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Stereoselective synthesis of MaR2$_{n\text{-}3\ DPA}$

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ABSTRACT

The first total synthesis of the n-3 docosapentaenoic derived oxygenated product MaR2$_{n\text{-}3\ DPA}$ has been achieved. The 13*R* and 14*S* stereogenic centers were introduced using 2-deoxy-D-ribose in a chiral pool strategy. The geometry of the *Z*,*E*,*E*-triene moiety was prepared using highly *E*-selective Wittig- and Takai-olefination reactions as well as the *Z*-stereoselective Lindlar reduction. LC/MS-MS data of synthetic MaR2$_{n\text{-}3\ DPA}$ matched data for the biosynthetic formed product that enabled the configurational assignment of this oxygenated natural product to be (7*Z*,9*E*,11*E*,13*R*,14*S*,16*Z*,19*Z*)-13,14-dihydroxydocosa-7,9,11,16,19-pentaenoic acid.

Recent studies have demonstrated that polyunsaturated fatty acids (PUFAs) derived specialized pro-resolving mediators (SPMs) actively govern and promote the resolution of inflammation [1]. PUFAs are enzymatically converted into different families of SPMs, e.g. the lipoxins, resolvins, protectins and maresins [2]. Maresin 1 (MaR1) is biosynthesized [3] from docosahexaenoic acid (DHA) in the presence of 12-lipoxygenase and was the first member of the maresin family of SPMs to be reported [4] and prepared by total synthesis [5].

In 2013 Dalli and co-workers reported several new SPMs biosynthesized from n-3 docosapentaenoic acid (n-3 DPA) [6]. n-3 DPA, consisting of 22 carbons and five all-*Z* double bonds, is an elongated product of eicosapentaenoic acid and an intermediate in the biosynthesis of DHA [7]. Using a self-limited model of inflammation and targeted metabololipidomics during the onset and resolution of acute inflammation, Dalli and co-workers [6] uncovered several novel n-3 DPA SPMs that are potent bioactive molecules. The structures of MaR1$_{n\text{-}3\ DPA}$ (**1**), MaR2$_{n\text{-}3\ DPA}$ (**2**) and MaR3$_{n\text{-}3\ DPA}$ (**3**) are shown in Fig. 1.

Based on their novel pro-resolving and anti-inflammatory bioactions, SPMs have attracted significant interest from the biomedical, pharmacological and synthetic organic communities [8]. SPMs act as agonists on individual GPCRs [9] exhibiting nanomolar pro-resolution and anti-inflammatory bioactions [10]. Some SPMs have entered initial clinical trial development programs [11]. These endogenously formed products are available in minute amounts from their natural sources and contain several stereogenic centers and conjugated *E*- and *Z*-double bonds. Hence, stereoselective synthesis for configurational assignment and extensive biological testing becomes necessary.

A few of the n-3 DPA-derived SPMs have recently been prepared [12] and subjected to biological evaluations [13], but MaR2$_{n\text{-}3\ DPA}$ (**2**) has not been synthesized to date and its absolute configuration at C-13 remained to be determined. These facts, as well as the high demand for sufficient material for biological and pharmacological testing, inspired us to report the first total synthesis of MaR2$_{n\text{-}3\ DPA}$ (**2**).

The three key intermediates **4**, **5** and **6** in our retrosynthetic analysis are depicted in Scheme 1. The stereogenic centers at C13 and C14 were assumed to be *R* and *S*, respectively, based on biosynthetic considerations [6]. Hence, 2-deoxy-D-ribose (**7**) was deemed a suitable commercially available starting material for preparing

