

Synthesis of Resolvin E1 and Its Conformationally Restricted Cyclopropane Congeners with Potent Anti-Inflammatory Effect

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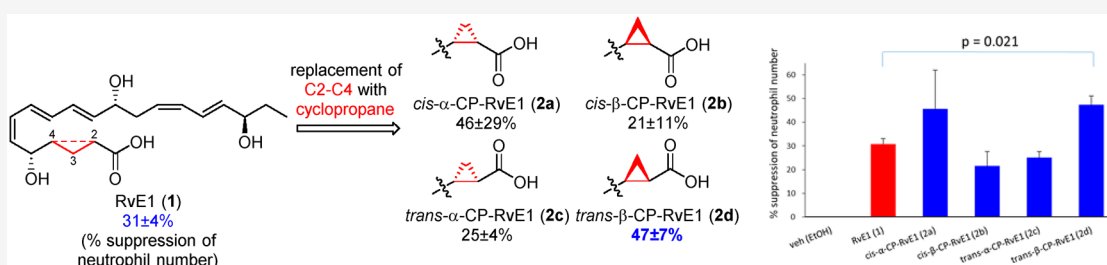
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ABSTRACT: RvE1 (1) is an endogenous lipid mediator with very potent anti-inflammatory activity, which is due to the inhibition of neutrophil chemotaxis and inflammatory cytokine production and the promotion of macrophage phagocytosis. On the basis of the conformational analysis of RvE1, we designed its four cyclopropane congeners (2a–d), in which the conformationally flexible terminal C1–C4 moiety of RvE1 was rigidified by introducing stereoisomeric cyclopropanes. The four congeners and also RvE1 were efficiently synthesized via a common synthetic route. The evaluation of the anti-inflammatory effects of the compounds in mice resulted in the identification of *trans*-β-CP-RvE1 (2d), which was significantly more active than RvE1, as a potential lead for anti-inflammatory drugs of a novel mechanism of action.

KEYWORDS: Resolvin E1, anti-inflammatory, cyclopropane congener, proresolving lipid mediator

Resolvin E1 (RvE1, 1), one of the four resolvin E-series, is an ω-3 fatty acid eicosapentaenoic acid (EPA) metabolite with very potent anti-inflammatory activity identified by Serhan et al. (Figure 1).^{1,2} Its remarkable anti-inflammatory effects are due to the inhibition of neutrophil chemotaxis and inflammatory cytokine production and the promotion of macrophage phagocytosis. Resolvins are widely studied,^{3,4} yet only a few analogues of RvE1 are reported, and its structure–activity relationship is almost unknown despite its remarkable

biological activity.^{5–7} In our continuous medicinal chemistry study on resolvins,^{8–15} here we report the synthesis and anti-inflammatory effects of RvE1 and its cyclopropane congeners.

In the RvE1 structure, five unsaturated bonds significantly restrict the conformation of the molecule, and the three hydroxy groups at the 5-, 12-, and 18-allylic positions also restrict the conformation due to allylic strain (Figure 2). Therefore, the C5–C12 and C14–C20 moieties seem to be rather rigid structures. In contrast, the C1–C4 moiety is conformationally flexible due to the continuous unsubstituted methylene chain. The unsubstituted C13 methylene also contributes to the conformational flexibility around this position. Thus the structure of RvE1 comprises three parts: the rather conformationally rigid C5–C12 and C14–C20 parts connected by the C13-methylene and the conformationally flexible C1–C4 part. Conformations analyzed by computational calculations with MacroModel supported the above

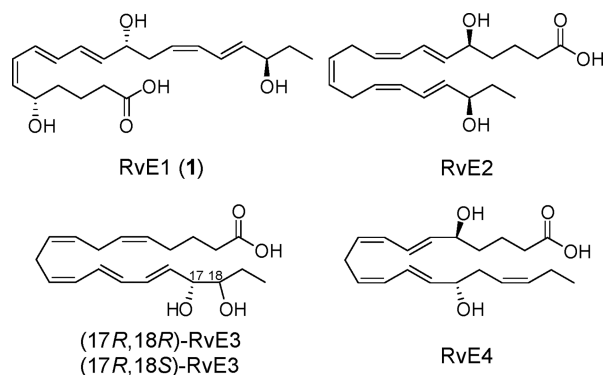


Figure 1. Structures of resolvin E-series.

