Stereoselective syntheses and biological activities of E-series resolvins

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Abstract

Recent research efforts focusing on the many mechanisms participating in the resolution of acute inflammation have uncovered a new genus of pro-resolving lipid mediators. These endogenous molecules include the lipoxins, resolvins, protectins and maresins, collectively coined specialized pro-resolving mediators (SPMs). SPMs are oxygenated polyunsaturated fatty acids biosynthesized by lipoxygenases and cyclooxygenases enzymes. These chemically sensitive molecules are produced in nano- to pico-gram amounts in vivo and exhibit potent anti-inflammatory and pro-resolving bioactions. In addition, SPMs clear bacterial infections, reduce pain and display bioactivities towards host defense, organ protection and tissue remodeling. Altogether, these bioactions and the need for synthetic SPMs for determination of absolute configuration and in vivo experiments have spurred a great interest in the synthetic and biomolecular communities. This review covers reported stereoselective total syntheses and outlines the most significant bioactions of the E-series resolvins.

Introduction

The resolution of inflammation is necessary to re-establish homeostasis after injury or infection.¹ The acute inflammatory response is protective, where phagocytes (neutrophils, polymorphonuclear leukocytes, PMNs) are among the first responders that leave post-capillary venules to phagocytize bacteria, other microbes, and cellular debris.² PMN, the most prominent leukocyte in human blood, neutralizes invaders and clears them to protect the host. However, excess PMN-swarming in tissues can inadvertently lead to tissue damage causing increased local inflammation. The excess accumulation of PMNs is a common mechanism in inflammatory tissues.^{3,4} Failure to undergo resolution may result in the development of chronic inflammation, a condition associated with numerous human diseases, such as asthma, atherosclerosis, autoimmune diseases, cancer and neuropathological disorders, including Alzheimer's and Parkinson's diseases.⁵ As of today, several chemical mediators have been identified that can initiate, modulate and reduce acute inflammation and stimulate resolution.^{6,7} The research efforts over the last two decades by Professor Serhan and co workers at Brigham and Women's Hospital, Harvard Medical School, have established that the return to homeostasis, catabasis,⁴ is mediated by active biosynthesis of novel families of natural products coined specialized pro-resolving mediators (SPMs).^{6,7} Recruitment of PMNs to the site of inflammation enables the active biosynthesis of SPMs from polyunsaturated fatty acids (PUFAs) during the resolution phase of acute inflammation by apoptotic PMNs and M2 macrophages.^{6,7} As of today, these findings constitute a basis for the biomolecular understanding of the resolution of the inflammatory driven diseases mentioned, and provides opportunities for drug discovery.^{8,9} Activation and recruitment of PMNs to sites of inflammation and infection depend on the surface-exposed chemoattractant receptors coined G protein-coupled receptors (GPCRs).¹⁰ SPMs display potent anti-inflammatory and pro resolving actions, often in the low nanomolar range, via GPCRs.¹¹ Approximately 35% of

all approved drugs mediate their pharmacological effects via this receptor class.¹² This active resolution processes governed by SPMs is considered a biomedical paradigm shift.⁸ The pharmacological hallmarks of neutrophil GPCRs¹³ and the potent bioactions of SPMs have spurred a great interest in drug discovery efforts.^{5,14,15} These efforts require stereoselective total synthesis of SPMs for configurational assignment and extensive biological evaluations. Isolation, identification and biosynthesis of the E-series resolvins In order to establish if novel molecules were produced during the resolution phase of inflammation that actively participate and promote the cessation of inflammation, the Serhan group developed an unbiased systems approach based on LC/MS–MS multiple reaction monitoring (MRM) methodology. By studying inflammatory exudates, they established that eicosapentaenoic acid (EPA) is converted into novel lipid mediators during acute self-limited inflammation. These mediators were coined E-series resolvins.^{16–18} Matching studies using LC/MS–MS MRM analysis with synthetic material paved the way for the configurational assignment and the exact structural elucidation of resolvin E1 (RvE1, see Scheme 1).^{16,19–21} RvE1 was first prepared by biogenic synthesis using isolated enzymes to confirm its potent bioactions.¹⁸ The term resolvin is a reflection of the presence of this family of lipid mediators in the resolution phase of inflammation, as well as their potent proresolution properties.²² To confirm the absolute configuration of the stereogenic centers present in the structure of RvE1, the biological material was compared with synthetic material.¹⁹ The combination of LC/MS–MS MRM analysis and biological evaluations has later been used to assign the absolute configuration of the stereogenic centers of other lipid mediators. After the identification of RvE1, two new members of the resolvin family derived from EPA followed, namely resolvin E2 (RvE2) and resolvin E3 (RvE3).^{23,24} Oxygenation of EPA, catalyzed by either acetylated COX-2 or cytochrome P450, generates 18*R*-(hydroperoxy)eicosapentaenoic acid (18*R*-HpEPE) which is reduced via a peroxidase to 18*R*-HEPE (Scheme 1). Acetylated COX-2 by acetylsalicylic acid acts as a modified dioxygenase enzyme inserting a molecule of oxygen into the carbon chain of EPA, resulting in the *R*-configuration at C18.⁷ For the biosynthesis of RvE1 and RvE2, a second lipoxygenation catalyzed by 5-LOX yields 5*S*-hydroperoxy-18*R*-HEPE (5*S*-Hp-18*R*-HEPE). This hydroperoxide can be transformed to 5*S*,6*S*-epoxy-18*R*-HEPE that undergoes enzymatic hydrolysis via a hydrolase enzyme to form RvE1.¹⁹ Alternatively, reduction of 5*S*-hydroperoxy-18*R*-HEPE via a peroxidase yields RvE2.²³ Lipoxygenation of 18*R*-HEPE by 15-LOX inserts a hydroperoxide with *R*-configuration at C17. This hydroperoxide is reduced into RvE3 by a peroxidase.^{24,25} In 2019, the Serhan group reported a new member of the E-series resolvins, named RvE4.²⁶ This SPM is produced in human macrophages and neutrophils activated during hypoxia conditions. RvE4 is most likely formed by two consecutive lipoxygenation reactions on EPA. In the first step, 15*S*-HpEPE is formed by 15-LOX. The second lipoxygenation is catalyzed by 5-LOX. Of note, 18*S*-configured epimers of RvE1, RvE2 and RvE3 have all been identified.^{25,27} Docosahexaenoic acid (DHA) and n-3 docosapentaenoic acid (n-3 DPA) are also substrates for the biosynthesis of SPMs, like the D-series and n-3 DPA resolvins, maresins and protectins, as well as the T-series resolvins.²⁸ The readers should consult recent reviews on the DHA.^{29,30} and the n-3 DPA^{13,31} derived families of SPMs.

Scheme 1 Outline of the biosynthesis of the E-series resolvins.

