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Pauline Fischer, Valérie Bultel-Poncé, Alexandre Guy, Ilyana Gonzales, Pierre-Alexis Conde, et al.. Straightforward Syntheses of Phytosteranes and Dihomo-phytosteranes-Non-enzymatic Metabolites of γ -Linolenic, Dihomo- γ -linolenic and Stearidonic Acids. *European Journal of Organic Chemistry*, 2022, 2022 (16), pp.e202200085. 10.1002/ejoc.202200085 . hal-04648718

HAL Id: hal-04648718

<https://hal.science/hal-04648718v1>

Submitted on 15 Jul 2024

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Straightforward Syntheses of Phytoprostanes and Dihomophytoprostanes-Non-enzymatic Metabolites of γ -Linolenic, Dihomo- γ -linolenic and Stearidonic Acids

Pauline Fischer,^[a] Valérie Bultel-Poncé,^[a] Alexandre Guy,^[a] Ilyana Gonzales,^[a] Pierre-Alexis Conde,^[a] Jean-Marie Galano,^[a] Thierry Durand,^[a] and Camille Oger*^[a]

γ -Linolenic (GLA; C18:3 n-6), dihomogamma-linolenic (DGLA; C20:3 n-6) and stearidonic (SDA; C18:4 n-3) acids are found in several botanic and marine oils and are sustainable sources of omega-6 and omega-3 polyunsaturated fatty acids (PUFAs). During oxidative stress (pollution, UV, hydric or nutrient stress), lipid peroxidation occurred to produce non-enzymatic oxylipins named phytoprostanes (PhytoPs). We report herein the first syntheses of six non-enzymatic PUFA metabolites originated from GLA, DGLA and SDA peroxidation. Our syntheses follow a

straightforward synthetic pathway from enantiopure common intermediates (lactol or monoacetates), further used Horner-Wadsworth-Emmons and Wittig reactions to set up the side chains, and Corey-Bakshi-Shibata enantioselective reduction. Our strategy once again proved to be highly efficient as the compounds were obtained after only 4 to 12 consecutive steps, starting from previously prepared intermediates, and in a range from 6.5 to 41.5% yield.

Introduction

Very long chain polyunsaturated fatty acids (PUFAs) are a class of nutrients of high interest as they are involved in brain development, cognition,^[1] and in many diseases such as cardiovascular pathologies,^[2,3] cancers,^[4] diabetes.^[5] PUFA are composed of eighteen to twenty-two carbon atoms and more than two double bonds (2 to 6). Two classes of PUFAs are defined, omega-3 (n-3) and omega-6 (n-6) that differ from the position of the first double bond from the terminal methyl group. Omega-3 fatty acids were reported to be cardio-^[2] and neuroprotectives,^[6] and most health organizations recommend intakes between 200 mg and 500 mg of long chain PUFA (LC-PUFA), eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3), per day for healthy adults.^[7] Today's EPA and DHA-rich food sources are mainly fat fishes (salmon, mackerel, sardine), that may have limitations in their nutritional intake. For instance, the EPA and DHA levels can differ according to the fish species and based on its source, i.e. some species of farmed fish have substantially lower omega-3 rates than their wild-caught counterparts. Also, consumers are

hesitant since many contaminants can be found in fishes, such as mercury derivatives, polychlorinated biphenyls, leading to general intakes below recommended levels.^[8]