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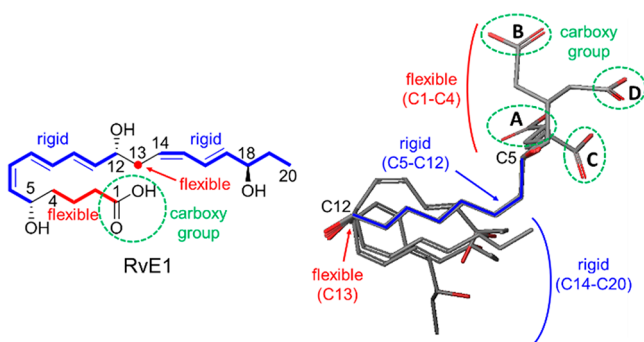


Figure 2. Stable conformation of RvE1.

speculation on the conformationally rigid and flexible parts of RvE1. The terminal carboxy group in RvE1 is likely essential for its biological activity, similar to other lipid mediators. Thus the relative spatial arrangement of the carboxy group to the rigid unsaturated parts might be key to the bioactive conformation. The calculated stable structure of RvE1 suggests the four stable conformations A–D for the flexible C1–C4 moiety, and one or some of these might be the bioactive forms (Figure 2).

We took advantage of the characteristic structural properties of cyclopropane, the smallest rigid ring, to restrict the 3D structure of various biologically active compounds, allowing us to improve the biological activity and to identify the bioactive conformations.^{16–19} Previously, we successfully applied the cyclopropane strategy to develop stable equivalents of RvE2.⁹ We thought that by introducing a cyclopropane ring into the flexible C1–C4 terminal moiety of RvE1, the relative positioning of the key terminal carboxy group in the molecule could be differentially restricted depending on the stereochemistry of the cyclopropane moiety (Figure 3). Thus we

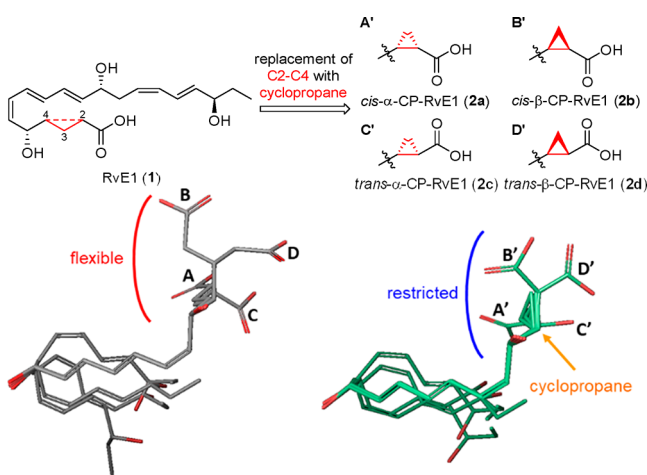


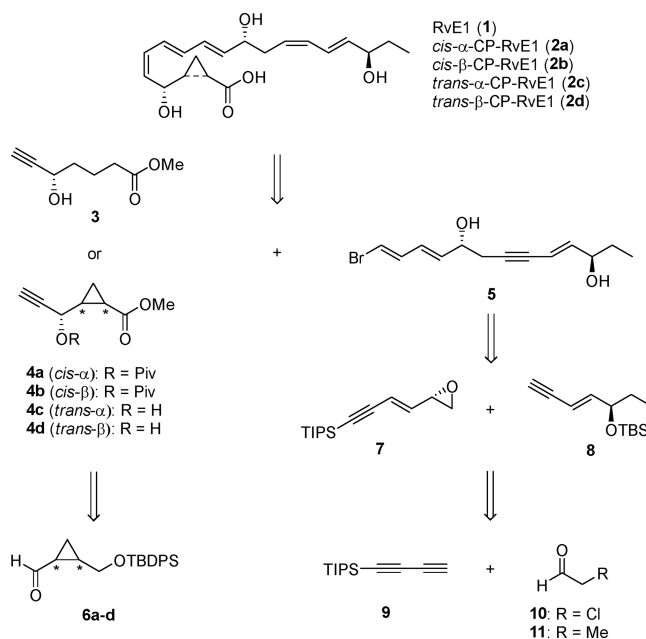
Figure 3. Design of the four CP-RvE1s (2a–d) mimicking the stable conformations of the C1–C4 moiety of RvE1 (1). The four stable conformations A–D of RvE1 (lower left) and the most stable conformations A'–D' of the four CP-RvE1s (lower right).

