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Total synthesis of resolvin E2

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ABSTRACT

Resolvin E2 (**2**) was synthesized stereoselectively using the C1–8 and C15–20 aldehydes **6** and **9**, which were connected to the C9–14 fragment by using Wittig reactions. The aldehyde **6** was prepared from the γ-silyl alcohol (*S*)-**20** by a sequence of reactions involving ozonolysis, oxidation with $NaIO_4$, and the Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCHO$, whereas the aldehyde **9** was synthesized from the corresponding γ-silyl alcohol through epoxidation, reaction with Et_2AlCN, and reduction with DIBAL-H.

During the study aimed at finding compounds that promote resolution of inflammation, a number of metabolites of the ω-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been isolated.[1,2] Among them, resolvins E1 and E2 (RvE1 and RvE2, respectively) carry potent counterregulatory and anti-inflammatory properties (Fig. 1). Since these compounds are available only in at most microgram quantities by enzymatic transformation of the ω-3 fatty acids, development of chemical synthesis has been an urgent subject in organic synthesis. RvE1 and RvE2 possess allylic alcohol moieties, which are conjugated to the stereodefined olefin(s). In general, the hydroxyl group and the cis olefin in the conjugated allylic alcohol moiety are chemically unstable so that transformations at the latter stage should be carried out under mild conditions. Recently, we succeeded in the synthesis of RvE1 (**1**) by using the Suzuki–Miyaura coupling reaction.[3] Then, we chose RvE2 (**2**) as a new target. Quite recently, Inoue published the synthesis of **2** by connecting the C1–10 and C13–20 bromides to acetylene followed by Lindlar reduction.[4] The hydroxyl groups involved in these bromides were constructed with 6–7:1 diastereoselectivities from 87% ee of the cyclobutene lactone. Consequently, the connection of these bromides of the somewhat low ee should produce the diastereoisomers. However, separation of the diastereoisomers is not

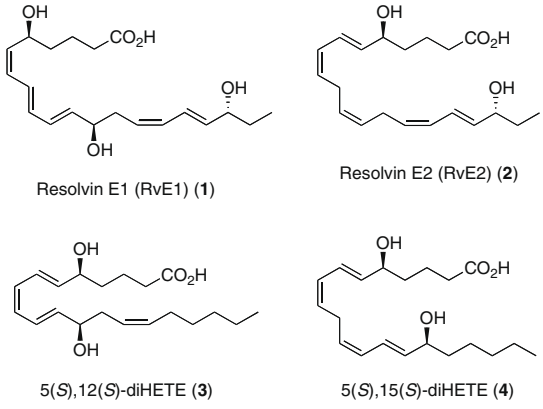
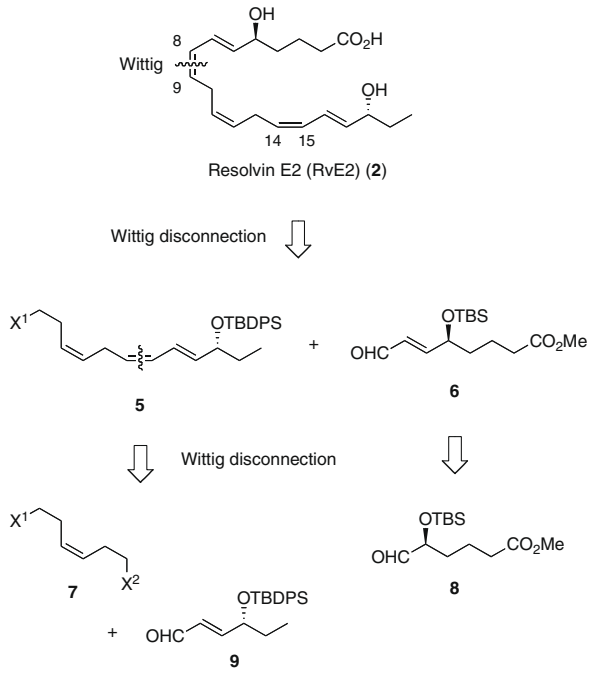


Figure 1. RvE1 and RvE2 derived from EPA and diHETEs derived from ARA.



Scheme 1. Disconnection of RvE2.

