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First total synthesis of pro-resolving and tissue-regenerative Maresin sulfido-conjugates

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ABSTRACT

The first stereospecific total synthesis of the pro-resolving and tissue-regenerative Maresin sulfido-conjugates: 13*R*,14*S*-MCTR1, 13*R*,14*S*-MCTR2 and 13*R*,14*S*-MCTR3, derived from docosahexaenoic acid, has been achieved. The key intermediate 13*S*,14*S*-epoxy-Maresin methyl ester was synthesized using a chiral pool strategy starting from 2-deoxy-D-ribose. Wittig reactions, selective epoxide formation and epoxide opening with glutathione, L-cysteinylglycine and L-cysteine methyl ester hydrochloride respectively, were the key steps in the synthesis.

Inflammation plays a central role in tissue repair after injury or bacterial and viral infection if the process is self-limited and achieves resolution of inflammation.[1] The duration of the inflammation decides whether it is beneficial or harmful. Chronic and uncontrolled inflammation is the underlining course in chronic diseases including autoimmune and neurological diseases.[2] It is well documented that ω-3 polyunsaturated fatty acids have anti-inflammatory activity in humans.[3–6] Investigating these fatty acids Serhan and collaborators have identified powerful anti-inflammatory and pro-resolution molecules derived from these ω-3 polyunsaturated fatty acids that were produced by lipoxygenase enzymes. These products, named specialized pro-resolving mediators (SPMs), were found in humans and include the Resolvins, Protectins, and Maresins.[7–11] Recently they identified a class of sulfido-conjugated lipid mediators during self-limited resolution of *Escherichia coli* infection.[12,13] These compounds promote pathogen clearance, wound healing, tissue repair, and regeneration. They proposed a biosynthetic pathway based on the identified precursor and its products formed as shown in Figure 1. Docosahexaenoic acid is converted by the platelet lipoxygenase into the 14*S*-hydroperoxide intermediate that undergoes epoxide formation to give the 13*S*,14*S*-epoxy-Maresin.[14] Enzymatic hydrolysis produced the Maresin 1 and Maresin 2.[15,16] The same 13*S*,14*S*-epoxy-Maresin is the substrate for the glutathione *S*-transferase to give the 13,14*S*-Maresin conjugate in tissue regeneration 1 (MCTR1), originally named SCI (sulfido conjugate I).[12,13] As Serhan and collaborators already pointed out it is likely that the stereochemistry at C13 is *R* similar as described for the peptido-leukotrienes via S_N2 epoxide opening by glutathione.[17,18] MCTR1 is further metabolized by γ-glutamyl transpeptidase to MCTR2 and finally by a dipeptidase to MCTR3.

Based on the reported biological and pharmacological properties and due to the limited availability from natural sources these SPMs have to be prepared by total synthesis to make them available for further pharmacological evaluation.[7,19–36]

In this Letter we wish to report the first total synthesis of the 14-series sulfido-conjugated mediators 13*R*,14*S*-MCTR1 [(4*Z*,7*Z*,9*E*,11*E*,13*R*,14*S*,16*Z*,19*Z*)-13-glutathionyl-14-hydroxy-4,7,9,11,16,19-docosahexaenoic acid (**1**)], 13*R*,14*S*-MCTR2 [(4*Z*,7*Z*,9*E*,11*E*,13*R*,14*S*,16*Z*,19*Z*)-13-cysteinylglycinyl-14-hydroxy-4,7,9,11,16,19-docosahexaenoic acid (**2**)] and 13*R*,14*S*-MCTR3 [(4*Z*,7*Z*,9*E*,11*E*,13*R*,14*S*,16*Z*,19*Z*)-13-cysteinyl-14-hydroxy-4,7,9,11,16,19-docosahexaenoic acid (**3**)]. As shown in the retrosynthetic approach (Fig. 2) **1**, **2**, and **3** have been prepared from the chiral 13*S*,14*S*-epoxy-Maresin methyl ester (**4**) via epoxide opening with glutathione, L-cysteinylglycine, and L-cysteine methyl ester hydrochloride respectively. The key intermediate **4** has been prepared from intermediates **5**, **6**, and **7**. The chiral centers of the epoxy-aldehyde **7** were generated using a chiral pool strategy starting from 2-deoxy-D-ribose (**8**).

The synthesis of **4** is outlined in Scheme 1. 2-deoxy-D-ribose (**8**) was converted to the 3,4-isopropylidene-2-deoxy-D-ribose (**9**) and