designed a series of cyclopropane congeners of RvE1, that is, 2a (*cis*-α-CP-RvE1), 2b (*cis*-β-CP-RvE1), 2c (*trans*-α-CP-RvE1), and 2d (*trans*-β-CP-RvE1), in which the C2–C4 moiety of RvE1 was replaced with cyclopropanes having different stereochemistries. For each CP-RvE1, MacroModel calculations were performed to obtain the stable conforma-

tion.²⁰ Each CP-RvE1 with a different stereochemistry assumed a 3D structure different in the C1–C4 moiety (Figure 3). Importantly, in the most stable conformations of the four congeners, the relative positioning of the carboxy group in the molecule effectively mimicked those in the four stable conformations of RvE1 obtained by calculations (Figure 2): A, B, C, and D in RvE1 were nearly superimposable to A' in 2a, B' in 2b, C' in 2c, and D' in 2d, respectively, in their calculated stable conformations. Thus we planned to synthesize the congeners 2a–d and evaluate their anti-inflammatory effects, which might provide a lead for new anti-inflammatory drugs and also some insight into the bioactive form of RvE1.

Although some total syntheses of RvE1 have been reported,^{21–24} we required an alternative synthetic route in which the C2–C4 moiety would be readily replaceable to effectively provide not only RvE1 itself but also its cyclopropane congeners 2a–d. Scheme 1 shows our retrosynthetic

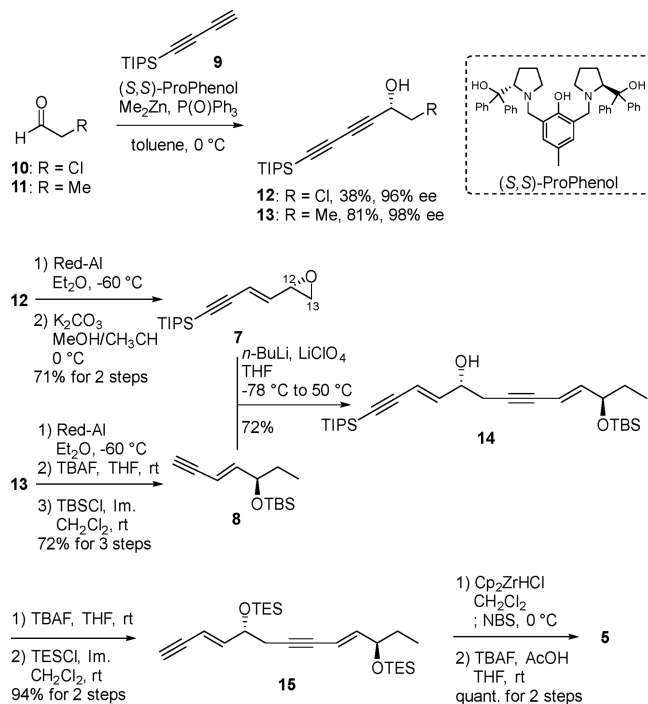
Scheme 1. Retrosynthetic Analysis of RvE1 (1) and Its Cyclopropane Congeners 2a–d



analysis of RvE1 (1) and CP-RvE1s (2a–d). All of the target compounds would be synthesized via Sonogashira coupling with *trans*-dienyl bromide 5 as a common key intermediate by changing the partner alkynes, that is, compound 3 or cyclopropane units 4a–d. All four stereoisomeric units 4a–d would be prepared from the corresponding stereoisomers 6a–d, which we previously developed as versatile cyclopropane units with stereochemical diversity.^{25,26} The dienyl bromide 5 was expected to be obtained by an epoxy ring opening of epoxide 7 with enyne 8. Both 7 and 8 would be obtained from diyne 9 and chloroacetaldehyde (10) or propanal (11) by adopting Trost's ProPhenol-catalyzed diynylation.^{27,28} Thus the two chiral centers in 5 would be efficiently constructed by the same catalytic reaction with diyne 9.