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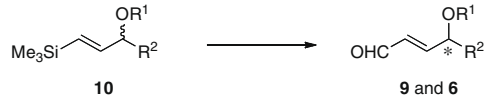
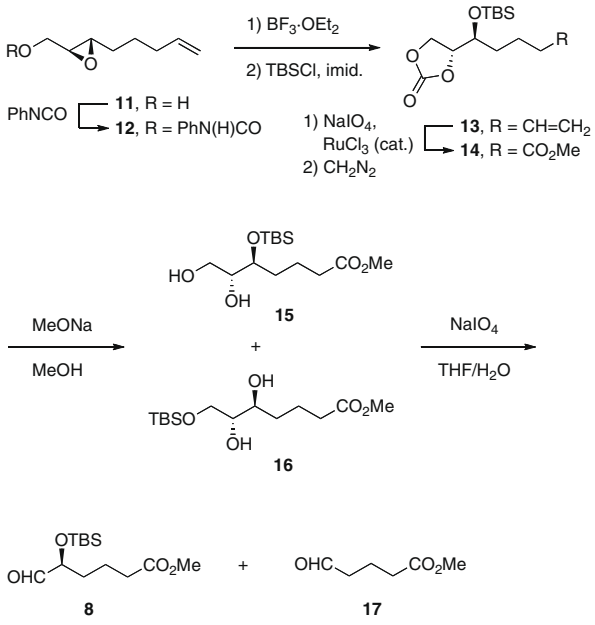


For **9** (ref. 3): (1) kinetic resolution/epoxidation; (2) Et_2AlCN; (3) DIBAL-H
For **6**: see the present text

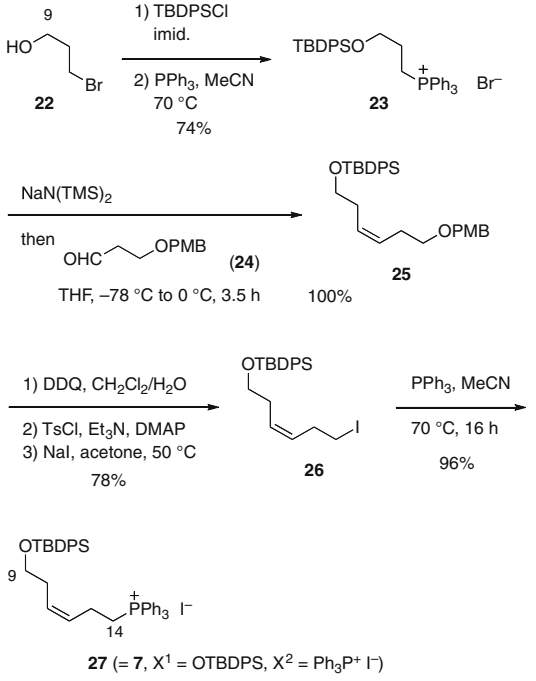
Scheme 2. An approach to unsaturated aldehydes.



Scheme 3. An approach to aldehyde **8**.

mentioned. Regarding the separation, our preliminary study revealed that a mixture of RvE2 and the diastereoisomers derived from the racemic parts by using the present method (vide infra) was little separated by routine chromatography on silica gel. Consequently, we chose reactions that deliver chiral alcohols with quite high ee.

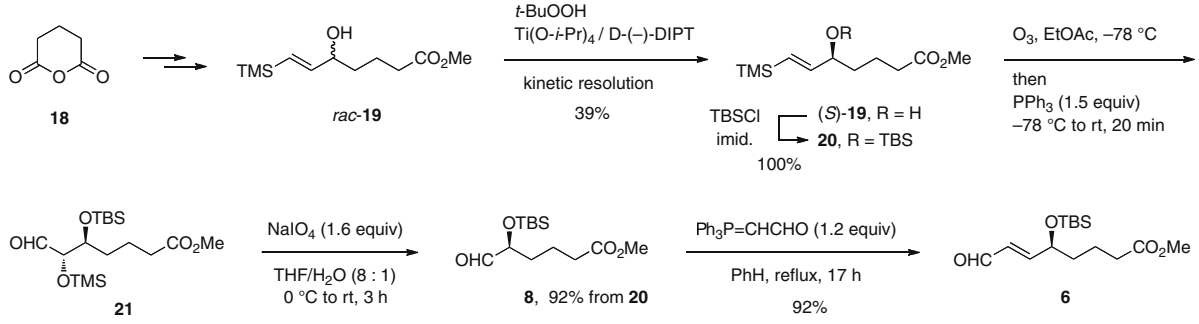
Similar structures to the conjugated dienyl alcohol moiety of **2** are seen in diHETEs such as 5(*S*),12(*S*)- and 5(*S*),15(*S*)-diHETEs (**3** and **4**), derivatives of arachidonic acid (ARA),[5,6] which have been the target compounds in the 1980–1990s.[7] However, we found that the previous syntheses of the intermediates and further constructions to diHETEs[8,9] are hardly applicable to **2** due to the structural difference. Instead, we planed to use Wittig reaction to construct the three cis olefins present in **2**. Scheme 1 shows the Wittig disconnection at the two olefins, giving α,β-unsaturated