Stereoselective syntheses of E-series resolvins

The absolute configuration of the secondary alcohols and the geometry of the double bonds of each individual SPM is critical for its activity.⁷ Since SPMs are produced in microgram to nanogram quantities in vivo, comparing endogenous material with material produced by total synthesis has been the method of choice for establishing the configuration of each individual SPM. In addition, total synthesis becomes necessary for providing enough material for extensive biological evaluations. Over the last 15 years, the synthetic organic community has, to the best of our knowledge, contributed with 11 total syntheses of E-series resolvins (RvE1, RvE2 and RvE3). Below we provide an outline of each synthesis.

Synthesis of RvE1 by Petasis

The first total synthesis of RvE1 was described in 2005 in a patent by Petasis.³² In a convergent manner, two of the chiral centres in RvE1 were obtained from the chiral pool, while the third was introduced by an asymmetric Midland Alpine borane reduction of a ketone. Synthesis of the omega-fragment 1 began from (*S*)-glycidol as outlined in Scheme 2. TES-protection of (*S*)-glycidol, followed by addition of methylmagnesium bromide in the presence of Cu(I), gave the secondary alcohol **2**. Another TES group was introduced to give the bis-TES protected compound **3**. Under Swern oxidation conditions, primary TES-groups are known to undergo selective deprotection and subsequent oxidation to yield the corresponding aldehydes, saving

one step.³³ This strategy worked well, providing aldehyde **4** in 50% yield from **3**. A Takai olefination on **4** furnished vinyl iodide **1**. Another key fragment was terminal alkyne **5** that was prepared in four steps from the acid chloride **6**. Reaction of **6** with bis(trimethylsilyl)acetylene in the presence of AlCl_3 gave the propargylic ketone **7** that was reduced stereoselectively in a Midland Alpine borane reduction, furnishing alcohol **8** in high yield and 90% ee. Two protection group manipulations on **8** afforded the terminal alkyne **5**.

Scheme 2 Synthesis of vinyl iodide **1** and terminal alkyne **5** by Petasis.³²

To complete the synthesis of RvE1, vinyl bromide **9** was also synthesized from (*S*)-glycidol and connected with the two key fragments **1** and **5** (Scheme 3). Addition of TMS-acetylene to TES-protected (*S*)-glycidol provided the secondary alcohol **10** in good yield. A TBS group was introduced on the secondary alcohol in **10**, and the primary TES-group was then selectively removed with camphorsulfonic acid to afford the primary alcohol **11**. A Swern oxidation of the primary alcohol **11**, followed by a Takai olefination of the resulting aldehyde, furnished vinyl iodide **12**. Next, this vinyl iodide was converted into the corresponding organozinc compound and reacted in a Negishi-cross coupling reaction with (*E*)-1-bromo-2-iodoethene (**13**) to afford the bromodiene **9**. A Sonogashira reaction with terminal alkyne **5** provided the conjugated dienyne **14**. The TMS group in **14** was removed, and the released terminal alkyne was reacted with vinyl iodide **1** in one additional Sonogashira reaction to afford compound **15**, containing the carbon skeleton of RvE1. After removal of the silyl groups with TBAF, the two internal alkynes could be stereoselectively reduced using either the Lindlar's catalyst or the Boland method³⁴ to furnish the methyl ester of RvE1. This first synthesis of RvE1 was achieved by the Petasis group in 20 total steps (13 steps in the longest linear sequence) using well-established chemical reactions. The exact yield could not be calculated. Two of the stereogenic alcohols were obtained from the chiral pool, while the third was introduced using asymmetric synthesis. Some of the key fragments have later been prepared with some modifications in other RvE1 syntheses described in this review. The synthetic material matched endogenous RvE1, thereby establishing the absolute configuration of RvE1.¹⁹

Scheme 3 Final steps in Petasis' synthesis of RvE1.³²

Synthesis of RvE1 reported by Ogawa and Kobayashi

The first total synthesis of RvE1 to be published in a peer reviewed scientific journal was that of Ogawa and Kobayashi in 2009.³⁵ In this convergent synthesis, one key fragment was the previously reported

Scheme 3 Final steps in Petasis' synthesis of RvE1.³²

borane **16**^{36, 37} prepared in 10 steps from the acid **17** as outlined in Scheme 4. Acid **17** was first converted into acid chloride **18** using thionyl chloride. A Stille reaction was employed on acid chloride **18** and stannane **19** to produce ketone **20**, which was reduced with sodium borohydride to furnish the racemic alcohol **21**. A Sharpless kinetic resolution reaction resolved (*S*)-**21** in excellent *ee* (99%). This alcohol was then transformed into the (*Z*)-vinyl bromide **22** in 81% yield with a three step protocol involving bromination, debromosilylation with TBAF and protection of the secondary alcohol with TBSCl. (*Z*)-Vinyl bromide **22** was connected to TMS-acetylene in a Sonogashira reaction to give terminal alkyne **23** after removal of the TMS-group with KCN and AgNO₃. Hydroboration of **23** furnished vinyl borane **16**. An alternative synthesis of terminal alkyne **23** was disclosed by the same group in 2019.³⁸

Scheme 4 Synthesis of borane **16**.³⁵

The Suzuki coupling partner for borane **16**, the vinyl iodide **24**, was prepared by a Wittig reaction between the conjugated aldehyde **25** and Wittig salt **26**, as outlined in Scheme 5. The preparation of the conjugated aldehyde **25** began with addition of TMS-acetylene to propionaldehyde. The resulting propargylic alcohol was treated with Red-Al to afford the racemic allylic alcohol **27**. A Sharpless asymmetric epoxidation reaction on **27** gave a mixture of the epoxy alcohol **28** and unreacted (*S*)-**27** (46%, 99% *ee*) that were separated by chromatography. The epoxy alcohol **28** was subjected to a Peterson olefination with Et_2AlCN , affording nitrile **29** after silyl-protection of the secondary alcohol. Reduction of the nitrile **29** with DIBAL-H furnished conjugated aldehyde **25**. The unconverted allylic alcohol (*S*)-**27** could also be transformed into **25** (not shown) to afford additional amounts of **25**.³⁵ Wittig salt **26** was prepared in 13 steps from 1,3-propanediol (Scheme 5). The propargylic ketone **30**, obtained in four steps from 1,3-propanediol (not shown), was reduced in a Noyori asymmetric transfer hydrogenation reaction to afford the secondary alcohol **31** in 87% yield and >98% *ee*. After some protection group manipulations, the resulting terminal alkyne **32** was reacted in a palladium catalyzed hydrostannylation reaction with tributyltin hydride followed by treatment with iodine to afford compound **33**. The PMB-protection group in **33** was removed with DDQ and the liberated alcohol was tosylated and converted into the corresponding iodide **34**. Finally, reaction of iodide **34** with triphenylphosphine generated the Wittig salt **26**. A Z-selective Wittig reaction between the aldehyde **25** and the ylide of Wittig salt **26** furnished vinyl iodide **24** after deprotection of the two alcohols with TBAF. The Suzuki-Miyaura cross-coupling of vinyl iodide **24** and borane **16** was performed in the presence of NaOH, which furnished compound **35**. Finally, removal of the remaining silyl group afforded RvE1 in 55% yield from **24**. Unfortunately, the chemical instability of the conjugated triene diminished the purity of RvE1 (92% purity based on ^1H NMR analysis). This synthesis of RvE1 by Ogawa and Kobayashi afforded RvE1 in 23 steps in the longest linear sequence with $\approx 3\%$ overall yield (29 total steps). A Suzuki-Miyaura cross-coupling reaction enabled the construction of the sensitive triene in RvE1 at a late stage of this synthesis. A major advantage of a strategy based on the Suzuki-Miyaura reaction is the retention of the configurations of the olefinic cross-coupling partners, rendering the need for stereoselective semihydrogenation of internal alkynes obsolete. Although this strategy is among the lengthier of the syntheses discussed herein, it has the advantage of avoiding stereoselective alkyne reductions, which are often challenging on a larger scale due to over-reductions and entailing purification challenges. All stereogenic centres were introduced by asymmetric methods.