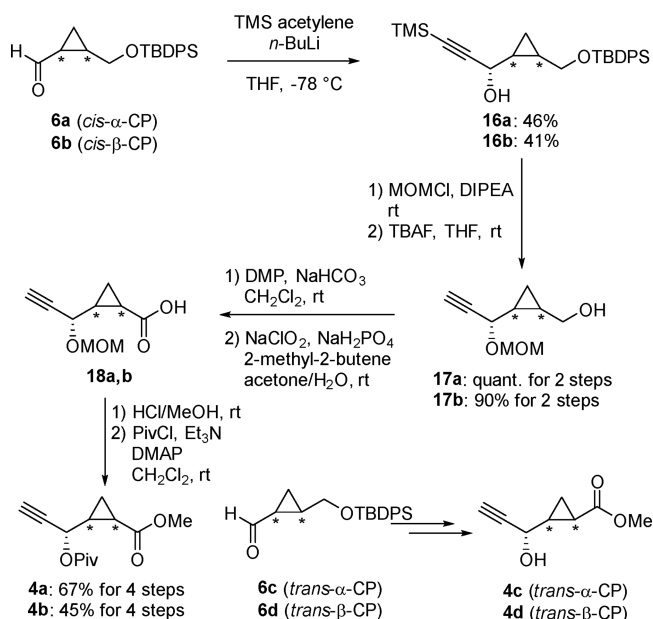
On the basis of the retrosynthesis, we first focused on the synthesis of the key intermediate 5, as shown in Scheme 2. When chloroacetaldehyde (10) or propanal (11) was subjected to the ProPhenol-catalyzed diynylation with 9 according to the previous report,^{27,28} the desired adduct 12

Scheme 2. Synthesis of the Common Intermediate 5



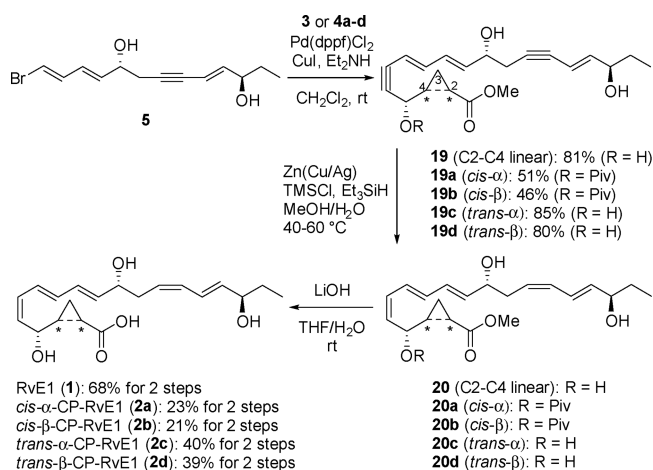
or 13 was obtained with high optical purity, respectively. The internal alkyne of 12 was regio- and stereoselectively reduced with Red-Al, and the resulting chlorohydrin was converted to epoxide 7. The internal alkyne of 13 was similarly regio- and stereoselectively reduced, the terminal silyl group of the resulting allylic alcohol was removed, and the hydroxy group was protected with a *tert*-butyldimethylsilyl (TBS) group to give 8. We next investigated the regioselective epoxy ring-opening reaction of epoxide 7 with lithiated enyne prepared from 8 in tetrahydrofuran (THF). The reaction with BF₃·Et₂O gave the desired allylic alcohol 14 in only low yield, where the undesired regioisomeric ring-opening at C12 predominantly occurred. When LiClO₄ was used as the Lewis acid,²⁹ however, the desired 14 was obtained as a single product in 72% yield. After manipulation of the silyl protecting groups of 14, the resulting 15 was treated with Schwartz's reagent and *N*-bromosuccinimide to give the corresponding *trans*-dienyl bromide regio- and stereoselectively,^{30,31} of which the two triethylsilyl groups were simultaneously removed to afford the key common intermediate 5.

Preparation of the *cis*-cyclopropane units 4a and 4b started from the chiral cyclopropanes 6a and 6b, respectively (Scheme 3).^{25,26} Nucleophilic addition to the aldehyde 6a with trimethylsilyl acetylene and BuLi was not stereoselective; however, the desired alcohol 16a was obtained in a pure form after silica gel column chromatography. After protecting-group manipulation to form alkyne 17a, its successive treatment with Dess–Martin periodinane^{32,33} and under Pinnik oxidation conditions afforded 18a, of which the MOM protecting group of the hydroxy group was changed to a pivaloyl group to give the desired methyl ester 4a. The stereoisomeric ester 4b was similarly obtained from 6b. Starting from the chiral *trans*-cyclopropane 6c or 6d, the corresponding *trans*-cyclopropane unit 4c or 4d, respectively, was also prepared (Supporting Information).