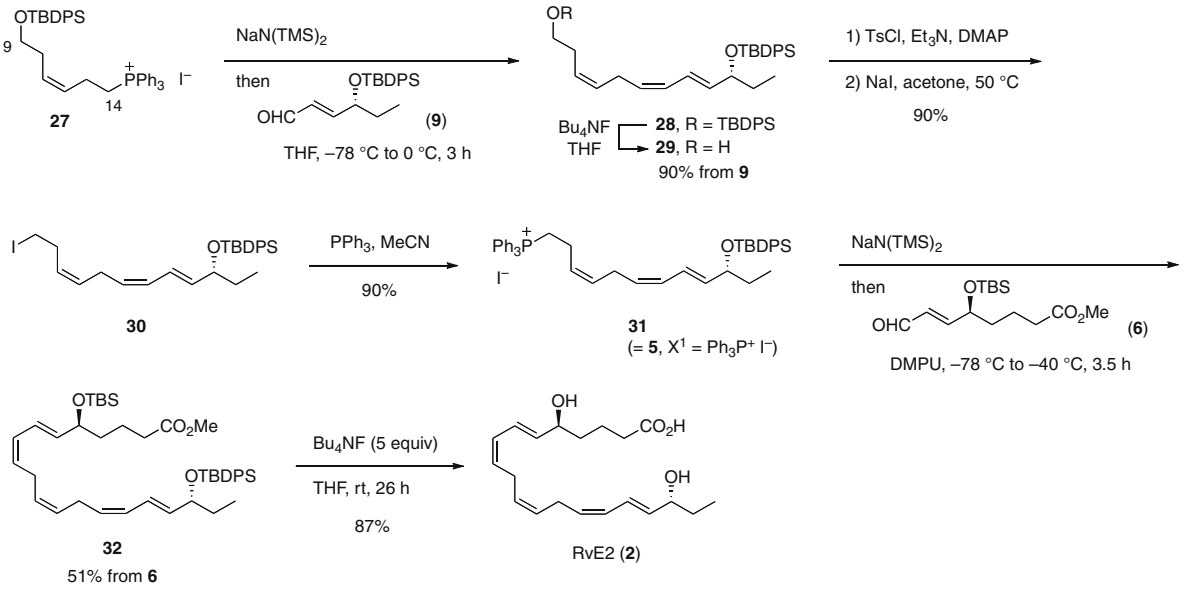
Scheme 5. Synthesis of the C9–14 intermediate **27**.

aldehydes **6** and **9**. Among these aldehydes the latter was synthesized from the corresponding racemic γ-TMS allylic alcohols via (1) the kinetic resolution[10] using the Sharpless asymmetric epoxidation;[11] (2) reaction with Et_2AlCN;[3] (3) reduction of the resulting CN group with DIBAL-H (Scheme 2). This transformation would be an attractive approach to the former aldehyde **6**. However, the ester group is incompatible with DIBAL-H and probably with Et_2AlCN, and the requirement of a synthetic equivalent to the ester group led us to choose an alternative construction of **6** from **8**[12] by using Wittig reaction.[13] Herein, we describe the synthesis of **8** by a new sequence of reactions and transformed to RvE2 (**2**).

In our first attempt to prepare **8**, epoxy alcohol **11** prepared by the Sharpless asymmetric epoxidation of the corresponding allylic alcohol according to the literature procedure[14] was converted to carbamate **12** (Scheme 3). $BF_3{\cdot}OEt_2$-assisted transformation of **12** at −18 °C for 2 h proceeded cleanly and the subsequent protection with TBSCl afforded carbonate **13** in 66% yield. $RuCl_3$-catalyzed oxidation of **13** with $NaIO_4$ followed by esterification with CH_2N_2 produced **14** in 92% yield. Unfortunately, exposure of carbonate **14** to NaOMe (0.5 equiv) in MeOH at room temperature for 20 h resulted in the production of **15** and **16** as the major and minor products. Without separation, the mixture was subjected to oxidation with $NaIO_4$ to produce aldehydes **8** and **17** in a 1:4 ratio by ^1H NMR



Scheme 4. Synthesis of the unsaturated aldehyde **6**.