Scheme 5 Synthesis of RvE1 by Ogawa and Kobayashi.³⁵

Synthesis of RvE1 reported by Schwartz and co-workers

In 2011, Schwartz and co-workers disclosed a synthesis of RvE1.^{39, 40} A key feature of their synthesis is two Sonogashira cross-coupling reactions that assemble the entire carbon skeleton of RvE1, and allows for the construction of the sensitive triene and diene motifs in a late stage of the synthesis. The syntheses of the vinylic iodides **36** and **37** for the two Sonogashira reactions are shown in Scheme 6. The synthesis of vinyl iodide **36** began with TBS-protection of (*S*)-glycidol and subsequent addition of TMS-acetylide to afford the secondary alcohol **38** in 77% yield over the two steps. Next, two protection group manipulations provided the primary alcohol **39**, that was subjected to a Parikh-Doering oxidation. The resulting aldehyde was reacted in a Wittig homologation reaction to give the conjugated aldehyde **40**. A Takai reaction on aldehyde **40** afforded a mixture of vinyl iodide **36** and its *Z*-isomer (*E/Z*, 6.2:1) which was not removed at this stage. TBS-protected (*S*)-glycidol (**41**) served as the starting material for the synthesis of vinyl iodide **37** (Scheme 6). Addition of a methyl cuprate to the epoxide in **41**, followed by silyl-protection of the resulting alcohol afforded compound **42**. Selective deprotection of the TBS-group was achieved with camphor sulfonic acid, and this resulting primary alcohol was also oxidized in a Parikh-Doering oxidation to furnish aldehyde **43**. Finally, a Takai reaction on aldehyde **43** and subsequent deprotection of the silylated alcohol yielded the desired vinyl iodide **37**. Only the *trans*-isomer was observed in this Takai olefination.

Scheme 6 Synthesis of vinyl iodides **36** and **37** by Schwartz and co-workers.^{39, 40}

Glutaric acid anhydride (**44**) served as the starting material for the synthesis of the terminal alkyne **45** (Scheme 7). Acetylide ring opening of **44** followed by esterification with *iso*-propanol afforded the isopropyl ester **46**. Asymmetric reduction of the ketone in **46** using a Noyori reduction provided the secondary alcohol in high yield with excellent enantioselectivity (>98% ee). The TMS-group was cleaved with TBAF to afford the terminal alkyne **45**. A Sonogashira cross-coupling reaction between terminal alkyne **45** and vinyl iodide **36** provided pure dienyne **47** after chromatography. Global deprotection of the silyl groups in **47** with TBAF was followed by a Sonogashira reaction with vinyl iodide **37** to afford the triol **48**. Stereoselective reduction of the conjugated alkyne was achieved using the Boland reduction. Finally, a basic hydrolysis produced RvE1, which was stored as its sodium salt in order to improve the chemical stability. This synthesis by Schwartz and co-workers furnished RvE1 in 6% yield with 12 steps in the longest linear sequence (22 total steps). The chiral pool was the origin of two of the stereogenic alcohols in RvE1, whereas the third was introduced by an asymmetric reduction reaction. This synthesis shares several features with the first synthesis of RvE1 reported by Petasis and discussed in 2.1. The use of the *E,E*-configured vinylic iodide **36**, is advantageous. Other advantages are the use of highly stereoselective methods.

Scheme 7 Synthesis of RvE1 by Schwartz and co-workers.^{39, 40}

Synthesis of RvE1 reported by Hansen and co-workers

We recently reported a total synthesis of RvE1 using hydroxy lactol **49**, (*R*)-butane-1,3-diol and pyridinium salt **50** (Schemes 8 and 9) as starting materials.⁴¹ Commercially available hydroxy-lactone **49** was protected and then reduced with DIBAL-H to afford the lactol **51** (Scheme 8). Lactone **51** exists in an equilibrium with its hydroxy aldehyde, and the aldehyde could be converted into alkyne **52** using the Colvin rearrangement. Both the Ohira-Bestmann reaction and the Corey-Fuchs reaction failed for this transformation. Swern oxidation of the primary alcohol **52** followed by an *E*-selective Wittig reaction on the resulting aldehyde furnished the conjugated ester **53**. A chemoselective reduction of the conjugated alkene in **53** was achieved with magnesium in methanol affording compound **5**. Alcohol **54**, obtained from (*R*)-butane-1,3-diol in two steps (not shown), was oxidized with Dess-Martin periodinane. The resulting aldehyde was subjected to an *E*-selective Wittig reaction. This produced conjugated ester **55**, which was reduced with DIBAL-H at 0 °C into the corresponding alcohol. Conversion of the alcohol into its iodide, followed by reaction with triphenylphosphine, produced Wittig salt **56**.

