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# First stereoselective total synthesis of 4(*S*),5(*S*)-oxido-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid, the biosynthetic precursor of resolvins D3 and D4<sup>†</sup>

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The first total convergent synthesis of 4(*S*),5(*S*)-oxido-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid (**1**) is described. The reported synthesis led to confirmation of the native epoxydocosahexaenoic acid as the biosynthetic precursor of lipid mediators resolvin D3 and resolvin D4. These potent enzymatic products of docosahexaenoic acid (DHA) are important signaling molecules in the resolution of inflammation. A stereocontrolled and chiral pool-based synthetic strategy was employed, with key features including epoxide transposition under basic conditions to form the oxirane ring, and a *cis*-selective Wittig reaction to secure the target docosahexaenoate backbone.

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## Introduction

Acute inflammation is an immunological response necessary to restore normal function in the face of injurious stimuli. Although this phenomenon is ideally self-limited, it can give rise to excessive inflammation if left unresolved.<sup>1</sup> Research efforts involving the enzymatic oxygenation of polyunsaturated fatty acids (PUFAs) during the acute inflammatory process have led to the discovery of several classes of lipid mediators (LMs) that switch on resolution responses and promote tissue healing.<sup>1</sup>

These studies uncovered a superfamily of pro-resolution lipid mediators, including the lipoxins<sup>2</sup> and the E-series resolvins<sup>3</sup> derived from arachidonic acid (AA) and eicosapentaenoic acid (EPA), respectively, as well as the D-series resolvins,<sup>4</sup> the protectins,<sup>5</sup> and the maresins<sup>6</sup> produced from docosahexaenoic acid (DHA). A recent addition to this class of bioactive metabolites are the LMs originated from docosapentaenoic acid (DPA), including T-series resolvins and n-3 DPA series of resolvins, protectins, and maresins.<sup>7</sup> Together, these hormone-

like autacoids are termed specialized pro-resolving mediators (SPMs).<sup>8</sup>

SPMs counter-regulate proinflammatory signals and govern leukocytic movement, *e.g.*, neutrophils and macrophages, at the inflamed site in order to protect the host.<sup>9</sup> Notably, these molecules are generated in minuscule quantities *in vivo* and are enzymatically formed by lipoxygenases (LOX), cyclooxygenases (COX), and cytochrome P450s, often exhibiting potent bioactions in the low nM to pM range.<sup>9</sup> Structurally, each SPM contains carbon-carbon double bonds with defined olefin geometry, as well as hydroxyl and peptidyl substituents with specified *R*- or *S*-configurations of tetrahedral centers. Due to their limited endogenous production,<sup>9</sup> complete structural elucidation of LMs demands direct matching of endogenous metabolites with stereochemically pure synthetic materials.

In the present report, we disclose the first stereocontrolled total synthesis of 4(*S*),5(*S*)-epoxy-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid (**1**). For storage and handling purposes, **1** was kept in the methyl ester form owing to its increased stability *vis-à-vis* the free acid and was readily hydrolysed as needed. The naturally occurring 4(*S*),5(*S*)-epoxy-docosanoid was originally postulated as the biosynthetic precursor to both resolvins D3 (RvD3) and D4 (RvD4).<sup>4</sup> The synthetic accessibility of this critical intermediate enabled biological investigations that corroborated this hypothesis, revealing that human leukocytes convert this transient epoxide to both RvD3 and RvD4.<sup>10</sup>

As autacoids acting on local tissues, both RvD3 and RvD4 are involved in restoring normal cellular functions following inflammatory insults. RvD3 evokes protective actions by

