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Total synthesis of Resolvin E1

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ABSTRACT

The enantioselective total synthesis of Resolvin E1 (RvE1), a naturally occurring small molecule mediator of inflammation resolution, is reported. Two routes are presented, both modular and convergent in nature, with an excellent control of all stereocenters. The C12- and C18-hydroxy groups are derived from (S)-glycidol while the C5-hydroxy group is installed via enantioselective reduction of a ketone precursor. Both the *cis*-alkenes are introduced with excellent control by the reduction of a late-stage bis-alkyne intermediate. The synthetic disconnections are very amenable to analog preparation, and further modifications to the chemistry have allowed for scale-up and First in Man testing of this novel pro-resolution molecule.

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1. Introduction

Inflammation is a normal and necessary response to tissue injury and noxious stimuli, yet uncontrolled inflammation is clearly problematic and underlies the pathology of many acute as well as chronic diseases. Many current anti-inflammatory agents fall into two general mechanistic classes, those agents that inhibit the production of pro-inflammatory mediators and those that block the action(s) of such mediators. However, a new paradigm for the control of inflammation has emerged in recent years and relates to the discovery and recognition of natural processes already in place to control and resolve inflammatory states.[1] Coincident with the advancement of this concept of inflammation resolution has been the discovery and characterization of a family of endogenous small molecules that are key mediators of resolution biology.[2] Representative of this new class of molecules is Resolvin E1 (RvE1; 5(*S*), 12(*R*), 18(*R*)-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-eicosapentaenoic acid; Fig. 1), an oxidative metabolite of the omega-3 fatty acid eicosapentaenoic acid (EPA).[3] RvE1 has been shown to possess a variety of potent anti-inflammatory and pro-resolution activities both in vitro and in vivo[4], and was selected as the starting point for a medicinal chemistry program focusing on design and synthesis of novel analogs. Herein, we present results from our early program for the total synthesis of RvE1.

2. Synthetic approaches

For the purposes of initially assembling RvE1 for biological testing as well as using the modularity of a convergent approach for analog preparation, we followed the chemistry described in the patent literature by Petasis and co-workers,[5] wherein a late-stage bis-alkyne was assembled from smaller fragments and subsequently reduced to provide the requisite pentaene backbone (Fig. 1). An alternative to this semi-hydrogenation approach has been presented by Kobayashi and Ogawa, and currently represents the only other published synthesis of RvE1.[6]

Our first approach is shown retrosynthetically in Figure 1, where Sonogashira couplings were used to make the C7–C8 and C15–C16 bonds and a Horner–Wadsworth–Emmons (HWE) olefination was employed for the C10–C11 *trans*-double bond. The C5-stereocenter was derived via a ketone reduction with Alpine Borane,[7] while the C12- and C18-stereocenters were derived from (*S*)-glycidol via epoxide ring opening reactions with organometallics.

While this route successfully provided RvE1 as well as a number of analogs, it was not ideal due to (1) a relatively lengthy synthesis of the allylic phosphonate, (2) a modest 91%ee for installation of the C5-stereocenter, (3) the need to prepare the C8–C10 fragment in several steps,[8] and (4) a modest and somewhat variable yield (~50%) and an *E*/*Z*-ratio (~3:1) for the HWE reaction. In fact, the allylic phosphonate anion showed significant thermal instability, thus allowing degradation pathways to compete with the desired addition pathway to the α-silyloxy aldehyde.[9]

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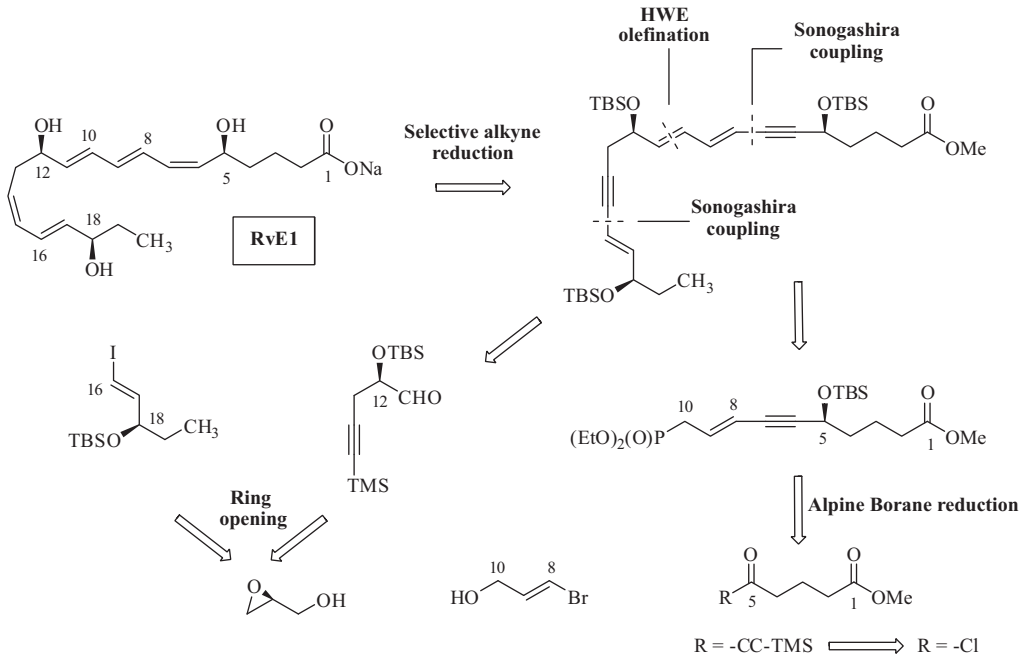


Figure 1. 1st Retrosynthetic approach to RvE1.