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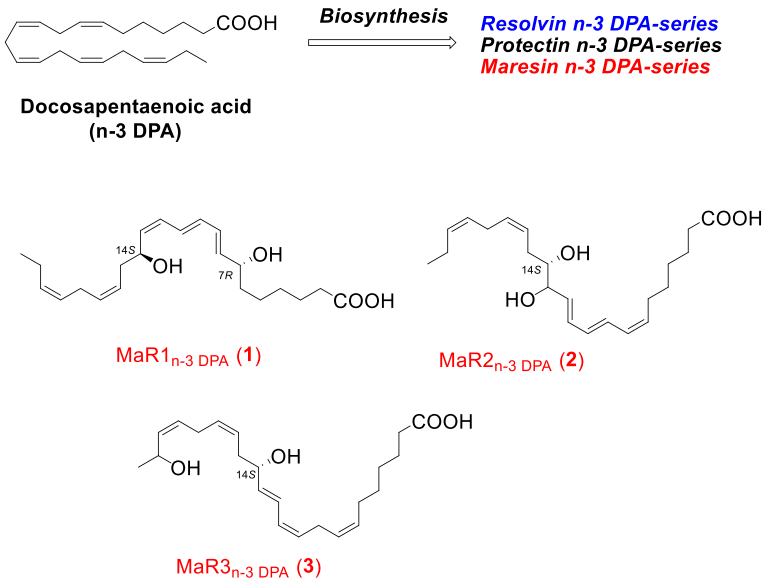
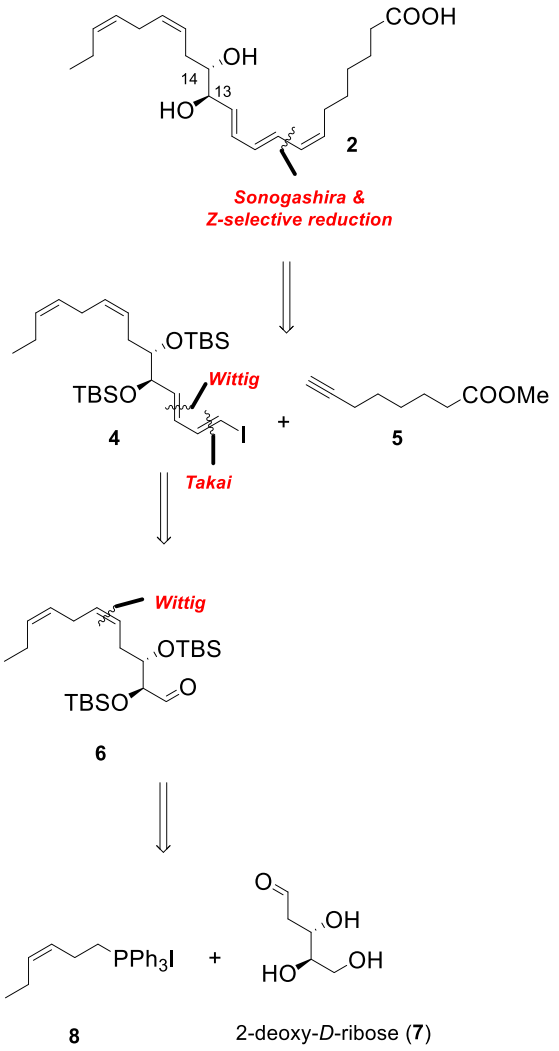


Fig. 1. Structures of $MaR1_{n\text{-}3\ DPA}$ (**1**), $MaR2_{n\text{-}3\ DPA}$ (**2**) and $MaR3_{n\text{-}3\ DPA}$ (**3**). The absolute configuration is presented where established.



Scheme 1. Retrosynthetic analysis of $MaR2_{n\text{-}3\ DPA}$ (**2**).

$MaR2_{n\text{-}3\ DPA}$ (**2**). This carbohydrate has been used in the stereoselective total synthesis of other SPMs [14].

The phosphonium salt **8** was synthesized from *Z*-hex-3-en-1-ol (**9**) as previously described [12c]. Intermediate **11** was obtained from known TBS-protected aldehyde **10** [12d] using a highly *Z*-selective Wittig reaction with the *in situ* generated ylide of **8** (Scheme 2). This produced **11** as one diastereomer in 84% yield (ESI). Next, selective deprotection of the primary TBS-group in **11** was achieved with *para*-toluene sulfonic acid (PTSA) in MeOH at −20 °C giving alcohol **12** that was oxidized (Dess-Martin periodinane (DMP), $NaHCO_3$, CH_2Cl_2) to its aldehyde **13** in 40% yield over the two steps. Aldehyde **13** was dissolved in toluene and 1.3 equiv. of the stabilized ylide (triphenyl-phosphoranylidene)acetaldehyde was added. The reaction mixture was heated at reflux for 19 h to afford the *E*-configured α,β-unsaturated aldehyde **14** in 60% yield after purification by column chromatography (ESI). To complete the formation of fragment **4**, a Takai reaction was performed on aldehyde **14**. After acidic work-up and purification by column chromatography the sensitive *E*,*E*-vinylic iodide **4** was isolated in 73% yield (Scheme 2).