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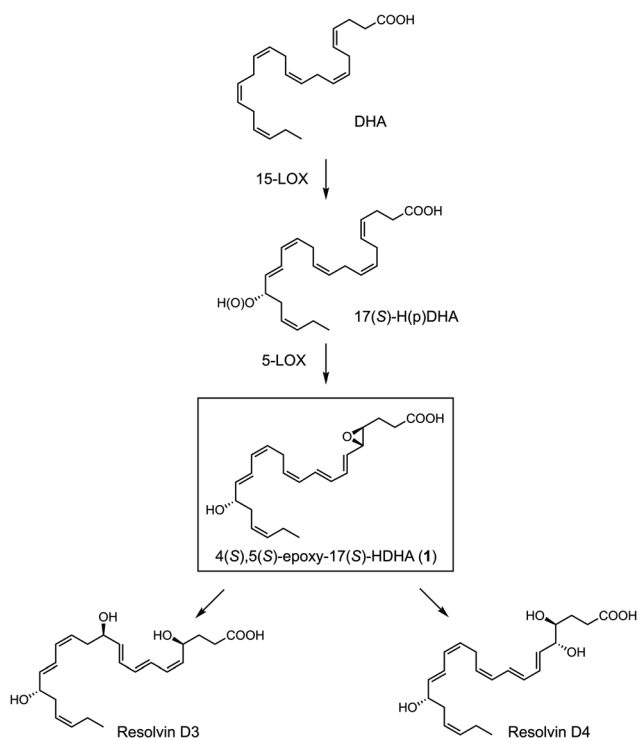
reducing pro-inflammatory cytokines, and enhancing human macrophage efferocytosis and neutrophil-bacterial phagocytosis; RvD3 and its 17*R*-epimeric isomer also initiate leukocytic actions, and relieve dermal inflammation.<sup>11</sup> Furthermore, RvD4 stimulates clearance of activated neutrophils by human macrophages at nM doses.<sup>12</sup> This chemical mediator also alleviates deep vein thrombosis in mice,<sup>13</sup> protects against secondary organ injury, inhibits PMN infiltration during skin infection, and enhances macrophage efferocytosis of cellular debris.<sup>12</sup>

The biosynthetic pathways involved in the conversion of DHA to the 4(*S*),5(*S*)-epoxy-17(*S*)-hydroxy-DHA, 4(*S*),5(*S*)-epoxy-17(*S*)-HDHA (**1**), and its derived pro-resolving products are illustrated in Scheme 1.<sup>4,12</sup> Enzymatic lipoxygenation of DHA catalyzed by 15-lipoxygenase (15-LOX) yields 17*S*-hydroperoxydocosahexaenoic acid (17*S*-HpDHA). A second oxygenation by 5-LOX generates a hydroperoxide at the C4 position, and this intermediate is further transformed to the 4(*S*),5(*S*)-epoxide (**1**),<sup>4</sup> a direct precursor to both RvD3 and RvD4.<sup>10</sup>

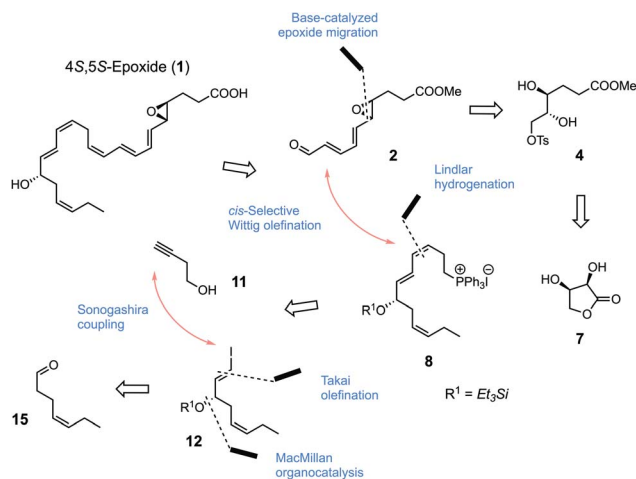
## Results and discussion

### Retrosynthetic analysis

An overview of retrosynthetic disconnections leading to the target compound (**1**) is outlined in Scheme 2. Following our previous strategies, we approached the current synthesis with similar guiding principles, by employing nonracemic and commercially available building fragments and relying on highly stereoselective transformations to establish desired



Scheme 1 Biosynthesis of resolvin D3 and resolvin D4 via 4(*S*),5(*S*)-epoxy-17(*S*)-HDHA (**1**).



Scheme 2 Retrosynthetic disconnections made for the target compound (**1**).

configurations of the target molecule—*viz.*, 4(*S*),5(*S*)-epoxy-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid (**1**).

Given the extreme lability of this polyunsaturated fatty acid epoxide, we devised and conducted the synthesis in a convergent manner. The retrograde analysis identified compounds **2**, **11**, and **12** as the key intermediates to be connected, with commercially available synthon **11** playing the role of a linker allowing the access to a phosphonane required for the final coupling.