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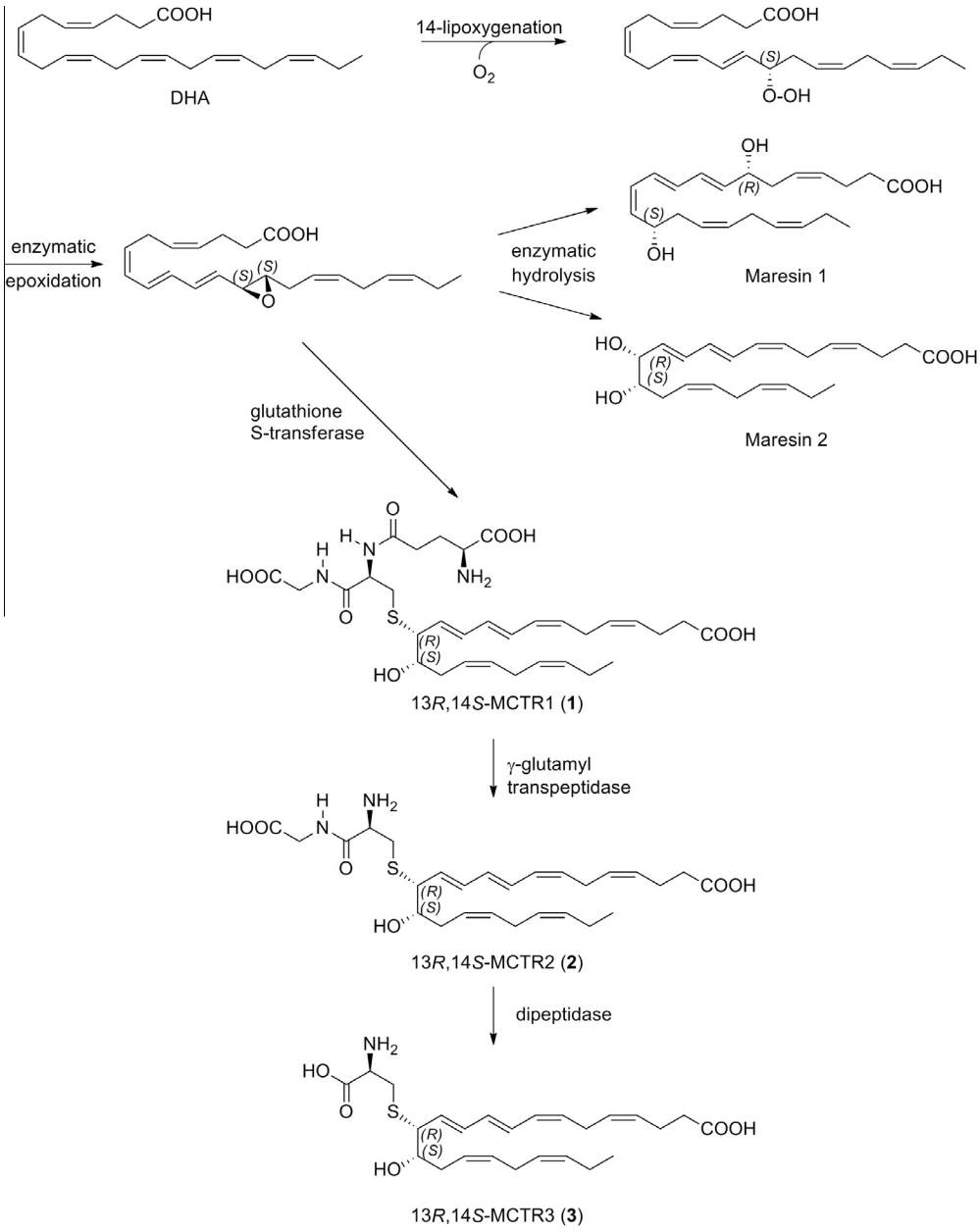

Figure 1. Biosynthesis of Maresin **1** and Maresin **2** from DHA and proposed biosynthesis of 13*R*,14*S*-MCTR1, 13*R*,14*S*-MCTR2, and 13*R*,14*S*-MCTR3.[12,13]

then submitted to Wittig reaction with the ylide prepared from the phosphonium iodide **10** with *n*-BuLi in THF at −78 °C to give the *Z*,*Z*-skipped diene **11** as recently described.[35] The free primary hydroxyl-group was converted to the tosylate with tosyl chloride in pyridine at rt in high yield. Cleavage of the isopropylidene protective group in **12** was achieved with HCl generated in situ from acetyl chloride in CH_3OH at 0 °C to rt to give **13** in 91% yield. Treatment of the tosylate **13** with 5 equiv of NaOMe in CH_2Cl_2/CH_3OH at rt afforded the desired chiral epoxy alcohol **14**, $[\alpha]_D^{25} = -22$ (c 0.83, $CHCl_3$) in 52% isolated yield. In this reaction a terminal epoxide is first formed that undergoes epoxide transposition under the basic condition as described by Rokach.[37,38] The epoxy alcohol **14** was cleanly transformed into the epoxy aldehyde **7** using Dess–Martin oxidation in CH_2Cl_2.[39] Four-carbon homologation of aldehyde **7** with recrystallized (2*E*)-4-triphenylphosphoranylidene-2-butenal (**6**)[40,41] in CH_2Cl_2 at rt for 18 h followed by treatment with catalytic iodine in benzene afforded the *E*,*E*-dienal **15**. Wittig reaction of **15** with the ylide prepared in situ from the crystalline phosphonium iodide **5**[42,43] with KHMDS at −78 °C in THF afforded the key epoxy ester **4** in 83% isolated yield.[44] Compound **4** was characterized by ^1H NMR, ^{13}C NMR, COSY, HSQC, and UV.[45] The geometry of the 9*E*,11*E*-diene unit in **15** ($J_{9,10} = 15.3$ and $J_{11,12} = 15.3$) and the 7*Z*,9*E*,11*E*-triene in **4** ($J_{7,8} = 11.4$, $J_{9,10} = 14.7$ and $J_{11,12} = 15.3$) was confirmed by the ^1H–^1H coupling constants.[45]

The conversion of epoxy ester **4** to 13*R*,14*S*-MCTR1 (**1**) was achieved in two steps as described in Scheme 2.[17,46,47] Reaction with 4 equiv of glutathione in CH_3OH/triethylamine/H_2O gave the monomethyl ester **16**. The excess of glutathione was removed using a reversed phase C-18 cartridges. Mild hydrolysis of **16** with 1 N LiOH in H_2O for 30 min gave 13*R*,14*S*-MCTR1 (**1**) that was purified by HPLC [Zorbax SB-C18 250 × 21.2 mm, 280 nm, CH_3OH/H_2O (0.1% NH_4OAc, pH 5.6, 0.05% EDTA disodium) 60/40]. The fraction containing **1** was desalted using reversed phase C-18 cartridges