Scheme 6. Synthesis of RvE2 (**2**).

spectroscopy (65%). Use of smaller quantities of NaOMe at lower temperatures (0 °C to rt) for shorter reaction times resulted in an incomplete conversion of carbonate **14**, whereas reaction did not proceed with MeOMgBr in MeOH.

We then investigated another preparation of **8**. According to the procedure published[15] glutaric anhydride (**18**) was converted to *rac*-**19**, which was subjected to the asymmetric epoxidation to give (*S*)-**19** (99% ee by ^{1}H NMR of the MTPA derivative). Protection with TBSCl as usual afforded **20** quantitatively (Scheme 4). Ozonolysis of the vinyl silane moiety of **20** at −78 °C in EtOAc followed by reductive workup with PPh_3 produced aldehyde **21**. In contrast, workup with Me_2S produced a mixture of products. Ozonolysis of the vinyl silanes was reported by Büchi and Wüest[16] and applied to the synthesis of artemisinin.[17] Recently, Tomooka and co-workers shed light on this class of ozone oxidation and they have successfully isolated the anti-peroxide intermediates in a reaction of chiral γ-silyl allylic alcohol derivatives.[18] Accordingly, product **21** should be the anti isomer as depicted, though the determination was unnecessary for the further transformation. Oxidation of **21** was carried out with $NaIO_4$ in THF and H_2O (8:1), under which deprotection of the TMS group and the oxidative cleavage of the resulting hydroxyaldehyde took place smoothly to produce aldehyde **8** in 92% yield from **20**. Finally, Wittig reaction with $Ph_3P{=}CHCHO$ in refluxing benzene produced the key aldehyde **6** in 92% yield.

Scheme 5 shows our synthesis of **27**, the C9–14 part of **2**. Phosphonium salt **23** was prepared from commercial bromoalcohol **22** in two steps and converted to the Wittig anion, to which aldehyde **24** was added to afford **25** as a sole stereoisomer quantitatively. The PMB (*p*-$MeOC_6H_4CH_2$) was removed and the resulting alcohol was converted to iodide **26** in 78% yield. Finally, reaction with PPh_3 in hot MeCN gave the phosphonium salt **27** in 96% yield.

An anion was generated from the Wittig salt **27** using $NaN(TMS)_2$ at 0 °C for 30 min and subjected to reaction with aldehyde **9**, which had been synthesized from the corresponding the γ-TMS allylic alcohol with the *R* configuration (>99% ee).[3] The reaction was carried out at −78 °C for 2 h and then at temperatures slowly raised to 0 °C over 1 h, producing cis olefin **28** exclusively.[19] The silyl protective group at the primary hydroxyl group was selectively removed with Bu_4NF (1 equiv) at 0 °C to rt for 3 h, and the resulting alcohol **29** was changed to iodide **30**, which was converted to the Wittig salt **31** in good yield. Finally, Wittig reaction between **31** (1.5 equiv) and **6** (1 equiv) was conducted at temperatures between −78 °C and −40 °C to give **32** as the sole product in 51% yield based on **6** after chromatography.[19] Finally, reaction of **32** with Bu_4NF at room temperature for 26 h gave RvE2 (**2**) in 87% yield. The ^{1}H and ^{13}C NMR spectra and the specific rotation were in accordance with those reported: $[\alpha]_D^{21}$ −4 (*c* 0.056, MeOH); lit.[4] $[\alpha]_D^{24}$ −2.1 (*c* 0.25, MeOH).

In conclusion, we have developed an efficient method to synthesize RvE2 (**2**) in which the cis olefins are constructed stereoselectively.[20] The asymmetric carbons with the hydroxyl groups at C5 and C18 were constructed in enantiomerically highly pure forms (generally >95% ee) by the epoxidation/kinetic resolution of the γ-silylallylic alcohols using the Sharpless epoxidation. In the ozonolysis of the γ-silylallylic alcohol to α-alkoxyaldehyde, reductive workup with PPh_3 was found to be the choice.

Acknowledgment

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Supplementary data

Supplementary data (the ^{1}H and ^{13}C NMR spectra of **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.109.

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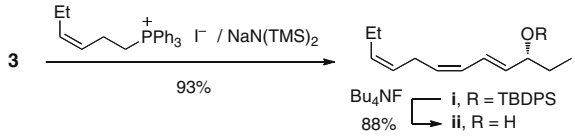
19. A model transformation of epoxy alcohol **3** (76% ee) to olefin **i** (−78 to 0 °C, 3 h then rt, overnight) afforded **ii**, which was 76% ee by ^{1}H NMR spectroscopy of the corresponding MTPA ester, thus confirming no racemization. The transformation was applied to that delineated in Scheme 6.