Scheme 3. Preparation of the *cis*-Cyclopropane Units 4a and 4b

The synthetic route of RvE1 is shown in Scheme 4. Sonogashira coupling of the bromide 5 with alkyne 3³⁴ was

Scheme 4. Synthesis of RvE1 (1) and CP-RvE1 (2a–d)



performed to afford the coupling product 19 in excellent yield. Partial reduction of 19 was achieved under conditions using Zn(Cu/Ag)^{35,36} but was not reproducible. The reduction conditions reported by Hansen using Zn (Cu/Ag) in the presence of trimethylsilyl chloride (TMSCl) as a zinc activator and Et₃SiH as a hydrogen source³⁷ successfully provided the pentaene 20 in excellent yield with good reproducibility. Finally, the methyl ester of 20 was hydrolyzed to furnish RvE1 (1).

We synthesized CP-RvE1s (2a–d) by the same procedure used for the synthesis of RvE1, as shown in Scheme 4. Sonogashira coupling of units 4a–d with dienyl bromide 5, partial reduction using the zinc reagent, and finally hydrolysis of the esters afforded the four target CP-RvE1s (2a–d).

Finally, we evaluated the anti-inflammatory activity of *cis*-α-CP-RvE1 (2a), *cis*-β-CP-RvE1 (2b), *trans*-α-CP-RvE1 (2c), and *trans*-β-CP-RvE1 (2d) as well as the parent proresolving

mediator RvE1 using an in vivo mouse model of bacteria-induced peritonitis (Figure 4).^{38–40} We have observed that the

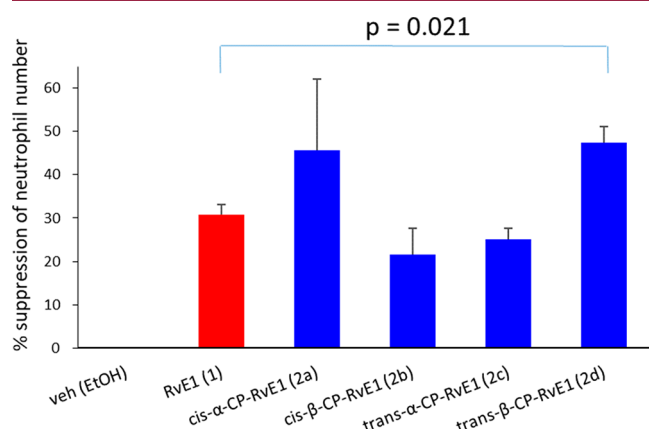


Figure 4. Anti-inflammatory activity of RvE1 (1) and CP-RvE1s (2a–d) in mice. % suppression of neutrophil number in ip administration of 300 pg of RvE1 or CP-RvE1s to a mouse ($n = 3–5$, pooled from three independent experiments). Student's two-tailed t tests were performed for statistical analyses of the data.

increase in the total number of cells in the peritoneal cavity during the acute inflammation after the intraperitoneal (ip) administration of heat-killed *Propionibacterium acnes* (*P. acnes*), a Gram-positive bacterium, is almost entirely due to the neutrophil increase.⁴⁰ The *P. acnes*-induced influx of neutrophils was significantly (~30%) suppressed by 300 pg of RvE1 injected intraperitoneally into mice. The anti-inflammatory effects of *cis*-β-CP-RvE1 (2b) and *trans*-α-CP-RvE1 (2c) were significantly reduced compared with that of RvE1; however, *cis*-α-CP-RvE1 (2a) and *trans*-β-CP-RvE1 (2d) showed remarkable anti-inflammatory effects in this system. In particular, *trans*-β-CP-RvE1 was significantly more active (~50% suppression) than parent RvE1. Thus the introduction of a cyclopropane into the terminal C1–C4 moiety of RvE2 changed the anti-inflammatory effects depending on the cyclopropane stereochemistry. These results suggest that the bioactivity of RvE1 can be related to the relative positioning of the carboxy terminal C1–C4 moiety in the molecule, and also the bioactive forms of the C1–C4 moiety in RvE1 might be analogous to conformations A and D, which were mimicked by *cis*-α-CP-RvE1 (2a) and *trans*-β-CP-RvE1 (2d). However, it should be noted that the biological activity evaluated in this study is an in vivo effect, which can be affected not only by the pharmacodynamic effect on the target biomolecule but also by the pharmacokinetic effect of compounds. Therefore, additional studies including an in vitro activity evaluation and a pharmacokinetic profile will be conducted in due course.

