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Total synthesis of resolvin E1

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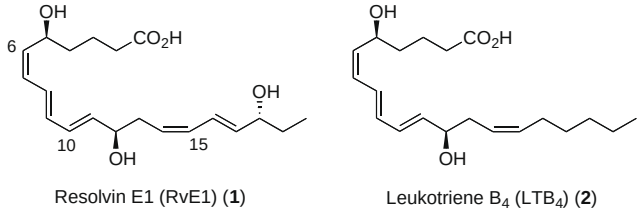
ABSTRACT

Resolvin E1 (RvE1), which is an endogenous mediator to resolve inflammation, was synthesized by Wittig reaction between the C15–C20 aldehyde and the C10–C14 phosphonium salt possessing the vinyl iodo moiety followed by Suzuki–Miyaura coupling of the resulting vinyl iodide with the vinyl borane of the C1–C9 part, which was derived from the corresponding acetylene by hydroboration. The C5 and C18 chiral centers in these parts were created by the kinetic resolution of the racemic γ-TMS allylic alcohols using the asymmetric epoxidation, while that of the C10–C14 part was constructed by the asymmetric hydrogen transfer reaction of the corresponding γ-TMS acetylene ketone.

Resolvin E1 (RvE1) is a metabolite of eicosapentaenoic acid (EPA) produced by aspirin-modified lipoxygenase.[1,2] At nanomolar levels, RvE1 suppresses inflammatory actions such as PMNL migration/infiltration and IL-12 production through binding to the specific receptor (ChemR23). These counter regulatory responses in inflammation strongly suggest that RvE1 is a natural endogenous regulator of the immune system against inflammation. In contrast to such a promising pharmaceutical property, the availability of RvE1 in the natural sources is limited to at most microgram levels,[3] and thus total synthesis of RvE1 is urgently required. The structure of RvE1 (**1**) is similar to that of LTB_4 (**2**), which, in contrast, induces inflammation intensively (Fig. 1).[4] The structural similarity implies that the (6*Z*,8*E*,10*E*)-triene unit of **1** is prone to isomerize to the chemically more stable (6*E*)-triene. On the other hand, the similarity suggests an idea that the established strategies for the synthesis of **2**[5–9] would be applicable for construction of the triene unit of **1**. In fact, the semi-hydrogenation strategy[8] with the corresponding bis-acetylene derivative is stated in a journal with a brief summary of the synthesis (Fig. 2 of Ref. 2b), whereas experimental details are available from a patent.[10] In brief, semi-hydrogenation was, as expected, halted at 60% conversion and the product, the methyl ester of **1**, was purified by using reverse phase HPLC though hydrolysis to RvE1 is not mentioned.[10]

In our consideration, the strategy using Suzuki–Miyaura coupling, which was developed by us,[9] was chosen since the construction of the conjugated triene unit of **2** is stereoselective to allow easy purification by chromatography on silica gel. For the synthesis of **1**, vinyl borane **3** and vinyl iodide **4** were the requisite coupling partners as disclosed in Scheme 1. Borane **3** is prepared by hydroboration of the corresponding acetylene,[9,11] while iodide **4** was disconnected to Wittig reagent **5** and aldehyde **6**. Herein, we report the synthesis of vinyl iodide **4** and the construction of **1**.

Synthesis of the C15–C20 intermediate **6** is delineated in Scheme 2. Propargylic alcohol **7** was prepared by addition of TMS–C≡C–Li to EtCHO and subjected to reduction with Red-Al to afford the racemic allylic alcohol *rac*-**8** with the trans olefin stereoselectively in high yield. Kinetic resolution of *rac*-**8** using asymmetric epoxidation[12,13] with *t*-BuOOH using Ti(O-*i*-Pr)$_4$/D-(−)-DIPT complex (1 equiv) at −20 °C for 24 h delivered a mixture of epoxy alcohol **9** and alcohol (*S*)-**8**, which was separated by chromatography on silica gel. Enantiomeric purity of the products **9** and (*S*)-**8** isolated in 45% and 46% yields were 99% and 98% ee, respectively, by ^{1}H NMR spectroscopy of the derived MTPA esters. Epoxide ring opening of **9** with Et_2AlCN took place smoothly and the resulting Et_2Al complex of **10** underwent *syn*-elimination under the reaction conditions, thus accomplishing the Peterson olefination reaction in one pot to afford **11** as a sole product.[14,15] Due to an expectation of a TBS ether of **11** being highly volatile, the hydroxyl group was protected with heavy TBDPSCl to afford the TBDPS ether **12**, which upon reduction with DIBAL furnished the key intermediate **6** in high yield. Alcohol (*S*)-**8** obtained above by the kinetic resolution of *rac*-**8** was converted to



Resolvin E1 (RvE1) (**1**) Leukotriene B_4 (LTB_4) (**2**)

Figure 1. Structures of RvE1 and LTB_4.