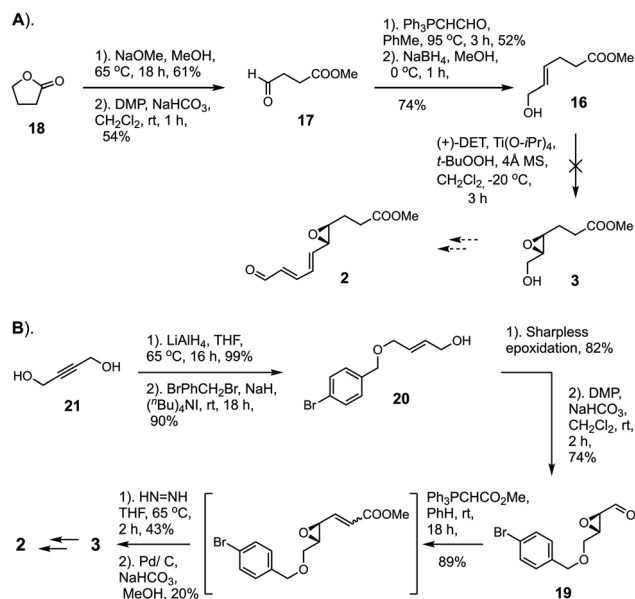
Epoxy aldehyde **2** was disconnected back to *D*-erythronolactone (**7**), with a base-mediated epoxide rearrangement planned as the critical step to install the epoxide functionality with absolute stereoselectivity. On the other hand, (*E*)-alkenyl halide **12** was deconstructed to *cis*-4-heptenal (**15**), with a highly enantioselective organocatalytic  $\alpha$ -oxidation<sup>14</sup> and a Takai olefination being key transforms in the forward direction.

The Sonogashira cross-coupling between linchpin **11** and vinyl iodide **12** was determined as the key reaction for furnishing a 1,3-enyne-containing intermediate, with the intent to create phosphonium salt **8** after further straight-forward manipulations.

Taking advantage of a *cis*-selective Wittig condensation in the final stages, we envisioned the union between the two segments, C1–C10 (**2**) and C11–C22 (**8**), to yield the desired docosahexaenoate carbon skeleton of compound (**1**). This approach was chosen over cross-coupling chemistry to avoid tampering with the labile epoxide group, as well as prevent possible double bond isomerization.

### Synthesis of C1–C10 $\alpha$ -fragment (**2**)

The synthesis commenced with the construction of the  $\alpha$ -segment **2**. As indicated in Scheme 3 (A), we initially envisioned installing the oxirane ring *via* a Sharpless asymmetric epoxidation,<sup>16</sup> borrowing from our previous strategies. To this end, we projected to generate a prochiral allylic alcohol substrate first.



Scheme 3 Initial approaches toward the C1–C10 fragment (2).

A straight-forward esterification of  $\gamma$ -butyrolactone **18** in basic methanol and a subsequent Dess–Martin oxidation of the resulting alcohol gave aldehyde **17** in fair yields. A two-carbon Wittig reaction extension followed by NaBH<sub>4</sub>-based reduction of the intermediary allylic aldehyde favorably led to allylic alcohol **16** in good yields. With the said substrate at hand, the epoxidation was executed with (+)-diethyl *l*-tartrate in methylene chloride under the prescribed conditions.<sup>16</sup>

Surprisingly, however, TLC and <sup>1</sup>H NMR analyses of the crude mixture, before workup, revealed no formation of epoxy alcohol **3**, despite clear consumption of the starting material. We suddenly learned that the close proximity of the methyl ester to the epoxide induced an intramolecular epoxy-ester decomposition involving these functionalities and the Lewis-acid, titanium-based catalyst employed in the procedure. In fact, Corey<sup>17</sup> reported a similar obstacle on an analogous substrate, in which the crude products did not seem to contain epoxide or ester units (<sup>1</sup>H NMR analysis).

In addition, Sharpless<sup>18</sup> himself also observed this phenomenon where the ester internally attacked the epoxide, cyclizing to a diol lactone. Although the use of catalytic amounts of Ti(O-*i*Pr)<sub>4</sub> has successfully yielded the epoxy alcohol in the case of the one methylene extended analogue,<sup>19</sup> this modification proved futile and thence we resorted to a different building block, but-2-yne-1,4-diol (**21**), for the synthesis as depicted in Scheme 3 (B).

At this point, we envisaged the alternative route to allow epoxide installation prior to methoxycarbonyl formation, thus bypassing said Lewis acid-mediated intramolecular attack. A similar strategy was employed to produce four isomeric epoxides critical in the synthesis of 2-nor-leukotriene analogs,<sup>20</sup> therefore making this a promising strategy.