Scheme 8 Synthesis of fragments **5** and **56** by Hansen and co-workers.⁴¹

Aldehyde **57** (Scheme 9) was obtained in five steps from pyridinium salt **50** as previously reported.⁴² Treatment of salt **50** with potassium hydroxide, followed by reaction with bromine and triphenylphosphine in dichloromethane yielded the useful bromodienal **58**⁴³ in 44% yield. Aldehyde **58** was then reacted in a stereoselective Evans-Nagao acetate aldol reaction with **59**, affording the secondary alcohol **60** in a high diastereomeric ratio (15.3:1) and excellent yield. After silylation of the secondary alcohol, the chiral auxillary was cleaved with DIBAL-H to release aldehyde **57**. Said aldehyde was then reacted in a *Z*-selective Wittig reaction with the ylid of Wittig salt **56** to furnish vinyl bromide **61** in 54% yield after removal of the significant amounts of the unwanted *E*-isomer (*Z/E*, 3.5:1). A Sonogashira cross-coupling reaction with alkyne **5** afforded ester **62** in high yield. After removal of the silyl groups with TBAF, the conjugated alkyne was stereoselectively reduced with the Boland method.³⁴ Finally, basic hydrolysis yielded RvE1. Overall, RvE1 was stereoselectively prepared in 3% yield in 12 steps in the longest linear sequence (20 total steps). Unfortunately, the *Z*-selectivity in the Wittig-reaction between the semi-stabilized ylide of **56** and aldehyde **57** was modest, severely diminishing the overall yield of RvE1. Gratifyingly, the unwanted *E*-isomer of **61** could be removed by silica-gel chromatography. Again, as in several other lipid mediator total syntheses by our group, the Evans-Nagao acetate aldol reaction was successfully employed.⁴⁴⁻⁴⁹

Scheme 9 Final steps in the synthesis of RvE1 by Hansen and co-workers.⁴¹

Synthesis of RvE1 reported by Anderson and co-workers

Recently, Anderson and co-workers reported a modular approach for the synthesis of resolvins, including RvE1.⁵⁰ Using a Hiyama-Denmark coupling, five- and six-membered cyclic alkenylsiloxanes served as key fragments in the assembly of the RvE1 carbon skeleton. The cyclic alkenylsiloxanes ensures control of the stereochemistry of the (*Z*)-alkenes in the resolvins polyene motifs. With this versatile strategy, both RvE1 and resolvins D1 were assembled, along

with a few novel resolvin hybrids.⁵⁰ The syntheses of the two cyclic alkenylsiloxanes **63** and **64** are outlined in Scheme 10. Starting from the previously discussed bromodienal **58**, obtained in 25% yield from pyridine sulfur trioxide complex (**50**), addition of allylmagnesium bromide afforded a racemic allylic alcohol which was resolved with the Sharpless asymmetric epoxidation reaction, affording alcohol **65** in 97% *ee*. After formation of a vinyltrimethylsilyl ether, a ring-closing metathesis mediated by the Schrock catalyst furnished the six-membered cyclic alkenylsiloxane **63** in high yield. The synthesis of the five-membered cyclic alkenylsiloxane **64** was achieved in five steps from the acid chloride **66**. Addition of benzyl(ethynyl)dimethylsilane as the alkynylzinc reagent **67** afforded propargylic ketone **68**. This ketone was an excellent substrate for a Noyori asymmetric transfer hydrogenation reaction (99% *ee*), affording compound **69** after acylation. A semihydrogenation of **69** provided the (*Z*)-benzyltrimethylsilyl alkenylsilane in high yield and stereoselectivity (*Z/E* > 20:1). Treatment with TBAF resulted in debenzylation, deacetylation, and cyclization to give the five-membered alkenylsiloxane **64**.

Scheme 10 Synthesis of cyclic alkenylsiloxanes **63** and **64** for the synthesis of RvE1.⁵⁰

The third fragment for their RvE1 synthesis, vinyl iodide **70**, was prepared in five steps from 2-pentyn-1-ol (Scheme 11). After a stereoselective reduction of this alkyne with LiAlH₄ followed by a Sharpless asymmetric epoxidation on the resulting (*E*)-pent-2-en-1-ol, epoxide **71** was obtained with 88% *ee*. Transformation of **71** into the iodide **72** set the stage for an elimination reaction with NaHMDS that furnished vinyl iodide **70** after acylation of the allylic alcohol. Coupling of vinyl iodide **70** with the six-membered alkenylsiloxane **63** proceeded smoothly to afford compound **73** after acylation. The authors found that free alcohols resulted in significantly decreased yields in the Hiyama-Denmark couplings. One more Hiyama-Denmark coupling connected vinyl bromide **73** and the five-membered alkenyl siloxane **64** to afford compound **74** after acylation. In this step, the acyl group was introduced to aid purification. Furthermore, **74** was also chemically more stable and suitable for storage than RvE1 itself. Saponification of **74** released RvE1 in high yield. The synthesis of RvE1 by the Anderson group provides RvE1 with 11 steps in the longest linear sequence (21 steps in total) in ~5% overall yield from pyridine sulfur trioxide complex (**50**). Their strategy of employing cyclic alkenylsiloxanes in Hiyama-Denmark coupling reactions is an appealing approach not featured

in other syntheses of SPMs. This highly modular and convergent approach has the advantage of enabling easy access to analogs, as demonstrated by the Anderson group.⁵⁰

Scheme 11 Final steps in the synthesis of RvE1 by Anderson and co-workers.⁵⁰

Synthesis of RvE2 reported by Inoue and co-workers

The first total synthesis of RvE2 was disclosed by Inoue and coworkers in 2009.⁵¹ The synthesis of one of the two key fragments, the terminal alkyne **75** is outlined in Scheme 12. Desymmetrization of the meso anhydride **76** with the organocatalyst **77**, developed by Song and coworkers,⁵² provided **78** in 87% *ee* and excellent yield. Chemoselective reduction of the ester group in **78** was achieved with lithium triethylborohydride (Super Hydride), affording hydroxy acid **79**, which in the presence of a catalytic amount of acid formed the lactone (+)-**80**. Reduction of **80** with DIBAL-H into its lactol allowed for a stereoselective addition of ethyl magnesium bromide to furnish diol **81** in a 7:1 diastereomeric ratio. After protection group manipulations, the resulting primary alcohol **82** was subjected to Swern oxidation conditions, whereby the formed aldehyde **83** underwent a thermal ring opening reaction to furnish the *E,Z*-diene **84**. The aldehyde in **84** was reduced with sodium borohydride, and the resulting alcohol brominated. This allylic bromide was coupled with the copper acetylide generated from ethynyl magnesium bromide and CuCl to furnish the terminal alkyne **75**.