Terminal alkyne **5** was conveniently prepared in a four-step sequence, starting from cycloheptanone (**15**), see Scheme 3. Bayer-Villiger oxidation on **15** followed by Fischer-esterification gave hydroxyl-ester **16** that was oxidized to aldehyde **17** and reacted in the Ohira-Bestmann reaction affording alkyne **5** in 12% yield from **15**.

The Sonogashira coupling reaction with key fragments **4** and **5** produced alkyne **18** in 50% isolated yield after careful chromatographic purification (Scheme 4). Next, removal of the two-TBS groups in **18** with excess TBAF in THF produced diol **19**. Reduction of the internal alkyne in **19** using the Lindlar-reduction (Pd-$CaCO_3$, EtOAc/pyridine/1-octene, H_2 1 atm) gave the methyl ester of $MaR2_{n\text{-}3\ DPA}$ (**20**) in 55% isolated yield over the two steps and with >95% chemical purity (HPLC, ESI). Finally, careful saponification (LiOH, H_2O, MeOH, 0 °C) of **20** gave $MaR2_{n\text{-}3\ DPA}$ (**2**) in 97% yield (Scheme 4). Data from NMR, LC/MS-MS and UV experiments (ESI) confirmed the structure of **2**.

We next tested whether synthetic **2** matched the endogenous $MaR2_{n\text{-}3\ DPA}$ (**2**) prepared from human samples. We first isolated

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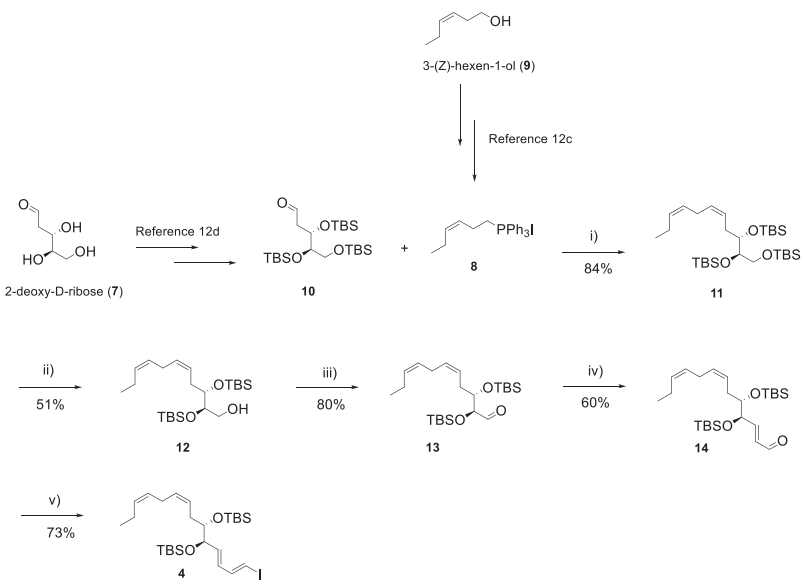
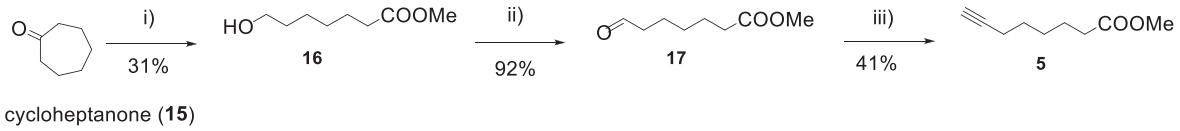
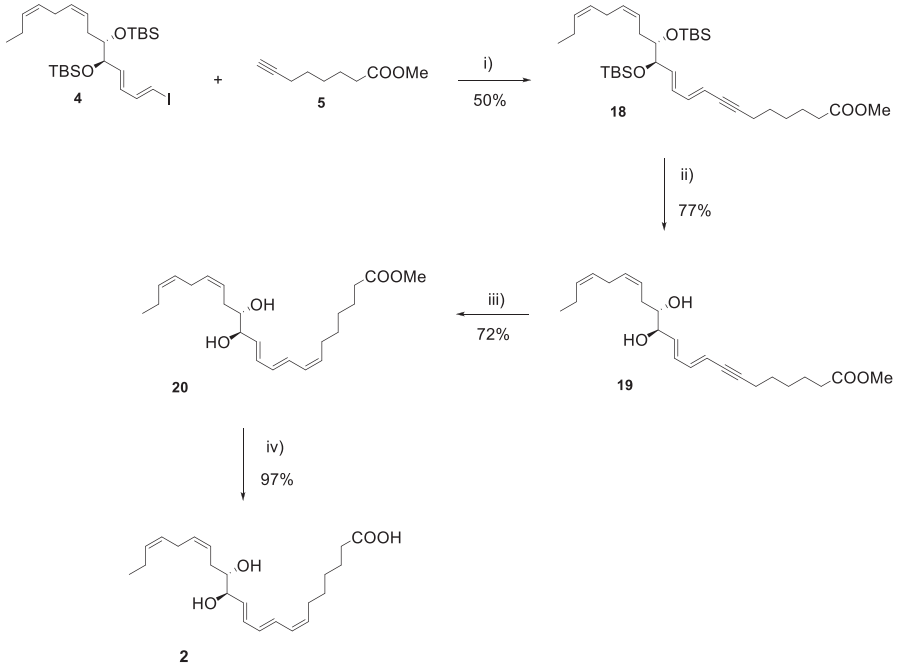