In conclusion, we designed the four cyclopropane congeners 2a–d of RvE1, in which the conformationally flexible but biologically important C1–C4 moiety of RvE1 was rigidified by introducing stereoisomeric cyclopropanes. The computational calculations suggested that the relative positioning of the C1-carboxy group in the four congeners effectively mimicked that of the four stable conformations of RvE1. RvE1 and its four congeners were systematically synthesized using the common key intermediate 5. The biological evaluation of the congeners showed that the anti-inflammatory effects can be changed depending on the cyclopropane stereochemistry. In

particular, *trans*-β-CP-RvE1 (2d) was significantly more active than parent RvE1; therefore, it may be a lead for anti-inflammatory drugs of a novel mechanism of action.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmmedchemlett.0c00639>.

Detailed experimental procedures, spectroscopic data, and biological assay (PDF)

¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Serhan, C. N.; Petasis, N. A. Resolvins and Protectins in Inflammation Resolution. *Chem. Rev.* **2011**, *111*, 5922–5943.
- (2) Serhan, C. N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* **2014**, *510*, 92–101.
- (3) Mayer, K.; Sommer, N.; Hache, K.; Hecker, A.; Reiche, S.; Schneck, E.; Weissmann, N.; Seeger, W.; Hecker, M. Resolvin E1 Improves Mitochondrial Function in Human Alveolar Epithelial Cells during Severe Inflammation. *Lipids* **2019**, *54*, 53–65.
- (4) Quiros, M.; Feier, D.; Birk, D.; Agarwal, R.; Zhou, D. W.; Garcia, A. J.; Parkos, C. A.; Nusrat, A. Resolvin E1 is a pro-repair molecule that promotes intestinal epithelial wound healing. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 9477–9482.
- (5) Arita, M.; Oh, S. F.; Chonan, T.; Hong, S.; Elangovan, S.; Sun, Y.-P.; Uddin, J.; Petasis, N. A.; Serhan, C. N. Metabolic inactivation of resolvin E1 and stabilization of its anti-inflammatory actions. *J. Biol. Chem.* **2006**, *281*, 22847–22854.
- (6) Hong, S.; Porter, T. F.; Lu, Y.; Oh, S. F.; Pillai, P. S.; Serhan, C. N. Resolvin E1 metabolome in local inactivation during inflammation-resolution. *J. Immunol.* **2008**, *180*, 3512–3519.
- (7) Oh, S. F.; Pillai, P. S.; Recchiuti, A.; Yang, R.; Serhan, C. N. Pro-resolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. *J. Clin. Invest.* **2011**, *121*, 569–581.
- (8) Sasaki, A.; Fukuda, H.; Shiida, N.; Tanaka, N.; Furugen, A.; Ogura, J.; Shuto, S.; Mano, N.; Yamaguchi, H. Determination of ω -6 and ω -3 PUFA metabolites in human urine samples using UPLC/MS/MS. *Anal. Bioanal. Chem.* **2015**, *407*, 1625–1639.
- (9) Fukuda, H.; Muromoto, R.; Takakura, Y.; Ishimura, K.; Kanada, R.; Fushihara, D.; Tanabe, M.; Matsubara, K.; Hirao, T.; Hirashima, K.; Abe, H.; Arisawa, M.; Matsuda, T.; Shuto, S. Design and Synthesis of Cyclopropane Congeners of Resolvin E2, an Endogenous Proresolving Lipid Mediator, as Its Stable Equivalents. *Org. Lett.* **2016**, *18*, 6224–6227.
- (10) Deyama, S.; Shimoda, K.; Suzuki, H.; Ishikawa, Y.; Ishimura, K.; Fukuda, H.; Hitora-Imamura, N.; Ide, S.; Satoh, M.; Kaneda, K.; Shuto, S.; Minami, M. Resolvin E1/E2 ameliorate lipopolysaccharide-induced depression-like behaviors via ChemR23. *Psychopharmacology* **2018**, *235*, 329–336.
- (11) Unno, Y.; Sato, Y.; Fukuda, H.; Ishimura, K.; Ikeda, H.; Watanabe, M.; Tansho-Nagakawa, S.; Ubagai, T.; Shuto, S.; Ono, Y. Resolvin E1, but not resolvins E2 and E3, promotes fMLF-induced ROS generation in human neutrophils. *FEBS Lett.* **2018**, *592*, 2706–2715.
- (12) Deyama, S.; Shimoda, K.; Ikeda, H.; Fukuda, H.; Shuto, S.; Minami, M. Resolvin E3 attenuates lipopolysaccharide-induced depression-like behavior in mice. *J. Pharmacol. Sci.* **2018**, *138*, 86–88.
- (13) Sato, M.; Aoki-Saito, H.; Fukuda, H.; Ikeda, H.; Koga, Y.; Yatomi, M.; Tsurumaki, H.; Maeno, T.; Saito, T.; Nakakura, T.; Mori, T.; Yanagawa, M.; Abe, M.; Sako, Y.; Dobashi, K.; Ishizuka, T.; Yamada, M.; Shuto, S.; Hisada, T. Resolvin E3 attenuates allergic airway inflammation via the interleukin-23–interleukin-17A pathway. *FASEB J.* **2019**, *33*, 12750–12759.
- (14) Murakami, Y.; Fukuda, H.; Muromoto, R.; Hirashima, K.; Ishimura, K.; Fujiwara, K.; Ishihara, J.; Matsuda, T.; Watanabe, M.; Shuto, S. Design and Synthesis of Benzene Congeners of Resolvin E2, a Proresolving Lipid Mediator, as Its Stable Equivalents. *ACS Med. Chem. Lett.* **2020**, *11*, 479–484.