The first step involved a reduction of **21** by LAH to give the *trans*-butenediol intermediate, which was directly mono-protected as its *p*-bromobenzyl derivative **20**. Notably, asymmetric Sharpless epoxidation<sup>16</sup> of **20** proceeded seamlessly with

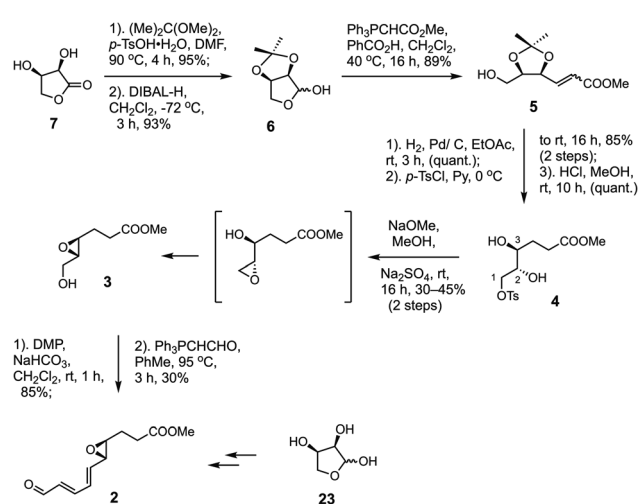
82% yield. Subsequent Dess–Martin oxidation of the free alcohol delivered the corresponding aldehyde **19** in adequate yield. A Wittig-type olefination of **19** with stabilized ylide Ph<sub>3</sub>PCHCO<sub>2</sub>Me gave the  $\alpha,\beta$ -unsaturated intermediate, which was submitted to a mild and complete hydrogenation of the double bond without tempering with the oxirane moiety. This critical step was accomplished by diazene generated *in situ* from 2,4,6-triisopropylbenzenesulfonyl hydrazide.

At this juncture, however, large-scale production of these building blocks was halted, creating a major hurdle to move in the forward direction.

In light of these outcomes, the synthetic routes were put to the side in favor of substitute and more robust strategies. Now we decided to build the C1–C10 epoxy aldehyde fragment (**2**) from chiral feedstocks instead of non-chiral materials.

Starting with *D*-erythronolactone (**7**) or *D*-erythrose (**23**), we envisioned to introduce the oxirane ring *via* epoxide transposition under basic conditions (Scheme 4).

Acetonide protection of **7** with excess 2,2-dimethoxypropane and catalytic *p*-TsOH·H<sub>2</sub>O in DMF, followed by smooth diisobutyl-aluminium hydride (DIBAL-H) reduction cleanly gave the isopropylidene lactol **6** in 95% and 93% yields, respectively. A Wittig-type olefination of lactol **6** with methyl-(triphenylphosphoranylidene)acetate in methylene chloride and catalytic amounts of benzoic acid at reflux afforded a *cis/trans* mixture of the  $\alpha,\beta$ -unsaturated isopropylidene ester **5** in 89%, predominantly in the *cis*-isomeric form.<sup>21</sup> Often without chromatographic purification, the isomeric mixture was submitted to complete hydrogenation using palladium on carbon, and the saturated primary alcohol was converted to the transient tosylate with *p*-TsCl in 85% yield, over two steps. Acid-catalyzed deisopropylidination cleanly gave **4** as a colorless oil after condensation under reduced pressure and without further purification. Treatment of the tosylate (**4**) with sodium methoxide in the presence of sodium sulfate evoked the base-catalyzed terminal epoxide migration,<sup>22</sup> affording the target chiral epoxy alcohol **3** in appreciable yields.



Scheme 4 Successful synthesis of the C1–C10 fragment (2).