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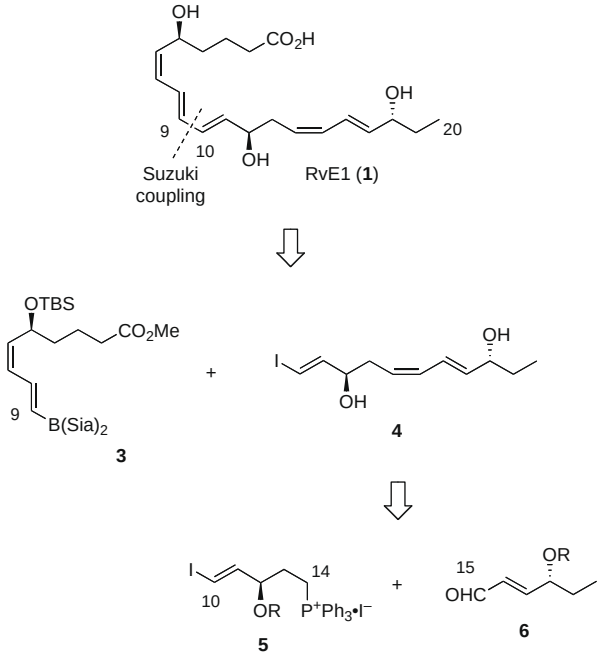
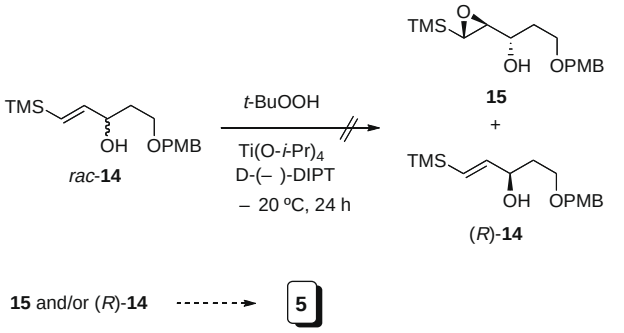
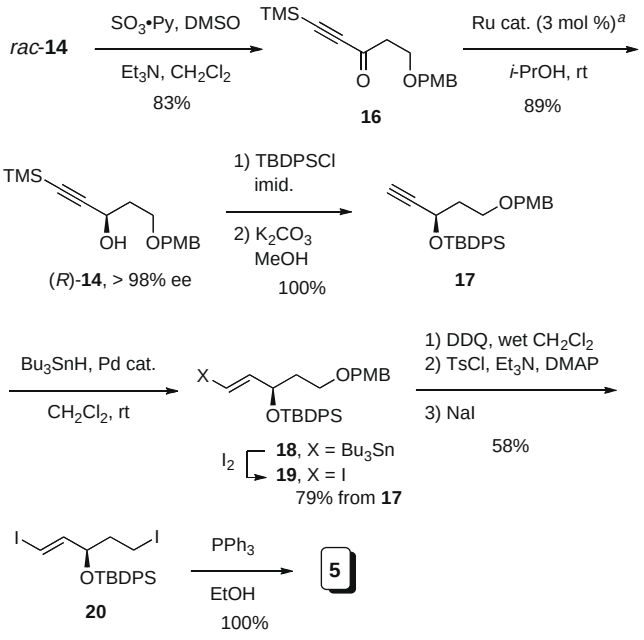


Scheme 1. Retrosynthetic analysis of RvE1. R in **5** and **6** = TBDPS.