- (15) Fukuda, H.; Ikeda, H.; Muromoto, R.; Hirashima, K.; Ishimura, K.; Fujiwara, K.; Aoki-Saito, H.; Hisada, T.; Watanabe, M.; Ishihara, J.; Matsuda, T.; Shuto, S. Synthesis of Resolvin E3, a Proresolving Lipid Mediator, and Its Deoxy Derivatives: Identification of 18-Deoxy-resolvin E3 as a Potent Anti-Inflammatory Agent. *J. Org. Chem.* **2020**, *85*, 14190–14200.
- (16) Kawamura, S.; Unno, Y.; List, A.; Mizuno, A.; Tanaka, M.; Sasaki, T.; Arisawa, M.; Asai, A.; Groll, M.; Shuto, S. Potent proteasome inhibitors derived from the unnatural cis-cyclopropane isomer of Belactosin A: synthesis, biological activity, and mode of action. *J. Med. Chem.* **2013**, *56*, 3689–3700.
- (17) Kawamura, S.; Unno, Y.; Tanaka, M.; Sasaki, T.; Yamano, A.; Hirokawa, T.; Kameda, T.; Asai, A.; Arisawa, M.; Shuto, S. Investigation of the noncovalent binding mode of covalent proteasome inhibitors around the transition state by combined use of cyclopropyl strain-based conformational restriction and computational modeling. *J. Med. Chem.* **2013**, *56*, 5829.
- (18) Mizuno, A.; Kameda, T.; Kuwahara, T.; Endoh, H.; Ito, Y.; Yamada, S.; Hasegawa, K.; Yamano, A.; Watanabe, M.; Arisawa, M.; Shuto, S. Cyclopropane-Based Peptidomimetics Mimicking Wide-Ranging Secondary Structures of Peptides: Conformational Analysis and Their Use in Rational Ligand Optimization. *Chem. - Eur. J.* **2017**, *23*, 3159.
- (19) For a review, see: Mizuno, A.; Matsui, K.; Shuto, S. From Peptides to Peptidomimetics: A Strategy Based on the Structural Features of Cyclopropane. *Chem. - Eur. J.* **2017**, *23*, 14394–14409.
- (20) The stable conformations of RvE1 were calculated using Maestro 9.9 MacroModel. The conditions of the calculation are as follows: solvent: water, force field: OPLS2005. There are four conformations within 1.5 kcal/mol from the energy of the most stable conformation of RvE1.
- (21) Ogawa, N.; Kobayashi, Y. Total synthesis of resolvin E1. *Tetrahedron Lett.* **2009**, *50*, 6079–6082.
- (22) Allard, M.; Barnes, K.; Chen, X.; Cheung, Y.-Y.; Duffy, B.; Heap, C.; Inthavongsay, J.; Johnson, M.; Krishnamoorthy, R.; Manley, C.; Steffke, S.; Varughese, D.; Wang, R.; Wang, Y.; Schwartz, C. E. Total synthesis of Resolvin E1. *Tetrahedron Lett.* **2011**, *52*, 2623–2626.
- (23) Urbitsch, F.; Elbert, B. L.; Llaveria, J.; Streatfeild, P. E.; Anderson, E. A. A Modular, Enantioselective Synthesis of Resolvins D3, E1, and Hybrids. *Org. Lett.* **2020**, *22*, 1510–1515.
- (24) Nesman, J. I.; Tungen, J. E.; Vik, A.; Hansen, T. V. Stereoselective synthesis of the specialized pro-resolving and anti-inflammatory mediator resolvin E1. *Tetrahedron* **2020**, *76*, 130821.
- (25) Kazuta, K.; Matsuda, A.; Shuto, S. Development of versatile cis- and trans-dicarbon-substituted chiral cyclopropane units: synthesis of (1S,2R)- and (1R,2R)-2-aminomethyl-1-(1H-imidazol-4-yl)-cyclopropanes and their enantiomers as conformationally restricted analogues of histamine. *J. Org. Chem.* **2002**, *67*, 1669–1677.
- (26) Watanabe, M.; Kazuta, Y.; Hayashi, H.; Yamada, S.; Matsuda, A.; Shuto, S. Stereochemical diversity-oriented conformational restriction strategy. Development of potent histamine H3 and/or H4 receptor antagonists with an imidazolylcyclopropane structure. *J. Med. Chem.* **2006**, *49*, 5587–5596.
- (27) Trost, B. M.; Chan, V. S.; Yamamoto, D. Enantioselective propenol-catalyzed addition of 1,3-dienes to aldehydes to generate synthetically versatile building blocks and diyne natural products. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.
- (28) Trost, B. M.; Quintard, A. Asymmetric catalytic alkynylation of acetaldehyde: Application to the synthesis of (+)-tetrahydropyrenophorol. *Angew. Chem., Int. Ed.* **2012**, *51*, 6704–6708.
- (29) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. Stereo- and regioselective metal salt-catalyzed alkynylation of 1,2-epoxides. *Tetrahedron Lett.* **1991**, *32*, 6617–6620.
- (30) Hart, D. W.; Schwartz, J. Hydrozirconation. Organic synthesis via organozirconium intermediates. Synthesis and rearrangement of alkylzirconium(IV) complexes and their reaction with electrophiles. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.
- (31) Schwartz, J.; Labinger, J. A. Hydrozirconation: A New Transition Metal Reagent for Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340.
- (32) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.
- (33) Dess, D. B.; Martin, J. C. A useful 12-I-5 triacetoxypseudoinane (the Dess-Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