Scheme 2. Synthesis of vinylic iodide **4**. Reagents and conditions: i) NaHMDS, CH_2Cl_2, − 78 °C; ii) *para*-toluene sulfonic acid (PTSA), MeOH, −20 °C; iii) DMP, $NaHCO_3$, CH_2Cl_2; iv) toluene, (triphenyl-phosphoranylidene)acetaldehyde, Δ; v) $CrCl_2$, dioxane, THF, CHI_3, 0 °C.



Scheme 3. Synthesis of alkyne **5**. Reagents and conditions: i) a) *m*-CPBA, CH_2Cl_2; b) MeOH, H_2SO_4; ii) DMP, $NaHCO_3$, CH_2Cl_2; iii) dimethyl(1-diazo-2-oxopropyl) phosphonate; K_2CO_3, MeOH.



Scheme 4. Total synthesis of $MaR2_{n\text{-}3\ DPA}$ (**2**). Reagents and conditions: i) CuI, Et_2NH, $Pd(PPh_3)_4$ (5%); ii) TBAF, THF; iii) $Pd/CaCO_3$, EtOAc/pyridine/1-octene, H_2; iv) LiOH, H_2O, MeOH, 0 °C.

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material from human serum and the retention time of the endogenous mediator using RP-HPLC-MS-MS lipid mediator profiling experiments [15]. Using multiple reaction monitoring (MRM) of the parent ion with *m/z* 361 and the daughter ions *m/z* 223 or *m/z* 193, we obtained a sharp peak with retention time (R_T) of 14.4 min (Fig. 2A). Of note, a similar retention time of 14.4 min was obtained with synthetic **2** (see Fig. 2A). Moreover, co-injection (2 μL) of a homogenous sample of biological MaR2$_{n\text{-}3\ DPA}$ (**2**) with synthetic **2** in a 1:10 M ratio, respectively, gave a single sharp peak in MRM experiments, with R_T 14.4 min (Fig. 2A). Similar findings were made with platelet rich plasma, where endogenous MaR2$_{n\text{-}3\ DPA}$ (**5**) gave a R_T of 14.4 min that co-eluted with synthetic **2** (Fig. 2B). To obtain further evidence that the chemical structure for synthetic **2** matches that of endogenous MaR2$_{n\text{-}3\ DPA}$ we next assessed the MS/MS fragmentation spectra. Here we found that, in accordance with published findings [6], MaR2$_{n\text{-}3\ DPA}$ from both human serum and platelet rich plasma gave the following ions *m/z* 361 = M−H, *m/z* 344 = M−H−H_2O, *m/z* 325 = M−H−2H_2O, *m/z* 317 = M−H−CO_2, *m/z* 299 = M−H−H_2O−CO_2, *m/z* 281 = M−H−2H_2O−CO_2, *m/z* 179 = 223-CO_2, *m/z* 161 = 223-H_2-O−CO_2, *m/z* 149 = 193-CO_2, ions that were also found in the MS/MS spectrum of synthetic **2** (Fig. 3).