20. *Spectral data of the intermediates*. *Aldehyde* **6**: $[\alpha]_D^{21}$ +16 (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 1.46–1.78 (m, 4H), 2.34 (t, *J* = 7 Hz, 2H), 3.68 (s, 3H), 4.41–4.49 (m, 1H), 6.28 (ddd, *J* = 15, 8, 1.5 Hz, 1H), 6.79 (dd, *J* = 15, 4.5 Hz, 1H), 9.58 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9 (+), −4.6 (+), 20.2 (−), 25.8 (+), 33.8 (−), 36.3 (−), 51.6 (+), 71.2 (+), 131.0 (+), 159.5 (+), 173.7 (−), 193.6 (+). *Alcohol* **29**: $[\alpha]_D^{21}$ +34 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.5, 3H), 1.07 (s, 9H), 1.40–1.61 (m, 2H), 2.30 (dt, *J* = 7, 7 Hz, 2H), 2.82 (dd, *J* = 7, 7 Hz, 2H), 3.62 (t, *J* = 7 Hz, 2H), 4.17 (ddd, *J* = 6, 6, 6 Hz, 1H), 5.28 (dt, *J* = 11, 7 Hz, 1H), 5.34–5.55 (m, 2H), 5.61 (dd, *J* = 15, 6 Hz, 1H), 5.90 (dd, *J* = 11, 11 Hz, 1H), 6.20 (dd, *J* = 15, 11 Hz, 1H), 7.30–7.45 (m, 6H), 7.61–7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0 (+), 19.5 (−), 26.2 (−), 27.1 (+), 30.7 (−), 30.8 (−), 62.2 (−), 75.2 (+), 125.1 (+), 125.9 (+), 127.4 (+), 127.5 (+), 128.5 (+), 129.0 (+), 129.5 (+), 129.6 (+), 130.8 (+), 134.4 (−), 134.6 (−), 136.0 (+), 136.1 (+), 136.3 (+). *Salt* **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, *J* = 7.5 Hz, 3H), 1.04 (s, 9H), 1.40–1.62 (m, 2H), 2.35–2.54 (m, 2H), 2.55 (dd, *J* = 7.5, 7.5 Hz, 2H), 3.62–3.86 (m, 2H), 4.13 (q, *J* = 6 Hz, 1H), 5.10 (dt, *J* = 11, 7.5 Hz, 1H), 5.27–5.40 (m, 1H), 5.54–5.69 (m, 2H), 5.84 (dd, *J* = 11, 11 Hz, 1H), 6.01 (dd, *J* = 15, 11 Hz, 1H), 7.26–7.44 (m, 6H), 7.59–7.87 (m, 19H). *Methyl ester* **32**: $[\alpha]_D^{24}$ +30 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.79 (t, *J* = 7.5, 3H), 0.89 (s, 9H), 1.07 (s, 9H), 1.41–1.79 (m, 6H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.81 (dd, *J* = 6.5, 6.5 Hz, 2H), 2.91 (dd, *J* = 6.5, 6.5 Hz, 2H), 3.65 (s, 3H), 4.08–4.24 (m, 2H), 5.19–5.51 (m, 4H), 5.60 (dd, *J* = 15, 6.5 Hz, 1H), 5.63 (dd, *J* = 15, 6.5 Hz, 1H), 5.90 (dd, *J* = 11, 11 Hz, 1H), 5.97 (dd, *J* = 11, 11 Hz, 1H), 6.18 (dd, *J* = 15, 11 Hz, 1H), 6.44 (dd, *J* = 15, 11 Hz, 1H), 7.29–7.45 (m, 6H), 7.62–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7 (+), −4.2 (+), 9.1 (+), 18.3 (−), 19.5 (−), 20.8 (−), 25.9 (+), 26.0 (−), 26.1 (−), 27.1 (+), 30.7 (−), 34.1 (−), 37.7 (−), 51.5 (+), 72.8 (+), 75.3 (+), 124.5 (+), 125.2 (+), 127.4 (+), 127.5 (+), 128.1 (+), 128.31 (+), 128.33 (+), 128.5 (+), 129.1 (+), 129.4 (+), 129.5 (+), 129.6 (+), 134.4 (−), 134.6 (−), 136.0 (−), 136.1 (−), 136.2 (−), 137.0 (−), 174.1 (−).