- (34) Götz, K.; Liermann, J. C.; Thines, E.; Anke, H.; Opatz, T. Structure elucidation of hypocreolide A by enantioselective total synthesis. *Org. Biomol. Chem.* **2010**, *8*, 2123–2130.
- (35) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. Sterospecific Syntheses and Spectroscopic Properties of Isomeric 2,4,6,8-Undecatetraenes. New Hydrocarbons from the Marine Brown Alga *Giffordia mitchellae*. Part IV. *Helv. Chim. Acta* **1987**, *70*, 1025–1040.
- (36) Gueugnot, S.; Alami, M.; Linstrumelle, G.; Mambu, L.; Petit, Y.; Larchevêque, M. An efficient total synthesis of 5-(S)-HETE. *Tetrahedron* **1996**, *52*, 6635–6646.
- (37) Mohamed, Y. M. A.; Hansen, T. V. Z-Stereoselective semi-reduction of alkynes: modification of the Boland protocol. *Tetrahedron* **2013**, *69*, 3872–3877.
- (38) Bialecka, A.; Mak, M.; Biedron, R.; Bobek, M.; Kasproicz, A.; Marcinkiewicz, J. S. Different Pro-Inflammatory and Immunogenic Potentials of *Propionibacterium Acnes* and *Staphylococcus Epidermidis*: Implications for Chronic Inflammatory Acne. *Arch. Immunol. Ther. Exp. (Warsz)* **2005**, *53*, 79–85.
- (39) Ananias, R. Z.; Rodrigues, E. G.; Braga, E. G.; Squaiella, C. C.; Mussalem, J. S.; Longhini, A. L.; Travassos, L. R.; Longo-Maugéri, I. M. Modulatory Effect of Killed *Propionibacterium Acnes* and Its Purified Soluble Polysaccharide on Peritoneal Exudate Cells From C57Bl/6 Mice: Major NKT Cell Recruitment and Increased Cytotoxicity. *Scand. J. Immunol.* **2007**, *65*, 538–548.
- (40) Hirashima, K.; Muromoto, R.; Minoguchi, H.; Matsumoto, T.; Kitai, Y.; Kashiwakura, J.; Shimoda, K.; Oritani, K.; Matsuda, T. The mechanism of Tyk2 deficiency-induced immunosuppression in mice involves robust IL-10 production in macrophages. *Cytokine+* **2020**, *130*, 155077.