The SPMs are among the most exciting small and naturally occurring molecules currently undergoing investigations towards drug development of new anti-inflammatory drugs [1,16]. The stereoselective synthesis of **2** using the Lindlar reaction, the Sonogashira coupling reaction and the Takai olefination produced multi milligram quantities of **2** that is now available for further biological and pharmacological evaluations to be conducted.

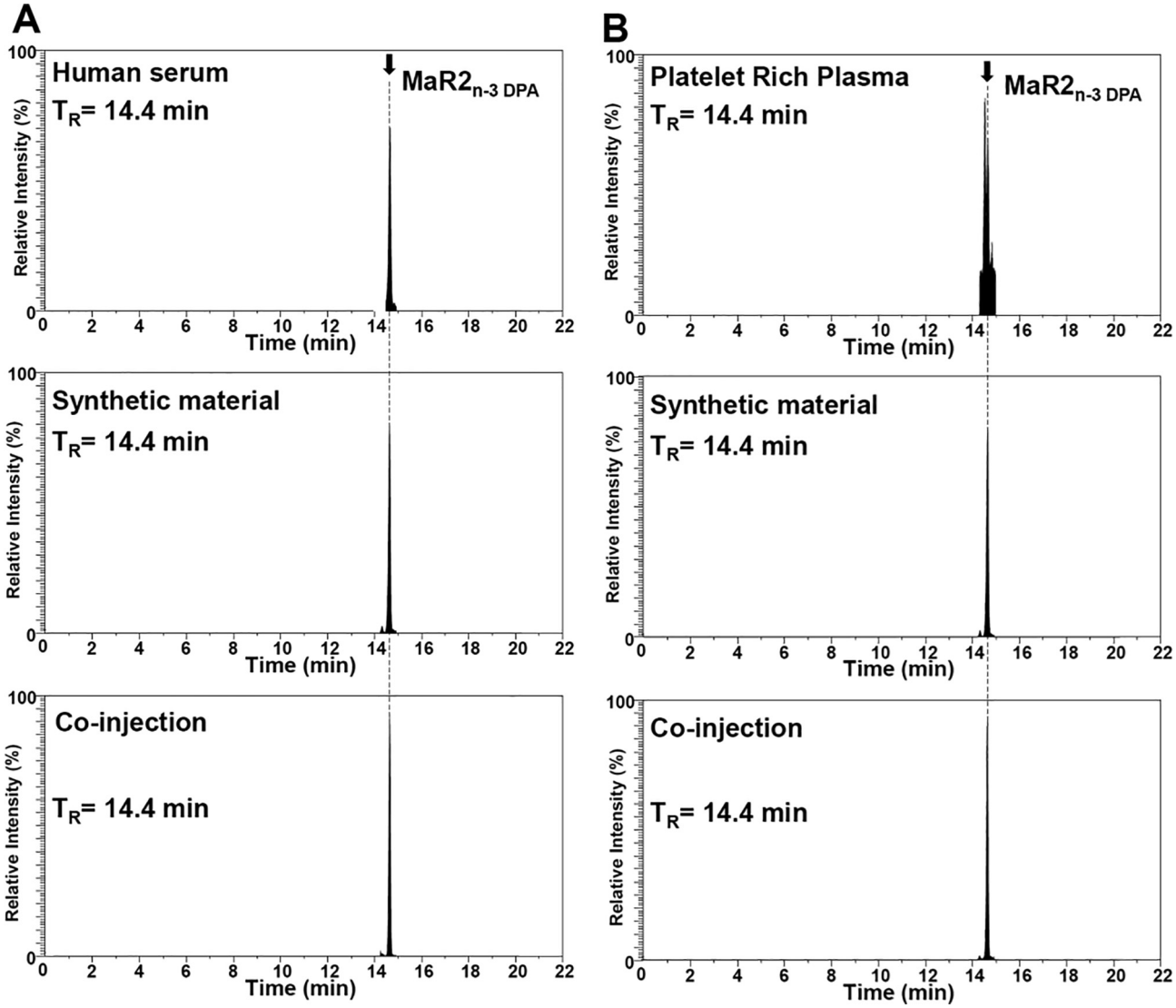

Fig. 2. Synthetic **2** matches endogenous MaR2$_{n\text{-}3\ DPA}$ in human serum and cells. (A) human serum (B) platelet rich plasma were collected, placed in ice-cold methanol, lipid mediators were extracted and MaR2$_{n\text{-}3\ DPA}$ was identified using lipid mediator profiling. Panels depict representative MRM chromatograms for *m/z* 361 > 223 (human serum) or *m/z* 361 > 193 (platelet rich plasma). Top panels depict the chromatograms obtained with biological material, center panels depict chromatograms obtained with synthetic **2** and bottom panels depict chromatograms obtained with the biological material co-injected with synthetic **2**. Results are representative of three determinations for A and n = 3 distinct human donors for B.