A second approach, more amenable to scale-up and analog synthesis, was then developed as outlined in Figure 2. Assembly of the C1–C15 framework centered around a Takai/Sonogashira bond forming sequence, and an improved enantioselective synthesis of the propargylic alcohol fragment was also achieved, as shown in Scheme 1.

Acetylide ring opening of glutaric anhydride (**1**, Scheme 1) proceeded smoothly and was followed by acid-catalyzed esterification to afford isopropyl ester **2**. Asymmetric reduction of the propargylic ketone moiety by a Noyori catalyst[10] gave the secondary alcohol in excellent enantiomeric purity (>98% ee). Fluoride mediated cleavage of the TMS-group gave the C1–C5 alkyne **3** in good overall yield for the four step sequence.

Preparation of the C11–C15 fragment followed from the Petasis patent, as shown in Scheme 2. After silyl protection of (*S*)-glycidol (**4**), Lewis-acid mediated ring opening afforded alcohol **5**. Protecting group manipulations and oxidation of primary alcohol **6** provided the desired aldehyde **7** in good overall yield, with no epimerization of the chiral center.[11]

Silyl protected (*S*)-glycidol was also the starting point for the preparation of the C15–C20 fragment (Scheme 3), whereby a methyl cuprate ring opening provided **8**, setting the C18-stereocenter. Manipulation of **8** provided aldehyde **9** and a Takai olefination[12] followed by protecting group cleavage gave the necessary vinyl iodide **11**. Only the *trans*-isomer **10** was observed from the Takai olefination.

With the key fragments in hand, coupling and elaboration to RvE1 were carried out as shown in Scheme 4. Wittig homologation of aldehyde **7** gave enal **12**, the substrate for another Takai reaction. Unlike the earlier example, this reaction produced a mixture of *cis*- and *trans*-olefin isomers (~6:1), which were carried directly into a Sonogashira coupling[13] with alkyne **3**. Following chromatographic separation, pure **13** could be isolated in 65% yield over two steps. Global silyl deprotection of **13** and subsequent Sonogashira coupling with vinyl iodide **11** afforded the bis-alkyne **14** in reasonable yield, setting the stage for the introduction of the *cis*-alkenes.

Treatment of **14** with an excess of Zn/Cu/Ag[14] at room temperature in aqueous isopropanol afforded the pentaene product without over-reduction or *cis*-alkene isomerization. In these early syntheses, ester hydrolysis was carried out with lithium hydroxide in aqueous THF, followed by passing the material through silica gel to provide the free acid, which was then converted to the sodium salt by treatment with 1 equiv of NaOH in methanol. The salt forms of RvE1 were found to be more stable than the free acid, when compared as neat oils or as ethanol solutions.

In conclusion, we have presented two modular, convergent routes to the natural product and pro-resolution mediator Resolvin E1. The chemistry described provided access to significant

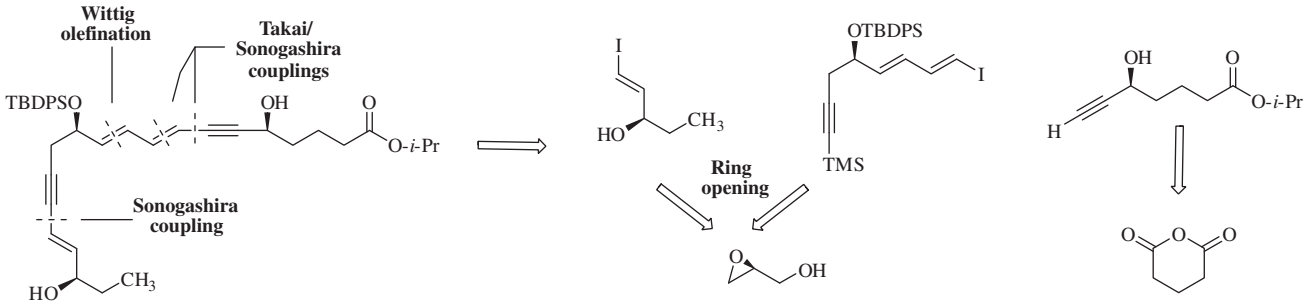
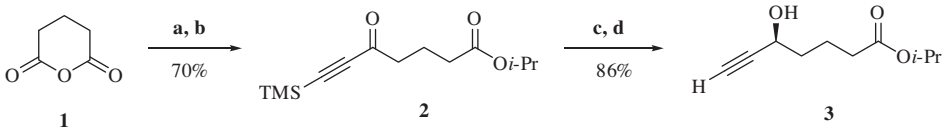
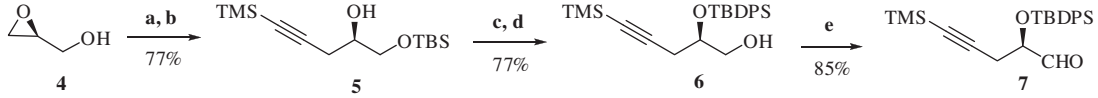