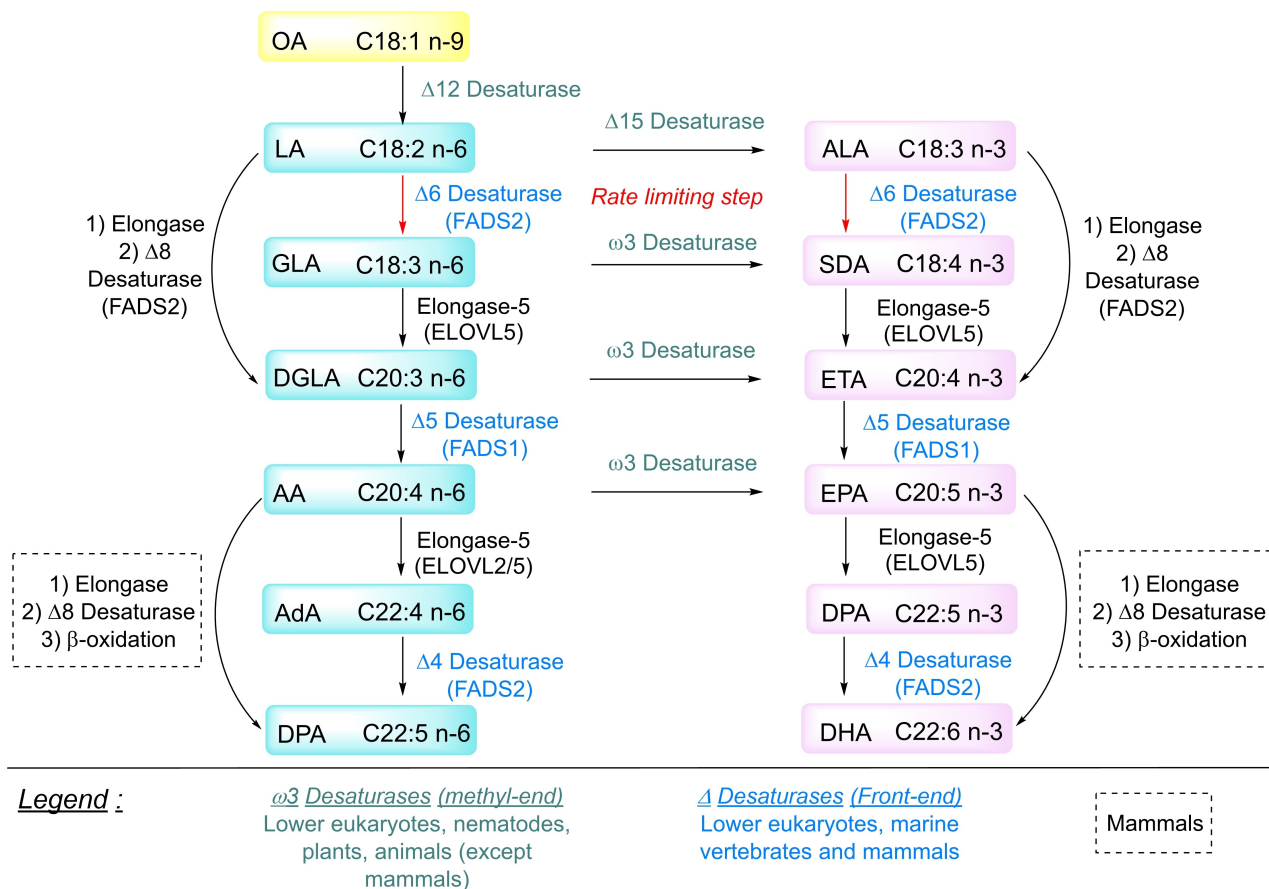
Other omega-3 PUFAs exist such as α -linolenic acid (ALA, C18:3 n-3), present in plants, seeds, and nuts (walnut, chia, flax). In the biosynthesis of PUFAs, ALA is the main omega-3 precursor and linoleic acid (LA, C18:2 n-6) is the one for the omega-6. LA and ALA are transformed into higher carbonated and unsaturated PUFAs such as arachidonic acid (AA, C20:4 n-6), adrenic acid (AdA, C22:4 n-6) or EPA and DHA, thanks to elongase and desaturase enzymes (Scheme 1).^[9] Given the lack of methyl-end desaturases (e.g. Δ 12 and Δ 15-desaturase) in mammals, LA and ALA are dietary essential fatty acids for humans. However, humans are able to convert only a small portion of these n-6 and n-3 precursors into C20/C22-PUFAs, with only 0.2–10% of EPA and less than 0.5% of DHA (from ALA), mainly because Δ 6-desaturase is the rate-limiting enzyme.

Therefore, PUFAs coming after this limiting step in the biosynthesis, i.e. γ -linolenic (GLA, C18:3 n-6) and stearidonic (SDA, C18:4 n-3) acids are sustainable sources of omega-6 and omega-3 fatty acids. In 2008, Harris *et al.* reported that SDA-enriched soybean oil diet significantly increased the omega-3 index (percentage of DHA and EPA in blood) in overweighted subjects. The intake of six parts of SDA raised the red blood cell EPA levels to the same level of one part of EPA, meaning that the efficiency of the bioconversion of SDA into EPA in this study was about 17% (compared to 0.09% from ALA).^[10] In addition, in a similar study, Lemke *et al.* found that a 1.6 g daily diet of SDA was equivalent to 350 mg of EPA/day.^[11] Interestingly, James *et al.* have shown that neither SDA or its immediate metabolite (ETA) were accumulated^[12] which suggested that both the elongase and Δ 5-desaturase were highly efficient to convert GLA into EPA. On the other hand, a study from Baker