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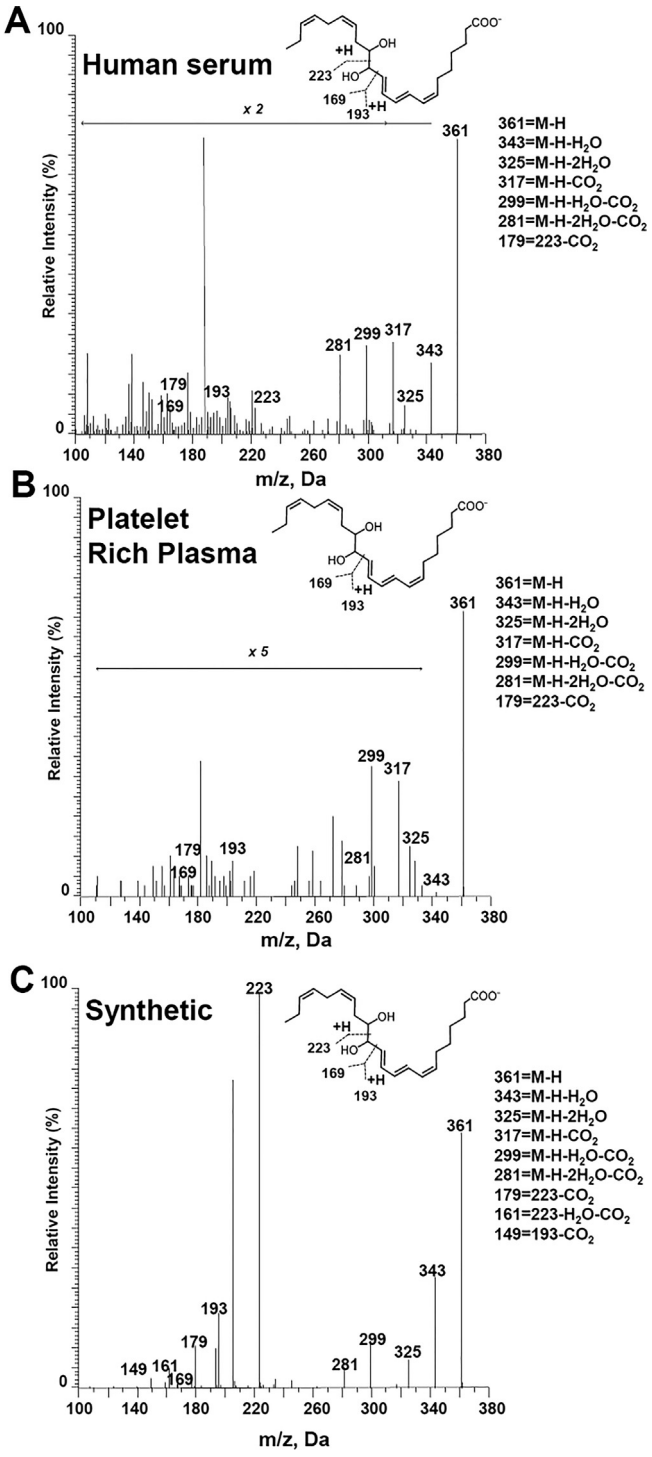

Fig. 3. MS/MS fragmentation spectra for synthetic **2** and MaR2$_{n\text{-}3\ DPA}$ from human serum and platelet rich plasma. Lipid mediators were extracted from (A) human serum and (B) platelet rich plasma and MS/MS spectra for endogenous MaR2$_{n\text{-}3\ DPA}$, together with those of (C) synthetic **2**, were obtained using lipid mediator profiling. Results are representative of n = 3 determination for A and C and 3 volunteers for B.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for intermediates and characterization data (UV/VIS spectra, HPLC chromatograms and LC/MS-MS spectra from matching experiments) of **2** as well as experimental procedures. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151510.

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