Scheme 12 Synthesis of terminal alkyne **75**.⁵¹

For the synthesis of allylic bromide **85** (Scheme 13), common intermediate **78** was transformed into (-)-**80** in a three step sequence; conversion of the acid group in **78** into an acid chloride, reduction of the acid chloride into a primary alcohol and acid catalyzed lactonization. Reduction of (-)-**80** into the corresponding lactol was followed by stereoselective addition of Grignard reagent **86** to give diol **87**. Next, a series of functional group manipulations afforded primary alcohol **88**. Swern oxidation of **88** produced the corresponding aldehyde, which immediately underwent a torque selective electrocyclic ring-opening to yield the *E,Z*-diene **89** as the sole isomer. The unstable aldehyde **89** was promptly reduced with NaBH₄ to the corresponding alcohol, which was brominated to afford the allylic bromide **85**. For the assembly of the two key fragments **75** and **85**, a copper-mediated coupling was applied to generate alkyne **90**. Reduction of the isolated triple bond in **90** was achieved using the Lindlar reduction. After acetal cleavage, the liberated aldehyde was subjected to a Pinnick oxidation to afford the corresponding carboxylic acid. Finally, global deprotection of the TBS groups with TBAF furnished RvE2. This synthesis by Inoue and co-workers prepared RvE2 in 16 steps in the longest linear sequence (32 total steps), affording RvE2 in $\approx 7\%$ yield. Their synthesis has a very interesting approach, where both key fragments (**75** and **85**) were prepared from the meso anhydride **76**. The stereoselectivity induced in the organocatalytic desymmetrization of anhydride **76** was modest (85% ee), but purification by chromatography of the following diastomeric mixtures, gave chemical pure RvE2 as one stereoisomer.

Kobayashi and co-workers have contributed a synthesis of RvE2⁵³ employing a series of Wittig reactions to assemble the carbon skeleton of RvE2. This synthesis includes two of the fragments, allylic alcohol (*S*)-**21** and aldehyde **25**, previously prepared in their synthesis of RvE1 discussed herein (Schemes 4 and 5). Wittig salt **91** was synthesized in 10 steps as outlined in Scheme 14. The ylide of Wittig salt **92** was reacted with aldehyde **93** in a Z-selective Wittig reaction to produce Z-alkene **94** in quantitative yield. The *p*-methoxybenzyl group was removed with DDQ and the liberated alcohol was converted into the Wittig salt **95** using a three step protocol. A Z-selective Wittig reaction of the ylide of **95** with aldehyde **25** furnished the bis-protected diol **96**. Regioselective deprotection of the primary silyl group was achieved with TBAF. The resulting primary alcohol **97** was converted into iodide **98**, which was reacted with triphenylphosphine to afford Wittig salt **91**.

Scheme 14. Synthesis of Wittig salt **91**.⁵³

The conjugated aldehyde **99** was prepared from allylic alcohol (*S*)-**21** as outlined in Scheme 15. TBS protection of (*S*)-**21** with subsequent ozonolysis and reductive work-up using triphenylphosphine afforded aldehyde **100**. Treatment of **100** with sodium periodate resulted in loss of the TMS group and oxidative cleavage of the resulting hydroxyaldehyde, affording aldehyde **101**. Finally, an *E*-selective Wittig reaction produced the conjugated aldehyde **99**. The ylide of Wittig salt **91** was generated with NaHMDS and reacted with aldehyde **99** to furnish the complete carbon skeleton of RvE2 containing the desired geometry of all of the double bonds. Finally, treatment with TBAF both removed both silyl groups and hydrolyzed the methyl ester, affording RvE2.

Scheme 15 Synthesis of RvE2 by Kobayashi and co-workers.⁵³

Recently, Kobayashi and co-workers also synthesized the bis-TBS ether of the RvE2 methyl ester (**102**), as briefly outlined in Scheme 16.⁵⁴ In this synthesis, the propargylic alcohol **103** was converted to epoxy (*S*)-alcohol **104** (syn/anti = 3:2) using Red-Al followed by epoxidation of the resulting allylic alcohol with *m*-CPBA. Addition of TMS-acetylide to the epoxide in a Hurdlick-Peterson reaction⁵⁵ gave enyne **105** after a selective desilylation. Enyne **105** was then converted into the methyl ester **106** in a five step straightforward sequence as shown in Scheme 16. The known dienyn **107**⁵⁶ was coupled with chloride **108** in a Cu-catalyzed reaction to afford vinylic bromide **109** after an Appel reaction on the primary alcohol group. A Cu-mediated coupling of propargylic bromide **109** and enyne **106** furnished the carbon skeleton of RvE2. Finally, a Boland reduction of the resulting triene furnished the bis-TBS ether of the methyl ester **102** of RvE2. This RvE2 synthesis by the Kobayashi and co-workers has 11 steps

in the longest linear sequence and produced RvE2 over 26 total steps. The exact yield could not be calculated. The stereogenic centra were installed based on earlier available fragments, see Schemes 4 and 5, which is a great advantage. The same group also prepared the bis-TBS ether of RvE2 methyl ester using the useful Hudrlick-Peterson reaction⁵⁵ as a key step.

Scheme 16 Synthesis of the bis-TBS ether of RvE2 methyl ester (**102**) by Kobayashi and co-workers.⁵⁴

Synthesis of RvE2 reported by Rodriguez and Spur

Rodriguez and Spur disclosed a total synthesis of RvE2 in 2012.⁵⁷ They relied upon a series of Sonogashira cross-coupling reactions to assemble the carbon skeleton of RvE2. The synthesis of the two vinyl iodides **110** and **111** for these coupling reactions are shown in Scheme 17. Vinyl iodide **110** was prepared in a five-step sequence from propargyl ketone **112**. The Noyori transfer hydrogenation of **112** with hexadecyl trimethyl ammonium bromide (CTABr) as a phase transfer catalyst provided chiral alcohol **113** in 93.7% *ee*. Protection of the secondary alcohol and subsequent deprotection of the terminal alkyne afforded alkyne **114** which was treated with tributyltin hydride and AIBN, followed by reaction with iodine to furnish the vinyl iodide **110**. For the synthesis of the second vinyl iodide **111**, the Noyori transfer hydrogenation was again relied upon, yielding alcohol **8** from ketone **7** in 93% *ee* and 65% yield. After removal of the TMS group and protection of the secondary alcohol, the resulting terminal alkyne was converted into vinyl iodide **111** using the same protocol as for the transformation of **114** into **110**.

Scheme 17 Synthesis of vinyl iodides **110** and **111** by Rodriguez and Spur.⁵⁷

The terminal alkyne **115** was prepared in two steps from (*Z*)-1,4-dibromobut-2-ene (**116**) and TMS acetylene (**117**), as previously reported⁵⁸ using a CuI-mediated coupling reaction (Scheme 18). Next, an AgNO₃ catalyzed monodesilylation of **118** yielded the terminal alkyne **115**. The first Sonogashira reaction of **115** with vinyl iodide **110** afforded terminal alkyne **119** after AgNO₃ induced removal of the remaining TMS group. This set the stage for a second Sonogashira reaction with vinyl iodide **111**. This afforded compound **120** with all the carbon atoms in RvE2 installed. Removal of the silyl groups was achieved using catalytic HCl generated in situ from acetyl chloride in methanol. Then, a Boland reduction of the two conjugated alkynes furnished the methyl ester of RvE2. Finally, basic hydrolysis followed by mild acidic work-up (aq. NaH₂PO₄) provided RvE2. This synthesis afforded RvE2 in nine steps in the longest linear sequence (19 total steps). The total yield was not possible to calculate. The Noyori transfer hydrogenation reaction was used twice in order to install the two secondary alcohols at C5 and C18, using both enantiomers of the *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN).