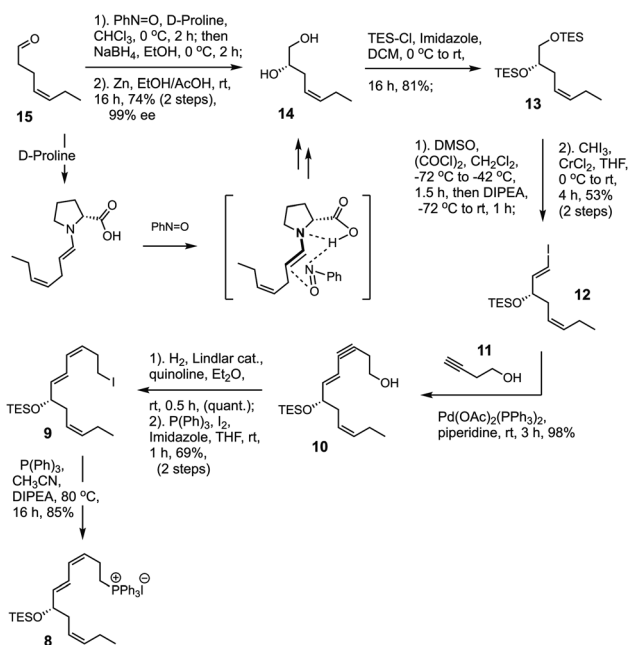
This epoxide cascade initially proceeds *via* the intermediacy of a 1,2-epoxy alcohol which is then transposed to the internal 2,3-position under basic conditions, with the inversion of the configuration of carbon 2 and the retention at carbon 3, *via*  $S_N2$  nucleophilic substitutions (Scheme 4).<sup>22</sup>

Smooth Dess–Martin oxidation of epoxy alcohol **3**, followed by a Wittig-type four-carbon chain homologation of the aldehyde intermediate with stabilized ylide(triphenylphosphoronylidene)acetaldehyde in toluene at 95 °C afforded the highly coveted C1–C10 segment (**2**) in fair yields. The latter transformation yielded a lower two-carbon vinylogue (data not shown), which was recycled back to furnish the desired intermediate.

In parallel, compound **2** was also constructed from the aldotetrose *D*-erythrose (**23**) and the oxirane stereochemistry was secured similarly to the erythronolactone strategy. However, this starting piece was disadvantageous due to its (i) physical state as a wet viscous syrup which, before use, required thorough drying under high vacuum for several hours and often resulting in significantly reduced residuum, as well as its (ii) relatively high price (~US\$355 per 8.3 mmol). Thus **7** was the preferred chiral synthon owing to its inexpensive commercial availability, and its highly efficient transformations in the onward sequence involving the protecting-group chemistry.

### Synthesis of C11–C22 $\omega$ -fragment (**8**)

Having successfully furnished the C1–C10  $\alpha$ -segment (**2**), the next objective was to build the C11–C22  $\omega$ -fragment (**8**) as illustrated in Scheme 5. The synthesis began with the commercially available *cis*-4-heptenal (**15**), proceeding *via* a highly enantioselective and organocatalytic MacMillan  $\alpha$ -oxyamination of the substrate using *D*-proline and nitrosobenzene, followed by an *in situ* aldehyde reduction with NaBH<sub>4</sub>. Cleavage



Scheme 5 Synthesis of the C11–C22 fragment (**8**).

of the O–N bond was accomplished using Zn dust and acetic acid, furnishing the known<sup>23</sup> diol **14** in 74% yield over 2 steps.<sup>14</sup>

The enantiopurity of this chiral intermediate was greater than 99% as determined by 400 MHz NMR on the Mosher's ester derivative (see, ESI†).<sup>14</sup> Subsequently, **14** was silylated with triethylsilyl (TES) to give **13** in 81% yield. This intermediate facilitated a direct regio-selective Swern oxidation of the primary alcohol and, using a Takai olefination,<sup>24</sup> the crude  $\alpha$ -siloxy aldehyde was directly converted to the (*E*)-alkenyl iodide **12** in 53% over 2 steps.

Next, the combination between alkynyl lynchpin **11** with vinyl iodide **12** was accomplished using an efficient copper-free Sonogashira cross-coupling to afford the 1,3-enyne containing intermediate **10** in 98% yield.<sup>15</sup> A mild *cis*-selective Lindlar hydrogenation of **10** in the presence of quinoline formed the 1,3-butadiene moiety, followed by conversion of the intermediate primary alcohol to iodide **9** in 69% over 2 steps. Finally, treatment of **9** with triphenylphosphine in the presence of DIPEA as a basic buffer afforded phosphonium salt **8** in 85% isolated yield.

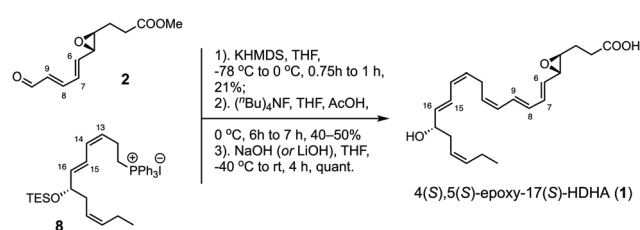
### Synthesis of the target compound (**1**)

With both the C1–C10 (**2**) and C11–C22 (**8**) segments at hand, the coupling of these building blocks was accomplished using a *cis*-selective Wittig olefination<sup>25</sup> under closely monitored conditions (Scheme 6).

