4.0–3.9 (d, *J* = 17.1 Hz, 1H), 3.9–3.8 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.8–3.7 (m, 1H), 3.7–3.6 (d, *J* = 17.1 Hz, 1H), 3.5–3.4 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.0–2.8 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.8–2.7 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.4–2.2 (m, 8H), 2.1–2.0 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH/H_2O 7/3) λ_{max} 295, 308, 323 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 309 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 9.4 min; HPLC/MS (m/z): 535.2 $[M-H]^-$. **7*S*,8R,17*S*-RCTR3** (**3**): ^1H NMR (CD_3OD, 300 MHz): δ 6.9–6.7 (m, 2H), 6.4–6.2 (m, 2H), 6.1–5.9 (m, 2H), 5.8–5.6 (m, 2H), 5.6–5.3 (m, 4H), 4.2–4.1 (m, 1H), 3.8 (td, *J* = 6.6, 3.6 Hz, 1H), 3.7–3.6 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.5–3.4 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.1 (dd, *J* = 14.7, 3.3 Hz, 1H), 2.8–2.7 (dd, *J* = 14.7, 10.2 Hz, 1H), 2.4–2.2 (m, 8H), 2.1–2.0 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). UV (CH_3OH/H_2O 7/3) λ_{max} 295, 308, 323 nm. HPLC/UV: Zorbax SB-C18, 1.8 µm, 50 x 2.1 mm, 309 nm, CH_3OH/H_2O (0.1% formic acid) 35:65–70:30, 0.2 mL/min, t_R = 10.1 min; HPLC/MS (m/z): 478.1 $[M-H]^-$. Compound **25**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.8–7.6 (m, 4H), 7.5–7.3 (m, 6H), 5.4–5.2 (m, 2H), 4.1–4.0 (m, 1H), 3.9 (t, *J* = 7.5 Hz, 1H), 3.9–3.8 (m, 1H), 3.8 (t, *J* = 7.5 Hz, 1H), 2.3–2.1 (m, 1H), 2.1–2.0 (m, 1H), 1.8 (br quint, *J* = 7.5 Hz, 2H), 1.3 (s, 3H), 1.3 (s, 3H), 1.0 (s, 9H), 0.8 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.04 (2C, CH), 135.97 (2C, CH), 134.10 (C), 134.03 (CH), 133.60 (C), 129.66 (CH), 129.64 (CH), 127.53 (2C, CH), 127.50 (2C, CH), 123.50 (CH), 108.73 (C), 77.76 (CH), 73.06 (CH), 66.00 (CH2), 31.96 (CH2), 27.00 (3C, CH3), 26.46 (CH3), 25.36 (CH3), 20.49 (CH2), 19.43 (C), 14.04 (CH3). R_f = 0.74 (hexane/EtOAc 9:1). Compound **26**: ^1H NMR ($CDCl_3$, 300 MHz): δ 9.6–9.5 (d, *J* = 1.5 Hz, 1H), 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 5.5–5.4 (m, 1H), 5.4–5.2 (m, 1H), 4.1–4.0 (td, *J* = 6.0, 1.5 Hz, 1H), 2.5–2.2 (m, 2H), 2.0–1.8 (br quint, *J* = 7.5 Hz, 2H), 1.1 (s, 9H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 203.43 (CH), 135.78 (4C, CH), 134.94 (CH), 133.04 (C), 132.92 (C), 130.01 (CH), 129.97 (CH), 127.79 (2C, CH), 127.73 (2C, CH), 121.99 (CH), 77.75 (CH), 30.96 (CH2), 26.88 (3C, CH3), 20.56 (CH2), 19.31 (C), 13.98 (CH3). R_f = 0.44 (hexane/EtOAc 9.5:0.5). Compound **28**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.7–7.5 (m, 4H), 7.5–7.2 (m, 6H), 7.0–6.8 (dd, *J* = 15.6, 5.1 Hz, 1H), 6.0–5.9 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.4–5.3 (m, 1H), 5.2–5.1 (m, 1H), 4.4–4.3 (m, 1H), 3.7 (s, 3H), 2.3–2.0 (m, 2H), 1.8–1.6 (br quint, *J* = 7.5 Hz, 2H), 1.1 (s, 9H), 0.8 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.00 (C), 150.19 (CH), 135.85 (2C, CH), 135.79 (2C, CH), 134.60 (CH), 133.79 (C), 133.29 (C), 129.79 (CH), 129.76 (CH), 127.62 (4C, CH), 122.59 (CH), 119.74 (CH), 72.26 (CH), 51.49 (CH3), 34.97 (CH2), 26.98 (3C, CH3), 20.50 (CH2), 19.33 (C), 14.00 (CH3). R_f = 0.27 (hexane/EtOAc 9.5:0.5). Compound **29**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 5.6 (ddt, *J* = 15.3, 6.3, 1.2 Hz, 1H), 5.5–5.2 (m, 3H), 4.2–4.1 (m, 1H), 3.9 (m, 2H), 2.4–2.1 (m, 2H), 1.9–1.8 (br quint, *J* = 7.5 Hz, 2H), 1.0 (s, 9H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.03 (2C, CH), 135.93 (2C, CH), 134.43 (C), 134.18 (C), 134.18 (CH), 133.65 (CH), 129.59 (CH), 129.50 (CH), 129.20 (CH), 127.49 (2C, CH), 127.35 (2C, CH), 124.01 (CH), 73.57 (CH), 63.08 (CH2), 35.77 (CH2), 26.99 (3C, CH3), 20.61 (CH2), 19.29 (C), 14.15 (CH3). R_f = 0.20 (hexane/EtOAc 9:1). Compound **30**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 5.8–5.6 (m, 2H), 5.4–5.3 (m, 1H), 5.3–5.1 (m, 1H), 4.2–4.1 (m, 