Scheme 18 Rodriguez and Spur synthesis of RvE2.⁵⁷

Synthesis of RvE2 by Shuto and co-workers

In connection with development of stable cyclopropane analogs of RvE2, Shuto and co-workers also prepared synthetic RvE2 (Scheme 19).⁵⁹ A copper mediated coupling of terminal alkyne **121** and propargylic bromide **122** afforded the diyene **123** in moderate yield. A Z-selective reduction of the non-protected alkyne in **123** using P-2 nickel gave the enyne **124** after removal of the silyl group. A Sonogashira coupling of the known vinyl iodide **110**, prepared in six steps from TBS-protected (*S*)-glycidol (**41**) as reported by Schwartz and co-workers (Scheme 6, 34% yield over six steps)^{39, 40} and terminal alkyne **124** afforded alcohol **125** in high yield. A Z-selective reduction of the conjugated alkyne was achieved with the Boland method, providing the triene **126**. The alcohol in **126** was converted into the Wittig salt **127** in two steps. Another key fragment, aldehyde **99**, was prepared in four steps from the previously reported alkyne **5**. The alkyne **5** was obtained in three steps from acid chloride **6** essentially as previously reported (57% yield),⁶⁰ but here a Noyori asymmetric transfer hydrogenation was performed on ketone **7** to install the chiral alcohol. A Lindlar reduction on alkyne **5** gave the terminal alkene **128**, that was reacted in a cross-metathesis reaction with acrolein diethyl acetal using the Grubbs second generation catalyst (Scheme 19). This provided the conjugated aldehyde **99** after deprotection of the silyl and acetal groups. A Z-selective Wittig reaction of the ylid of salt **127** with conjugated aldehyde **99** afforded RvE2 after removal of the two silyl groups. This synthesis of RvE2 contains 12 steps in the longest linear sequence (22 total steps), affording RvE2 in $\approx 11\%$ overall yield. Again, the stereoselective Noyori hydrogenation reaction was relied upon in a total synthesis of SPM. Of note, Shuto and co-workers were the first to apply a cross-metathesis reaction for making a resolvins, namely in their preparation of α,β -unsaturated aldehyde **99**.

Scheme 19. Synthesis of RvE2 by Shuto and co-workers.⁵⁹

Synthesis of RvE3 reported by Inoue and co-workers

In 2012, Inoue and coworkers reported the syntheses of four isomers of RvE3.⁶¹ The absolute configuration of the diol motif was not known at the time,²⁴ and hence all four possible stereoisomers of the diol were prepared. Two stereoisomers of RvE3 exist in nature,²⁴ now known to possess a 17*R*,18*S* and 17*R*,18*R* configuration on the dihydroxy moiety, respectively.²⁵ Both compounds displayed potent anti-inflammatory actions, both in vitro and in vivo. Unlike RvE1 and RvE2, which are both biosynthesized by neutrophils via the 5-LOX pathway, RvE3 is biosynthesized via the 15-LOX pathway in humans (Scheme 1). Herein we focus on the synthesis of 18*R*-RvE3, outlined in Schemes 20 and 21. The synthesis of two of the key fragments, aldehyde **129** and tosylate **130**, are presented in Scheme 20. Preparation of aldehyde **129** began with a Sharpless asymmetric dihydroxylation of methyl 2*E*-pentenoate (**131**). In the presence of a chiral ligand ((DHQD)₂PHAL) under osmylation conditions, the diol **132** was obtained with 99% *ee* in 58% yield. The diol was converted into the bis-silyl compound **133**, and the methyl ester group was reduced into alcohol **134** using DIBAL-H at 0 °C. A Dess-Martin oxidation of **134** provided aldehyde **129**. The C1-C10 fragment **130** was synthesized in a two step protocol from the two known compounds, tosylate **135** and terminal alkyne **136**. First, a Cu(I)-mediated alkylation of alkyne **136** with tosylate **135** afforded alcohol **137**. Subsequent tosylation of the primary alcohol group in **129** furnished tosylate **122**.

Scheme 20 Synthesis of aldehyde **129** and tosylate **130**.⁶¹

In the endgame of their synthesis, phosphonate **138** and aldehyde **129** were connected in a Horner-Wadsworth-Emmons reaction (Scheme 21). Unfortunately, this gave a mixture of *E/Z* isomers in a 2.5:1 ratio, respectively. However, isomerization of the *E/Z* mixture using iodine resulted in a significant improvement of the *E/Z*-ratio (15:1) for **139** which allowed for separation of the isomers by flash chromatography on silica gel. Removal of the TMS group was achieved with K₂CO₃ in methanol to give terminal alkyne **140**. Cu(I)-mediated alkylation of the terminal alkyne **140** with tosylate **130** and subsequent Lindlar reduction of the two internal alkynes afforded pentaene **141**. Cleavage of the acetal in **141**, followed by a Pinnick-Lindgren oxidation of the released aldehyde and subsequent removal of the silane groups, afforded 18*R*-RvE3. The three other possible stereoisomers of aldehyde **129** were also prepared from methyl 2*E*-pentenoate (**131**), and could be employed in the preparation of the three other 17,18-stereoisomers of RvE3, including the naturally occurring epimer 18*S*-RvE3.⁶¹ This synthesis contains 12 steps in the longest linear sequence, affording RvE3 in ~4% overall yield. A highly

selective Sharpless asymmetric dihydroxylation provided the diol moiety. A stereoselective reduction of three internal alkyne functional groups, using the classical Lindlar-reduction, provided the three *Z*-double bonds in RvE3.

Scheme 21 Synthesis of 18*R*-RvE3 by Inoue.⁶¹

Synthesis of RvE3 reported by Tanabe and Kobayashi

Tanabe and Kobayashi published a synthesis of both the 18*R*-RvE3 and the epimer 18*S*-RvE3.⁶² Only the synthesis of the 18*R*-RvE3 is discussed herein, since the strategy for the synthesis of both stereoisomers is very similar. Scheme 22 outlines the synthesis of the aldehyde **142** that was prepared from propionaldehyde in 11 steps. First, TMS-acetylene was added to propionaldehyde. The resulting propargylic alcohol was oxidized using PPC to give the propargylic ketone **143**. A Noyori asymmetric reduction on propargylic ketone **143** afforded alcohol **144** in high *ee*. Deprotection of the alkyne in **144** and a subsequent Sonogashira coupling of the resulting terminal alkyne with vinyl iodide **145** was performed one pot to furnish the enyne **146**. The conjugated alkyne in **146** was stereoselectively reduced using the Boland method to provide the *Z,E*-diene **147**. A stereoselective epoxidation on **147** with *m*CPBA afforded the epoxide **148** in a very high diastereomeric ratio (97.5:2.5). Next, a palladium catalyzed reaction with AcOH afforded diol **149** in high yield. The diol **149** was then reacted with triphosgene to give a cyclic carbonate ester. The silyl group was removed under acidic conditions. After a Swern oxidation of the liberated primary alcohol, the resulting acetoxy group was eliminated to form the conjugated aldehyde **142**.