Reaction of aldehyde **2** with the ylide prepared *in situ* from phosphonium iodide **8** with KHMSD at -78 °C in THF afforded the silyl protected epoxy methyl ester in modest 21% yield ( $\epsilon_{282} \approx 40\,000\text{ M}^{-1}\text{ cm}^{-1}$ ). Given the high sensitivity of this product, it was subjected to coarse and rapid column chromatography to avoid possible decomposition.

The silyl ether was cleaved in THF with <sup>n</sup>Bu<sub>4</sub>NF buffered with acetic acid affording the methyl ester of **1** in 40–50% yield, after coarse purification. The structures of both the TES ether and methyl ester of **1** were confirmed by 600 MHz <sup>1</sup>H NMR, including a wet1D pulse sequence to attenuate the dominant H<sub>2</sub>O and C<sub>6</sub>D<sub>6</sub> protium signals, in addition to two-dimensional pulsed field gradient COSY experiments (ESI†).

The vinylic configuration of the direct building blocks of the target compound, namely the 13(*Z*), 15(*E*)-diene unit in **8** ( $J_{13,14} = 10.92$  and  $J_{15,16} = 14.98$ ) and the 6(*E*), 8(*E*)-diene in **2** ( $J_{6,7} = 15.32$  and  $J_{8,9} = 15.36$ ) were confirmed by proton coupling constants. Similarly, the 6(*E*), 8(*E*), and 15(*E*) olefinic regions ( $J_{6,7} = 15.26$ ,  $J_{8,9} = 14.97$  and  $J_{15,16} = 15.20$ ) in the methyl ester of



Scheme 6 Assembly of target compound (**1**).



1 were confirmed using 2D  $^1\text{H}$  NMR, while the other alkenyl protons exhibited overlapping resonances. Due to the inherent instability and limited amount of the target molecule and its protected versions,  $^{13}\text{C}$  NMR scans were not procured.

Since the methyl ester of **1** was the preferred form for storage, as the free acid is prone to facile decomposition, only a fraction of this compound was subjected to mild hydrolysis under basic conditions to yield epoxy resolvin **1** quantitatively ( $\epsilon_{282} \approx 40\,000\ \text{M}^{-1}\ \text{cm}^{-1}$ ). In addition to high-resolution mass spectral information, this target material gave a UV signature with a triplet band of absorption,  $\lambda_{\text{max}}^{\text{MeOH}}$ , at 282 nm and shoulders at 273 nm and 295 nm, characteristic of a conjugated triene system. A single broad absorption at 229 nm was also observed, typical of a conjugated diene moiety present in **1** (see, ESI<sup>†</sup>). However, readable NMR absorption signals were, at this stage, unattainable.

With the synthetic epoxydocosanoid available, cell-type specific biological studies further validated its intact stereochemical structure *via* direct conversion to both resolvin D3 and resolvin D4,<sup>10</sup> and provided evidence of its previously proposed central role in the biosynthesis of these biologically active chemical agents.<sup>4</sup> In addition, when aqueous solutions of **1** were adjusted to physiological pH, epoxide hydrolysis proceeded to give a mixture of expected products<sup>10</sup> resulting from non-stereoselective attack of water on the delocalized cation intermediate, yielding the all-*trans* triene isomers of RvD3 and vicinal diols of RvD4.

## Conclusions

In summary, the first stereocontrolled total synthesis of 4(*S*),5(*S*)-epoxy-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid (**1**) has been achieved. The reported synthetic strategy is convergent and stereospecific, allowing the production of this indispensable epoxydocosanoid in unambiguous manner. The synthetic availability of this metastable material provides the basis of recent<sup>10</sup> and forthcoming investigations focused on its role in mediating the endogenous formation of chemical mediators that trigger inflammatory resolution processes, facilitating the studies of its biological properties and significance.

## Author contributions

N. A. P. and C. N. S. conceived the project. R. N. and N. A. P. designed the experiments. R. N. and T. F. L. conducted the experiments. S. A. acquired HRMS data. R. N. and N. A. P. wrote the manuscript. All authors discussed the results and gave approval to the final manuscript.

## Conflicts of interest

The authors declare no competing financial interests.

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