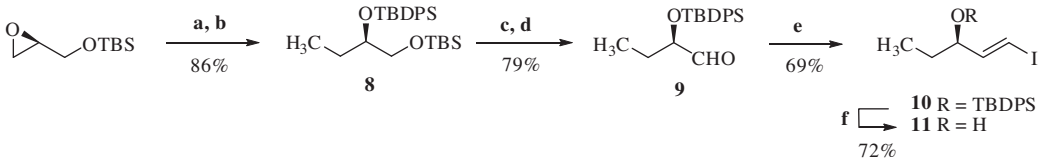
Figure 2. 2nd Retrosynthetic approach to RvE1.



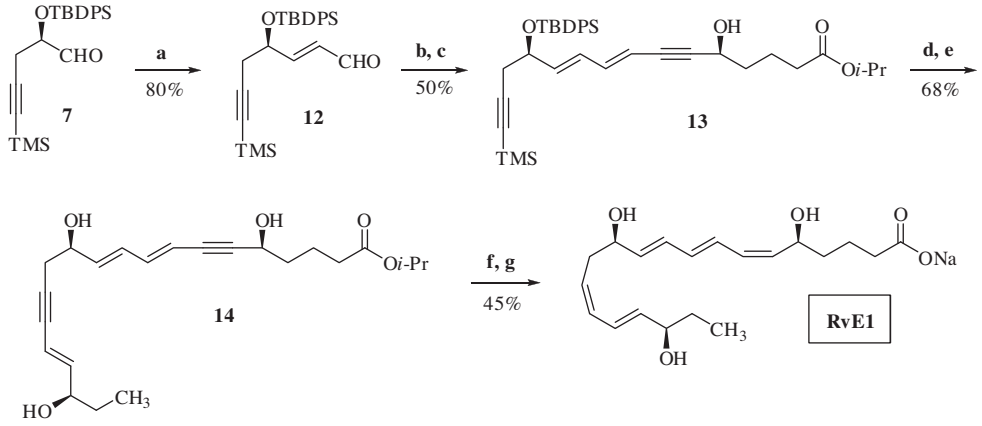
Scheme 1. Synthesis of C1–C5 fragment. Reagents and conditions: (a) $AlCl_3$, *bis*(trimethylsilyl) acetylene, CH_2Cl_2, 0 °C to rt, 24 h; (b) TsOH, *i*-PrOH, 65 °C, 24 h; (c) Noyori catalyst: Ru[(*S*,*S*)-TsDPEN](*p*-cymene), *i*-PrOH, 0 °C to rt, 2 h, >98 %ee; (d) TBAF, NH_4Cl, THF, 0 °C to rt, 2 h.



Scheme 2. Synthesis of C11–C15 fragment. Reagents and conditions: (a) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 1 h ; (b) trimethylsilylacetylene, *n*-BuLi, BF_3-Et_2O, THF, −78 °C to rt, 1 h; (c) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 16 h; (d) CSA, CH_2Cl_2, MeOH, −5 °C, 20 min; (e) Pyr-SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 3 h.



Scheme 3. Synthesis of C16–C20 fragment. Reagents and conditions: (a) CH_3MgBr, CuI, THF, −78 °C, 2 h; (b) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 17 h; (c) CSA, MeOH, CH_2Cl_2, 0–5 °C, 3 h; (d) Pyr-SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 3 h; (e) $CrCl_2$, CHI_3, THF, 0 °C to rt, 1 h; (f) TBAF, THF, 0 °C, 2 h.



Scheme 4. Fragment assembly and elaboration to RvE1. Reagents and conditions: (a) $Ph_3PCHCHO$, CH_3CN, 30 °C, 15 h; (b) $CrCl_2$, CHI_3, THF, −10 to 10 °C, 1.5 h; (c) **3**, $Pd(PPh_3)_4$, CuI, Et_2NH, rt, 15 h; (d) TBAF, NH_4Cl, THF, 0 °C to rt, 2 h; (e) **11**, $Pd(PPh_3)2Cl_2$, CuI, piperidine, benzene, rt, 2 h; (f) Zn (Cu/Ag), MeOH, H2O, 40 °C, 15 h; (g) LiOH, THF,H_2O, rt, 2 h; silica gel; NaOH, MeOH.

quantities of RvE1 for pharmacological evaluation, and also provided flexibility for the design and synthesis of a wide array of analogs. Further route modifications have allowed the large scale preparation of RvE1 for preclinical development activities and subsequent First in Man testing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.035.

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