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

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**ABSTRACT:** RvE1 (**1**) is an endogenous lipid mediator with very potent anti-inflammatory activity, which are due to the inhibition of neutrophil chemotaxis and inflammatory cytokine production, and promotion of macrophage phagocytosis. Based on 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 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 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 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

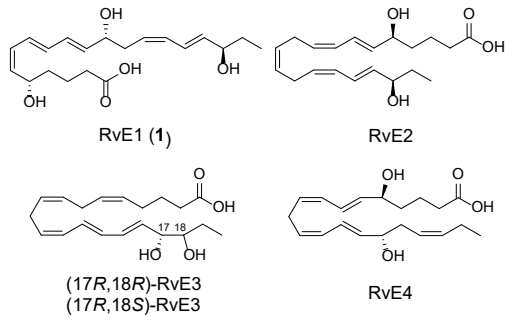



**Figure 1.** Structures of resolvin E-series.

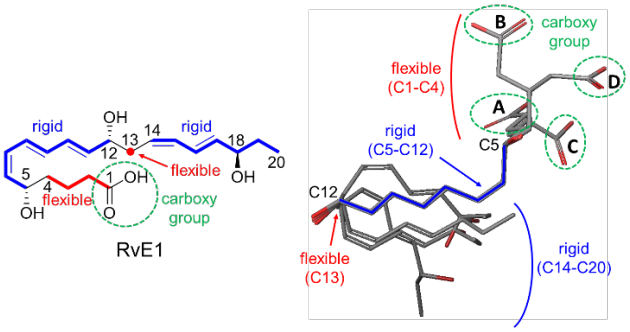



**Figure 2.** Stable conformation of RvE1.

structures. In contrast, the C1-C4 moiety is conformationally flexible due to the continuous unsubstituted methylene chain. The unsubstituted C13-methylene also contributes to 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 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).

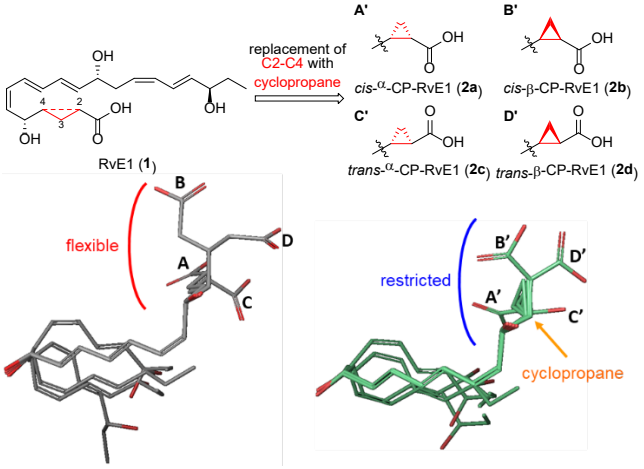
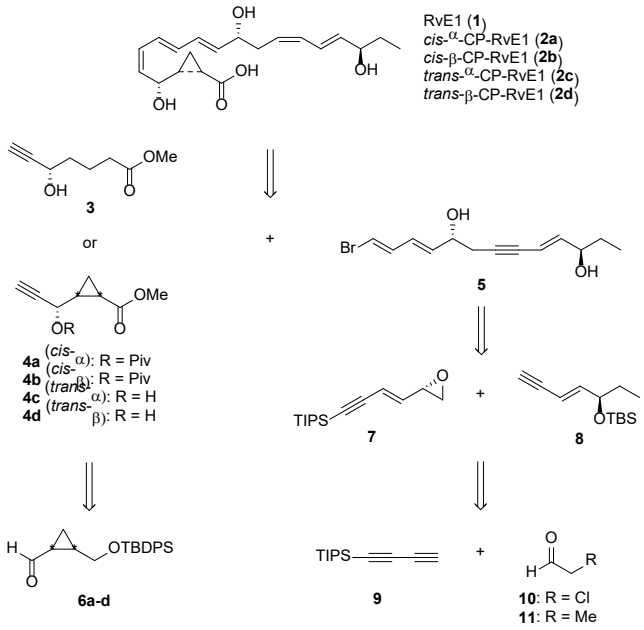



**Figure 3.** Design of the four CP-RvE1s (**2a-d**) mimicking the stable conformations of the C1-C4 moiety of RvE1 (**1**); The four stable conformations **A-D** of RvE1 (lower left) and the most stable conformations **A'-D'** of the four CP-RvE1s (lower right).