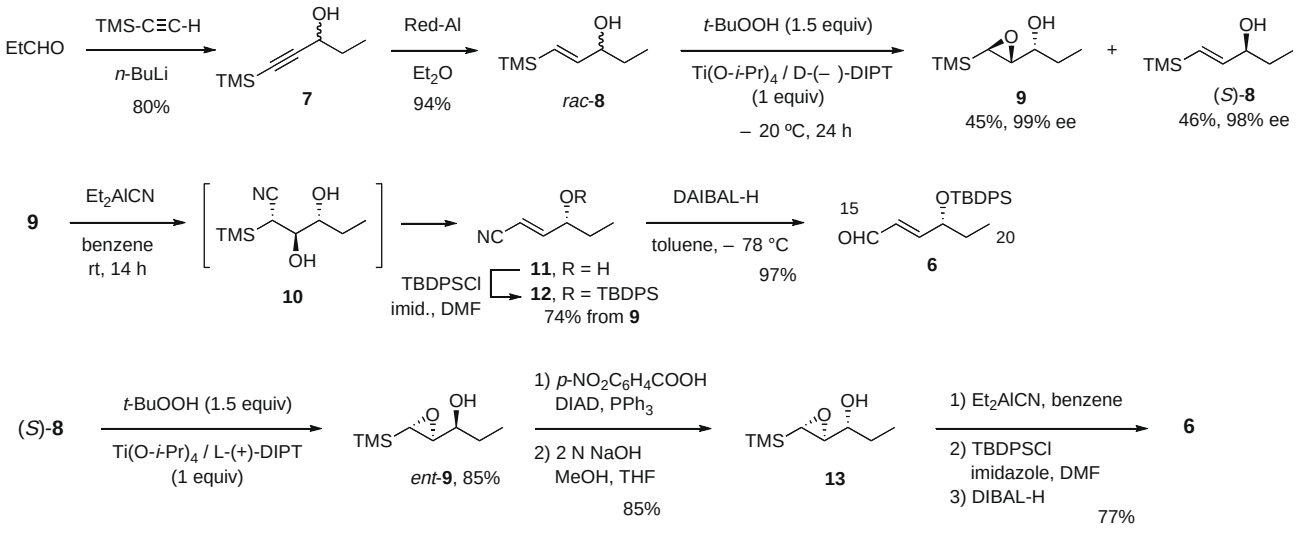
Scheme 3. An attempted synthesis of the C10–C14 intermediate **5**.



Scheme 4. Synthesis of the C10–C14 intermediate **5**. [a]Ru cat. = Ru[(*R*,*R*)-TsDPEN](*p*-cymene).

the intermediate **6** as shown in the scheme. Thus, epoxidation of (*S*)-**8** with *t*-BuOOH using Ti(O-*i*-Pr)$_4$/L-(+)-DIPT produced *ent*-**9**, which upon Mitsunobu inversion followed by hydrolysis afforded **13** in 72% yield from (*S*)-**8**. Finally, the above three-step conversion including the Peterson olefination with Et$_2$AlCN was applied to **13**, furnishing **6** in good yield. The combined overall yield from *rac*-**8** through **9** and (*S*)-**8** was 58%.

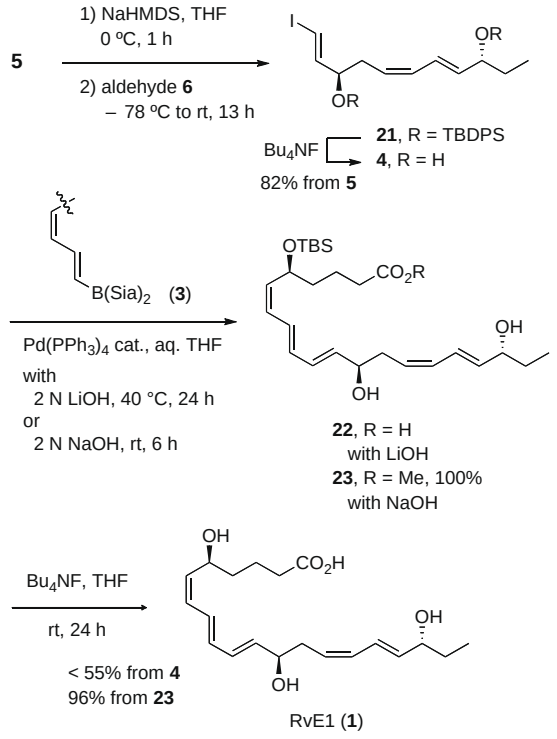
Investigated next was synthesis of the Wittig reagent **5**, for which we envisioned similar transformation through kinetic resolution/epoxidation of racemic allylic alcohol *rac*-**14**.[16] However, epoxidation with *t*-BuOOH and Ti(O-*i*-Pr)$_4$/D-(−)-DIPT gave a mixture of products containing a small quantity of the allylic alcohol and the epoxy alcohol by ^{1}H NMR spectroscopy and TLC analysis (Scheme 3).[17] Next, another synthesis involving asymmetric reduction of ketone **16** was investigated (Scheme 4). Racemic alcohol *rac*-**14** was oxidized to ketone **16** in 83% yield. Asymmetric reduction was carried out with Ru[(*R*,*R*)-TsDPEN](*p*-cymene)[18] as a catalyst in *i*-PrOH to give (*R*)-**14**, which had >98% ee by ^{1}H NMR