Scheme 22. Synthesis of aldehyde **142**.⁶²

The Wittig salt **150** was prepared in seven steps as outlined in Scheme 23. First, the acetylide of **151** was added to paraformaldehyde, and the resulting primary alcohol was converted into bromide **152**. This propargylic bromide reacted well in a Cu-mediated coupling with terminal alkyne **153** to afford a diyne which was reduced with P-2 nickel to give diene **154**. After acid catalyzed deprotection of the silyl group, the liberated alcohol was transformed into the Wittig salt **150** via its iodide. Then, a Wittig reaction of aldehyde **142** with the ylide of salt **150** afforded (17*R*, 18*R*)-RvE3 after hydrolysis of the methyl ester group. This synthesis afforded 18*R*-RvE3 in 13 steps (18 total steps) in 17% overall yield. The key step was a highly enantioselective asymmetric Noyori reduction of propargylic ketone **143** to set the absolute configuration at C18. This stereogenic center set the configuration at C17 after a highly diastereoselective epoxidation of the *Z*-olefin in **147** was performed. By performing a Mitsunobu inversion of epoxy alcohol **148**, the resulting (*S*)-alcohol was subjected to the same reaction sequence to afford 18*S*-RvE3 in 10% overall yield.

Scheme 23. Synthesis of 18*R*-RvE3 by Tanabe and Kobayashi.⁶²

Synthesis of RvE3 by Shuto and co-workers.

In 2020, Shuto and co-workers published a synthesis of RvE3, along with its 17- and 18-deoxy derivatives by a common route.⁶³ Interestingly, the anti-inflammatory activities of the 18-deoxy derivative in mice was more potent than RvE3 itself.⁶³ The synthesis of a key fragment in their RvE synthesis, the diyne **155**, was achieved in six steps as outlined in Scheme 24. Protection of the alkyne in propargyl bromide followed by a Cu-catalyzed coupling with propargyl alcohol (**156**) afforded the diyne **157** in 50% yield over two steps. An apple reaction on alcohol in **157** provided bromide **158**, which was reacted in a second Cu-catalyzed coupling reaction with the commercial alkyne **153** to give the triyne **159** in fair yield. A Lindlar reduction of **159** furnished diyne **155** after removal of the silyl protection group with TBAF. The same reduction on **159** was first attempted using P-2 nickel, but this gave a mixture containing overreduced products and **155**.

Scheme 24. Synthesis of alkyne **155**.⁶³

The second key fragment in the Shuto-synthesis of RvE3 was the vinyl iodide **160**, prepared in 11 steps from oxazolodinone **161** as outlined in Scheme 25. Acylation of **161** with benzyloxycarbonyl chloride produced oxazolodinone **162**, that was submitted to an Evans aldol reaction with propionaldehyde in the presence of *n*-Bu₂BOTf and triethylamine. This afforded syn aldol product **163** in very high stereoselectivity (98:2). After protection group manipulations and removal of the oxazolodinone auxiliary with lithium borohydride, the primary alcohol **164** was obtained in 90% over three steps. Oxidation of the alcohol **164** into the corresponding aldehyde and a subsequent Horner-Wadsworth-Emmons reaction afforded the ester **165** in excellent yield. The ester was converted in two steps into aldehyde **166**, which was subjected to a Takai olefination reaction, affording vinyl iodide **160** after removal of the two silyl groups with TBAF. The yield and stereoselectivity in the Takai reaction were initially quite poor, but both were significantly improved by employing a large excess of CH₃I and CrCl₂, providing **160** in 79% yield and E/Z 10:1. A Sonogashira reaction between vinyl iodide **160** and the terminal alkyne **155** provided compound **167** in very high yield. Partial reduction of the alkyne in **167** was achieved with the Boland method, providing 18*R*-RvE3 after hydrolysis of its methyl ester. This synthesis afforded 18*R*-RvE3 in 19% yield over 14 steps from oxazolodinone **161** (20 total steps). A key feature in this synthesis was the use of the Evans aldol reaction to introduce the chiral diol motif.

Scheme 25. Synthesis of 18R-RvE3 by Shuto and co-workers.⁶³

Summary of syntheses of E-series resolvins

Over the last two decades or so, an impressive number of SPM syntheses have been published. The research groups mentioned herein are also responsible for most of the other reported SPM syntheses.³⁰ Comparing and ranking the syntheses discussed herein is difficult. It should be considered that some of the syntheses were carried out for the purpose of structural determination, while others were planned to allow for the synthesis of analogs to be part of biological evaluations. Of the many syntheses reviewed herein, we would like to direct the readers to the RvE1 synthesis reported recently by the Anderson group.⁵⁰ Their method of employing cyclic alkenylsiloxanes in Hiyama-Denmark coupling reactions to obtain Z-alkenes is an original approach that we envision will be advantageous in other SPM syntheses. Many methods and strategies in the discussed syntheses are, unsurprisingly, familiar. The use of the Sonogashira cross-coupling reaction, or Cu-catalyzed coupling of propargylic bromides with terminal alkynes, are two common features in several of these syntheses.⁶⁴ However, the successful partial reduction of alkynes are very often challenging,⁶⁵ and predicting a suitable reduction method in each case is seldom possible. In addition, the Z-selective Wittig reaction is still frequently encountered in syntheses of SPM. However, its poor atom economy, cryogenic conditions and frequent requirement for the putative carcinogen co-solvent HMPA are disadvantageous. In the future, we strongly believe that the field of SPM synthesis would benefit greatly from Z-selective olefin cross metathesis reactions. Significant progress in developing such methods has been achieved in recent years.⁶⁶ Recently a cyclometalated ruthenium-based catalyst was employed on rather advanced intermediates in prostaglandin total synthesis.⁶⁷ Moreover, we are also sure that the use of stereoselective organocatalysts in reactions will be employed for the total synthesis of SPMs, as witnessed the preparation of various other natural products.⁶⁸⁻⁷⁴ One such example is the synthesis of RvE2 by Inoue and co-workers reviewed herein.⁵¹ Organocatalysis offers numerous appealing advantages.⁷⁵ As recently highlighted by Nicolaou and Rigol,⁷⁶ the science of total synthesis of natural occurring compounds should preferably include elements of new methodology, and should also be

conducted for structural elucidations and the potential for biological or medicinal studies as part of collaborations. It is gratifying to observe that the biomedical paradigm shift coined resolution of inflammation mediated by SPMs fulfill all of these scientific criterias, as well as providing a solid platform for education in synthetic organic chemistry.