We took advantage of the characteristic structural properties of cyclopropane, the smallest rigid ring, to restrict the three-dimensional 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 restrict depending on stereochemistry of the cyclopropane moiety (Figure 3). Thus, we designed a series of cyclopropane congeners of RvE1, i.e., **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 stereochemistry. For each CP-RvE1, MacroMode

**Scheme 1. Retrosynthetic analysis of RvE1 (1) and its cyclopropane congeners 2a-d.**

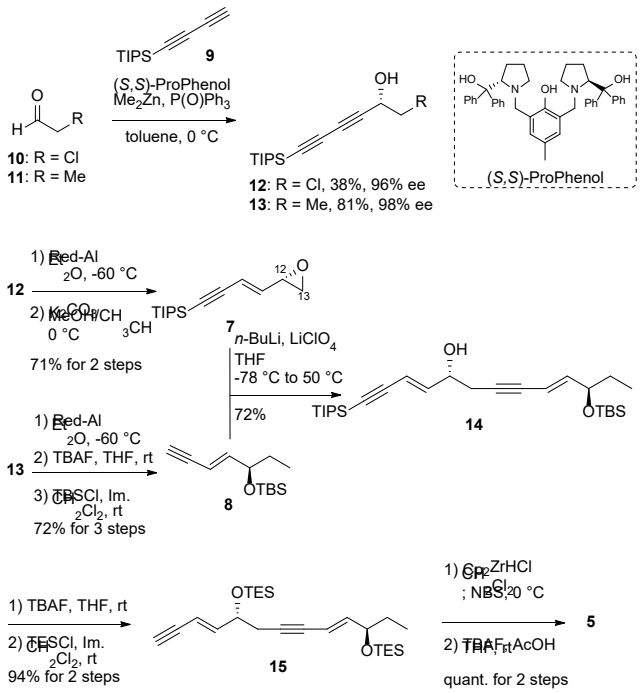



el calculations were performed to obtain the stable conformation.[20] Each CP-RvE1 with a different stereochemistry assumed a three-dimensional structure different in the C1-C4 moiety (Figure 3). Importantly, in the most stable conformations of the four congeners, the relative positionings of the carboxy 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 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, i.e., 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**.

Based on the retrosynthesis, we first focused on synthesis of the key intermediate **5**, as shown in Scheme 2. When chloroacetaldehyde (**10**) or propanal (**11**) was subjected to the

**Scheme 2. Synthesis of the common intermediate 5.**

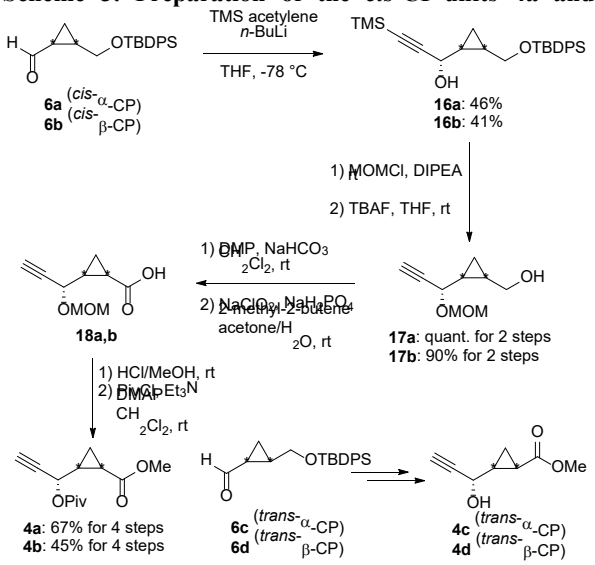


ProPhenol-catalyzed diynylation with **9** according to the previous report,[8] the desired adduct **12** or **13** was obtained with high optical purity, respectively. The internal alkyne of **12** was regio- and stereoselectively reduced with Red-Al, and the resulting chlorohydrin was converted to 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 TBS group to give **8**. We next investigated the regioselective epoxy ring-opening reaction of epoxide **7** with lithiated enyne prepared from **8** in THF. The reaction with $BF_3 \cdot Et_2O$ gave the desired allylic alcohol **14** in only low yield, where the undesired regioisomeric ring-opening at C12 predominantly occurred. When $LiClO_4$ 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 Schwarz reagent and *N*-bromo succinimide 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**.