Scheme 2. Synthesis of the C15–C20 intermediate **6**.

spectroscopy of the derived MTPA ester. The hydroxyl group of (*R*)-**14** was protected as the TBDPS ether and the TMS group was removed by using K_2CO_3 in MeOH to produce acetylene **17** quantitatively. Palladium-catalyzed hydrostannation[19] with Bu_3SnH at room temperature proceeded cleanly to afford the *trans* stannyl olefin **18** stereoselectively in good yield, and subsequent exposure to I_2 gave iodide **19** in 79% yield from **17**. Note that AIBN-catalyzed hydrostannation under refluxing toluene gave **18** with several minor products in our hand. Three-step transformation of **19** given in the scheme was successful in affording di-iodide **20**, which upon reaction with PPh_3 in hot EtOH produced the Wittig reagent **5** in 58% yield from **19**.

An anion derived from **5** and NaHMDS was subjected to Wittig reaction with aldehyde **6** (0.67 equiv) between −78 °C and room temperature for 13 h to afford diene **21**, which upon desilylation with Bu_4NF afforded the intermediate **4** (Scheme 5). Although the ^1H NMR spectrum of **21** suffered from broadening the signals, that of alcohol **4** was quite sharp in establishing stereoselective production of the desired (14*Z*,16*E*)-diene part (δ 5.3–6.7 ppm).[20] Suzuki–Miyaura coupling of **4** with the borane reagent **3** (1.5 equiv), generated in situ from the corresponding acetylene and Sia_2BH in THF, was carried out with $Pd(PPh_3)_4$ (5 mol %) and excess LiOH (12 equiv) in aqueous THF at 40 °C. During the coupling reaction, the methyl ester part of the product underwent hydrolysis to afford acid **22**. Chromatography of the crude acid on silica gel was, however, contaminated with minor unidentified products probably derived from the reagents. The mixture was subjected to desilylation with Bu_4NF in THF to furnish RvE1 (**1**). Unfortunately, chromatographic purification of crude **1** on silica gel was unsuccessful, giving a mixture of **1** and a small quantity of by-products. We then repeated the coupling reaction with NaOH in place of LiOH to produce the methyl ester **23**, which was isolated cleanly by chromatography on silica gel. Finally, desilylation with Bu_4NF furnished **1**, which was free of the by-product(s). For confirmation of the structure, **1** was converted to the methyl ester with CH_2N_2, and its ^1H and ^{13}C NMR spectra in C_6D_6 were found to be



Scheme 5. Synthesis of RvE1.

consistent with those published.[10,21] The spectra in $CDCl_3$ given in Ref. 20 also support the structure.

Similarly, the (6*E*)-isomer of **1** was synthesized (Scheme is not shown). With the ^1H NMR spectrum of the isomer in hand, the purity of **1** we have synthesized above was calculated to be more than 92%.[22] The decreased stereoselectivity might be due to the chemical instability of the conjugated triene unit as mentioned in the introduction. We believe that the purity would be sufficient for the biological study of RvE1 (**1**).