Biological activities of the E-series resolvins

Biological activities of RvE1

Biological investigations have shown that resolvins potently promote the termination of inflammation and exhibit potent pro-resolving bioactions.^{18 27, 77-79} RvE1 and RvE2 directly counter-regulate the biosynthesis of pro-inflammatory eicosanoids and TNF- α .¹⁸ Of significance for biomedical chemistry research, the biological actions of RvE1 at controlling leukocyte responses, were found to be more potent than either aspirin or dexamethasone.¹⁸ RvE1 was also reported to regulate both central and peripheral responses with only 10 ng per mouse, when administered intrathecally. Peripheral administration of RvE1 gave highly potent effects as low as in the 285-570 pmol range. In vitro, effects were observed at concentrations as low as 3 nM.⁷⁷⁻⁷⁹ Also of great interest for medicinal and biomolecular chemistry research, the antinociceptive properties of RvE1 were reported to be more potent than those displayed by the COX-2 inhibitor NS398 or morphine.⁷⁷ Very recently, RvE1 was shown to prevent hyperinsulinemia and hyperglycemia, and that host genetics are a critical factor in the metabolic response to RvE1.⁸⁰ Park and co-workers have reported that RvE1 reduced atopic dermatitis in mice after 2,4-dinitrofluorobenzen (DNFB) challenge.⁸¹ Moreover, RvE1 significantly suppressed the production of pro-inflammatory markers (interferon-gamma, IFN- γ) and interleukin 4 (IL-4) reduced DNFB-induced infiltration of eosinophils, mast cells, CD4⁺ T cells, and CD8⁺ T cells in skin lesions.⁸¹ RvE1 is an agonist towards the ERV1/ChemR23 receptor on macrophages and the BLT1 receptor on neutrophils.²⁰ Recently it was reported that the expression and function of the ERV1/ChemR23 was upregulated in T2D neutrophils, and not the BLT1 receptor. Reduced phagocytosis of diabetic neutrophils was rescued by higher doses of RvE1 compared with healthy neutrophils.⁸²

Biological activities of RvE2

In 2006, Serhan and co-workers reported that RvE2 displayed anti-inflammatory properties similar to RvE1.²³ In the same study, it was shown that RvE2 was additive at low doses, indicating two separate anti-inflammatory pathways. In addition, human neutrophils enabled the biosynthesis of RvE2 in a higher amount than RvE1. This observation renders support for a significant role for RvE2 as a lead in drug discovery related to treating a range of inflammatory disorders.²³ Barden and colleagues investigated the effects omega-3 PUFAs supplementation exhibited on patients with inflammatory arthritis. These authors found an association between the synovial fluid concentrations of RvE2 and joint pain.⁸³ Increasing concentrations of RvE2 were found to be associated with lower pain scores in patients with arthritis.⁸³ Deyama and co-workers reported that RvE2 display antidepressant effects.⁸⁴ Intracerebroventricular injections with only 10 ng per mouse diminished depression via the activation of mTORC1 signaling pathway in the medial prefrontal cortex and hippocampal dentate gyrus.⁸⁴ RvE2 displays partial agonistic effects towards the same receptors as RvE1.⁸⁵

Biological activities of RvE3

Isobe and colleagues reported that 18*R*-hydroxy-eicosapentaenoic acid, e.g. the precursor for both RvE1 and RvE2, is converted by eosinophils to RvE3 (Scheme 1).²⁴ This mediator

displayed the characteristic anti-inflammatory properties of SPMs at 10-100 ng per mouse, including the ability to attenuate neutrophil recruitment.^{24, 25} Since both RvE1 and RvE2 have been reported to display anti-depressant effects, Minami and co-workers investigated if RvE3 also shows this biological activity. Using an in vivo model of lipopolysaccharide (LPS)-induced depression, it was observed that mice showed an enhanced immobility time, dose-dependently enhanced by intracerebroventricular infusion of RvE3 (10 or 100 ng). Using either a LPS induced inflammation model or by intracerebroventricular infusion of RvE3 on locomotor activity, no effects were observed. Hence, RvE3 may also provide antidepressant effects.⁸⁶

Biological activities of RvE4

In 2019 another member of the E-series resolvins was reported and named RvE4.²⁶ Inducing conditions of hypoxia, RvE4 was produced in human macrophages and neutrophils. The 15*S*-configuration of RvE4 was assigned based on biosynthetic studies. The 15*S*-configuration is, in contrast to RvE1, RvE2 and RvE3. RvE4 is formed after two consecutive lipoxygenation reactions on EPA (Scheme 1). Earlier, 18*S*-configured epimers of RvE1, RvE2 and RvE3 have been identified.^{25, 27} This is of significance for the biomolecular chemistry community, since SPMs exhibit their pro-resolution bioactions in a stereodefined manner.^{7, 13} The Serhan-group has reported that the 18*S*-epimer of RvE1 gave the same anti-inflammatory activities as RvE1.¹⁹ Moreover, 18*S*-RvE1 is produced in healthy human subjects.²⁷ The novel resolvin RvE4, produced in M2 macrophages under physiological hypoxia conditions (1% O₂), stimulated efferocytosis of senescent erythrocytes.²⁶ This stimulation was reported to be more potent than aspirin in mouse hemorrhagic exudates. The biosynthesis of RvE4 in neutrophils was increased in the presence of 2-deoxyglucose, an established glycolysis inhibitor. Biosynthetic formation of the other SPM families (lipoxins, resolvins, protectins and maresins) was also reported.²⁶

Conclusions

The biochemical pathways, molecular and cellular mechanisms leading to the resolution of inflammation have paved the way for a new paradigm in our understanding of the inflammatory process. We envision that the development of resolution pharmacology using SPMs will progress further, eventually enabling new treatments against many human diseases. Also, recent clinical trials with GMP produced EPA have proven very effective in reducing cardiovascular inflammation,⁸⁷ likely due to local E-series resolvin biosynthesis. This provides further support for using these potent bioactive mediators in treating human diseases. As presented herein, stereoselective total syntheses were needed for the structural assignment, biosynthesis and biological activities of the resolvins E1, E2 and E3. As recently reviewed, the pharmacology of these SPMs as individual GPCR agonists, is complex, deserving further investigations.⁸⁸ In order to address the challenging and interesting biology of GPCR agonism of SPMs, access to synthetic materials of the E-series resolvins are essential.

Conflicts of interest

There are no conflicts to declare.

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