1H), 3.9–3.8 (d, *J* = 6.9 Hz, 2H), 2.3–2.1 (m, 2H), 1.8 (br quint, *J* = 7.5 Hz, 2H), 1.1 (s, 9H), 0.8 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 137.55 (CH), 135.92 (2C, CH), 135.90 (2C, CH), 134.06 (C), 133.95 (CH), 133.78 (C), 129.65 (CH), 129.57 (CH), 127.53 (2C, CH), 127.47 (2C, CH), 126.18 (CH), 123.46 (CH), 72.83 (CH), 35.55 (CH2), 32.42 (CH2), 27.01 (3C, CH3), 20.56 (CH2), 19.29 (C), 14.12 (CH3). R_f = 0.88 (hexane/EtOAc 9:1). Compound **8**: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.9–7.7 (m, 9H), 7.7–7.6 (m, 6H), 7.6–7.4 (m, 4H), 7.4–7.2 (m, 6H), 6.2 (dt, *J* = 15.3, 4.6 Hz, 1H), 5.6–5.4 (m, 1H), 5.3–5.1 (m, 1H), 5.0–4.8 (td, *J* = 15.3, 7.2 Hz, 1H), 4.9–4.8 (m, 1H), 4.7–4.5 (td, *J* = 15.3, 7.2 Hz, 1H), 4.3–4.1 (m, 1H), 2.2–1.8 (m, 2H), 1.7–1.5 (m, 2H), 0.9 (s, 9H), 0.7 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 143.75 (d, *J* = 13.3 Hz, CH), 135.75 (2C, CH), 135.62 (2C, CH), 134.85 (d, *J* = 2.9 Hz, 3C, CH), 134.17 (CH), 133.99 (d, *J* = 9.8 Hz, 6C, CH), 133.85 (C), 133.40 (C), 130.27 (d, *J* = 12.1 Hz, 6C, CH), 129.74 (CH), 129.71 (CH), 127.65 (2C, CH), 127.57 (2C, CH), 122.93 (CH), 118.28 (d, *J* = 85.4 Hz, 3C, C), 113.66 (d, *J* = 9.2 Hz, CH), 72.47 (d, *J* = 1.7 Hz, CH), 34.86 (d, *J* = 3.4 Hz, CH2), 27.42 (d, *J* = 49.5 Hz, CH2), 26.95 (3C, CH3), 20.50 (CH2), 19.30 (C), 14.09 (CH3). R_f = 0.46 (CH_2Cl_2/CH_3OH 9:1). Compound **5**: ^1H NMR (C_6D_6, 300 MHz): δ 7.9–7.7 (m, 4H), 7.3–7.2 (m, 6H), 6.7–6.5 (m, 2H), 6.4–6.2 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.1–6.0 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.0–5.8 (m, 2H), 5.8–5.6 (dd, *J* = 15.0, 6.6 Hz, 1H), 5.5–5.2 (m, 5H), 4.5–4.3 (m, 1H), 3.3 (s, 3H), 3.0 (dd, *J* = 7.8, 1.8 Hz, 1H), 2.9–2.8 (td, *J* = 5.1, 1.8 Hz, 1H), 2.5–2.3 (m, 2H), 2.3–2.0 (m, 6H), 2.0–1.8 (m, 2H), 1.2 (s, 9H), 0.8 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (C_6D_6, 75.5 MHz): δ 172.64 (C), 137.52 (CH), 136.38 (2C, CH), 136.34 (2C, CH), 134.55 (C), 134.41 (C), 134.06 (CH), 133.97 (CH), 132.65 (CH), 131.70 (CH), 130.88 (CH), 130.01 (2C, CH), 129.98 (CH), 129.45 (CH), 129.01 (CH), (4CH under the C_6D_6 signals), 126.03 (CH), 125.19 (CH), 124.36 (CH), 74.52 (CH), 60.06 (CH), 57.65 (CH), 50.98 (CH3), 36.36 (CH2), 33.84 (CH2), 30.00 (CH2), 27.27 (3C, CH3), 23.12 (CH2), 21.00 (CH2), 19.62 (C), 14.32 (CH3). UV (Hexane/Et_3N 10/0.1) λ_{max} 296, 309, 324 nm.

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39. To a 0.1 M solution of phosphate buffer pH 8.5 (10 ml) containing lipoxidase from soybean (Fluka cat. # 62340, EEC No. 2328531, 10.8 U/mg) (2 mg) was added at rt and with stirring compound **21** (0.6 mg, $1.29x10^{-3}$ mmol) dissolved in CH_3OH (20 µl) and H_2O (180 µl). An aliquot was taken immediately to analyze the starting material (**21**) by UV showing λ_{max} at 281 nm. After 1 min the bathochromic shift from 281 nm to 310 nm indicated that the reaction was completed. The solution was purged with argon and TCEP-HCl (3 mg, 0.01 mmol) was added. After stirring for 1 min the reaction mixture was passed through a reversed phase C–18 cartridge, washed with H_2O and compound **3** eluted with $CH_3OH:H_2O$ (7:3). Purification by HPLC [Zorbax SB-C18 250 × 21.2 mm, 309 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 60/40] and desalting gave pure 7*S*,8*R*,17*S*-RCTR3 (**3**) (0.35 mg, 56%).
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Highlights

- The first total synthesis of pro-resolving and tissue-regenerative resolvin sulfido conjugates has been achieved.
- Chiral centers at C-7 and C-8 were obtained using a chiral pool strategy starting from 2-deoxy-D-ribose.
- The chiral center at C-17 was generated by an enzymatic hydroxylation with lipoxidase in the first approach.
- The chiral center at C-17 was obtained using a chiral pool strategy starting from D-(-)-arabinose in the second approach.