Acknowledgment

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16. Prepared from propane-1,3-diol by a sequence of following reactions: (1) PMBCl, NaH, DMF, 70%; (2) SO_3·Py; (3) TMS-acetylene, *n*-BuLi, 85% over two steps; (4) Red-Al, Et_2O–toluene, 97%.
17. The PMB-oxy group seems responsible for the unexpected result since the compound with the benzyl-oxy group undergoes epoxidation without any event.[13] Epoxidation with other catalysts such as $Ti(O\text{-}i\text{-}Pr)_4$ and $VO(acac)_2$ also gave a mixture.
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20. Compound **4**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.59 (d of quint, J = 2.5, 7 Hz, 2H), 1.65–1.84 (br s, 1H), 1.85–2.04 (br s, 1H), 2.46 (t, J = 7 Hz, 2H), 4.03–4.25 (m, 2H), 5.43 (dt, J = 11, 7 Hz, 1H), 5.75 (dd, J = 15, 6.5 Hz, 1H), 6.19 (t, J = 11 Hz, 1H), 6.39 (dd, J = 14, 1 Hz, 1H), 6.47 (dd, J = 15, 11 Hz, 1H), 6.60 (dd, J = 14, 6 Hz, 1H). RvE1 (**1**): ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3H), 1.1–2.3 (m, 10H), 2.41 (t, J = 7 Hz, 2H), 2.49 (t, J = 7 Hz, 2H), 4.12 (q, J = 6.5 Hz, 1H), 4.25–4.34 (m, 1H), 4.59–4.66 (m, 1H), 5.43 (dd, J = 11, 10 Hz, 1H), 5.48 (dt, J = 11, 7 Hz, 1H), 5.72 (dd, J = 15, 6.5 Hz, 1H), 5.79

(dd, J = 15, 6.5 Hz, 1H), 6.09 (t, J = 11 Hz, 1H), 6.16 (t, J = 11 Hz, 1H), 6.23 (dd, J = 15, 11 Hz, 1H), 6.31 (dd, J = 15, 11 Hz, 1H), 6.45–6.54 (m, 2H). Methyl ester of RvE1 in $CDCl_3$: ^{1}H NMR (500 MHz) δ 0.93 (t, J = 7 Hz, 3H), 1.19–1.94 (m, 6H), 1.8–2.0 (br s, 3H), 2.34 (t, J = 6.5 Hz, 2H), 2.43–2.55 (m, 2H), 3.67 (s, 3H), 4.11 (q, J = 6.5 Hz, 1H), 4.27 (q, J = 6.5 Hz, 1H), 4.56–4.62 (m, 1H), 5.43 (t, J = 11 Hz, 1H), 5.46 (dt, J = 11, 8 Hz, 1H), 5.73 (dd, J = 15, 6.5 Hz, 1H), 5.79 (dd, J = 15, 6.5 Hz, 1H), 6.09 (t, J = 11 Hz, 1H), 6.16 (t, J = 11 Hz, 1H), 6.23 (dd, J = 15, 11 Hz, 1H), 6.32 (dd, J = 15, 11 Hz, 1H), 6.45–6.56 (m, 2H); ^{13}C NMR (75 MHz) δ 9.8, 20.9, 30.2, 33.9, 35.8, 36.8, 51.7, 67.7, 71.9, 74.1, 125.5, 126.7, 127.8, 130.2, 130.6, 131.1, 133.9, 134.0, 136.5, 137.2, 174.1. Methyl ester of RvE1 in C_6D_6: ^{1}H NMR (500 MHz) δ 0.89 (t, J = 7.5 Hz, 3H), 1.08–1.82 (m, 6H), 1.8–2.3 (br s, 3H), 2.12 (t, J = 7.5 Hz, 2H), 2.38–2.54 (m, 2H), 3.33 (s, 3H), 3.94 (q, J = 6 Hz, 1H), 4.12 (q, J = 6 Hz, 1H), 4.45–4.52 (m, 1H), 5.39 (t, J = 10.5 Hz, 1H), 5.47 (dt, J = 11, 8 Hz, 1H), 5.62 (dd, J = 15, 6 Hz, 1H), 5.67 (dd, J = 15, 6 Hz, 1H), 6.00 (t, J = 10.5 Hz, 1H), 6.11–6.20 (m, 2H), 6.34 (dd, J = 15, 11 Hz, 1H), 6.55 (dd, J = 15, 11 Hz, 1H), 6.62 (dd, J = 15, 11 Hz, 1H); ^{13}C NMR (75 MHz) δ 9.9, 21.2, 30.6, 33.8, 36.2, 37.1, 51.0, 67.6, 71.9, 73.5, 125.3, 126.9, 128.4 (overlapped with C_6D_6), 129.7, 130.4, 131.1, 134.1, 134.9, 137.1, 137.8, 173.5. The ^{1}H and ^{13}C NMR spectra were identical with those reported.[10]

21. The ^{1}H NMR spectrum of the free acid (RvE1) is not given in Ref. 10.
22. On the other hand, purity of the methyl ester over the (6*E*)-isomer was ca. 85%.