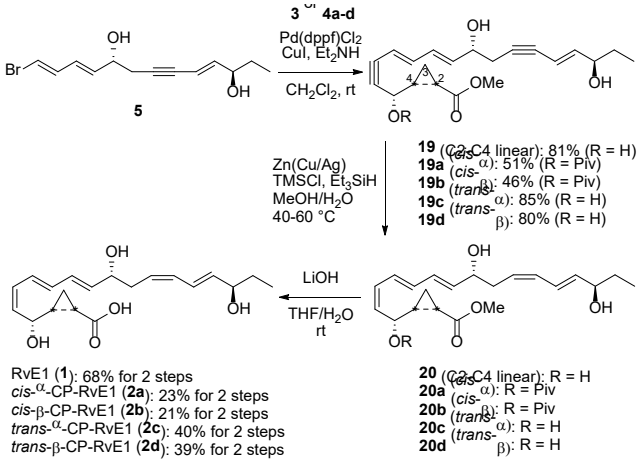
Preparation of the *cis*-cyclopropane units **4a** and **4b** started from the chiral cyclopropanes **6a** and **6b**, respectively (Scheme 3).[25-26] Nucleophilic addition to the aldehyde **6a** with trimethylsilyl acetylene and BuLi was not stereoselective, however, the desired alcohol **16a** was obtained in a pure form after silica gel column chromatography. After protecting-group manipulation forming alkyne **17a**, its successive treatment with Dess-Martin periodinane[32-33] and under Pinnik oxidation conditions afforded **18a**, of which MOM protecting group of the hydroxyl was changed to 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** and **4d**, respectively, was also prepared (Supporting Information).

The synthetic route of RvE1 is shown in Scheme 4. Sonogashira coupling of the bromide **5** with alkyne **3**[34] was performed to afford 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

**Scheme 3. Preparation of the *cis*-CP-units 4a and 4b.**




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




TMSCl as zinc activator and $Et_3SiH$ as a hydrogen source[37] 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 the units **4a-d** with dienyl bromide **5**, partial reduction using the zinc reagent, and finally hydrolysis of the esters afforded the four targets 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 increase in the total number of cells in the peritoneal cavity during the acute inflammation after intraperitoneal administration of heat-killed *Propionibacterium. acnes* (*P. acnes*), a Gram positive bacterium, is almost entirely due to neutrophil increase.[40] The *P. acnes*-induced influx of neutrophils was significantly (~30%) suppressed by 300 pg of RvE1 injected intraperitoneally in 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-

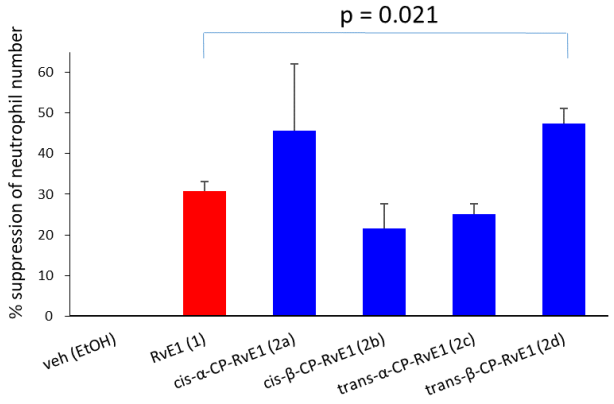



**Figure 4.** Anti-inflammatory activity of RvE1 (**1**) and CP-RvE1s (**2a-d**) in mice; % suppression of neutrophil number in ip-administering 300 pg of RvE1 or CP-RvE1s to a mouse (n = 3-5, pooled from three independent experiments). Student's two-tailed t-tests were performed for statistical analyses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

RvE1 (**2a**) and *trans*-β-CP-RvE1 (**2d**) showed remarkable anti-inflammatory effects in this system. Particularly, *trans*-β-CP-RvE1 was significantly more active (about 50% suppression) than parent RvE1. Thus, 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 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/or **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 in vivo effect, which can be affected not only by the pharmacodynamic effect to the target biomolecule but also by the pharmacokinetic effect of compounds. Therefore, additional studies including in vitro activity evaluation and 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 positionings 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. Particularly, *trans*-β-CP-RvE1 (**2d**) was significantly more active than parent RvE1, and 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 on the ACS Publications website.

Detailed experimental procedures, spectroscopic data, biological assay, and $^{1}H$ and $^{13}C$ NMR spectra

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### Notes

The authors declare no competing financial interest.

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

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