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ejoc.202200085>

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Scheme 1. PUFA biosynthesis from C18 to C22 in eukaryotes. OA = oleic acid, LA = linoleic acid, GLA = γ -linolenic acid, DGLA = dihomogamma-linolenic acid, AA = arachidonic acid, AdA = adrenic acid, DPA = docosahexaenoic acid, ALA = α -linolenic acid, SDA = stearidonic acid, ETA = Eicosatetraenoic acid, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

et al. suggested that the observed GLA anti-inflammatory effects were the result of its immediate metabolite, namely DGLA. However, if there is still to discover in this field, these studies highlight the importance of GLA and SDA as alternative resources. In this sense, GLA is found in cow or human milk fat, some leafy green vegetables or algae,^[13] evening primrose (*Oenothera biennis* and *lamarckiana*), borage (*Borage officinalis*) or blackcurrant (*Ribes nigrum*) oils,^[14,15] as well as in microalgae.^[16] SDA on its side, can be found in echium (*Echium plantagineum*), hemp (*Cannabis sativa L.*), blackcurrant, Buglossoides (*Buglossoides arvensis*) seed oils.^[17]

More importantly, in comparison to DHA, EPA or docosapentaenoic acids (DPA: C22:5 n-6 or n-3), GLA and SDA are more stable, due to their lower unsaturation index (Figure 1). The presence of unsaturations is a major concern, as PUFAs contain bis-allylic positions that are highly prone to hydrogen abstraction, by free radicals released in the membrane. These reactive species undergo lipid peroxidation leading to the formation of PUFA metabolites grouped under the name of oxylipins. These metabolites are formed without the intervention of enzymes, are called non-enzymatic oxylipins. Non-enzymatic oxylipins were first discovered by Morrow *et al.*^[18] from arachidonic acid (AA, C20:4 n-6), and since 1990 non-

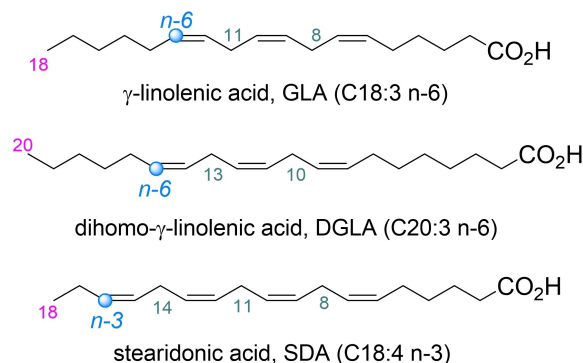


Figure 1. Structures of GLA, DGLA and SDA fatty acids.

enzymatic metabolites were detected *in vivo* from other PUFAs (AA, ALA, DHA, EPA, AdA).^[19,20] Therefore, it can be indubitably assumed that GLA, DGLA and SDA will also be peroxidized.

Three main family of non-enzymatic oxylipins were discovered.^[20] In this work, we focused on isoprostanoids, composed of a cyclopentan-1,3-diol (Figure 2). Two chains are attached to this cyclopentane core, the α -chain, which contain the carboxylic acid function (drawn on the top by convention),

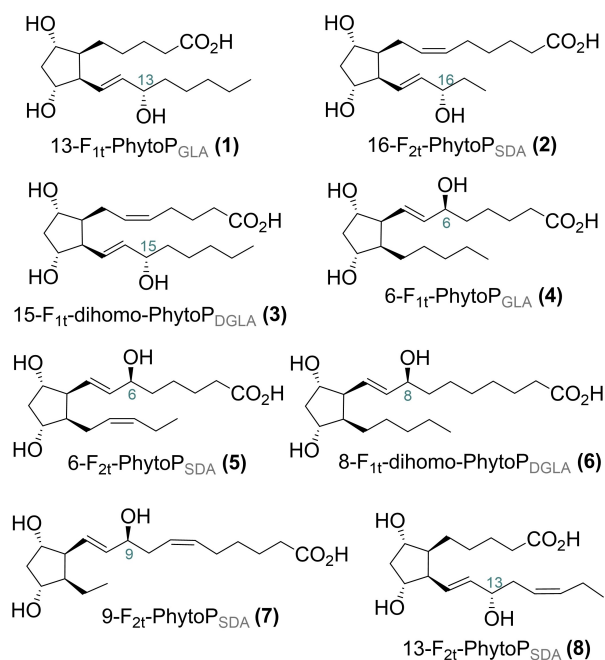


Figure 2. GLA, DGLA and SDA non-enzymatic oxylipins.

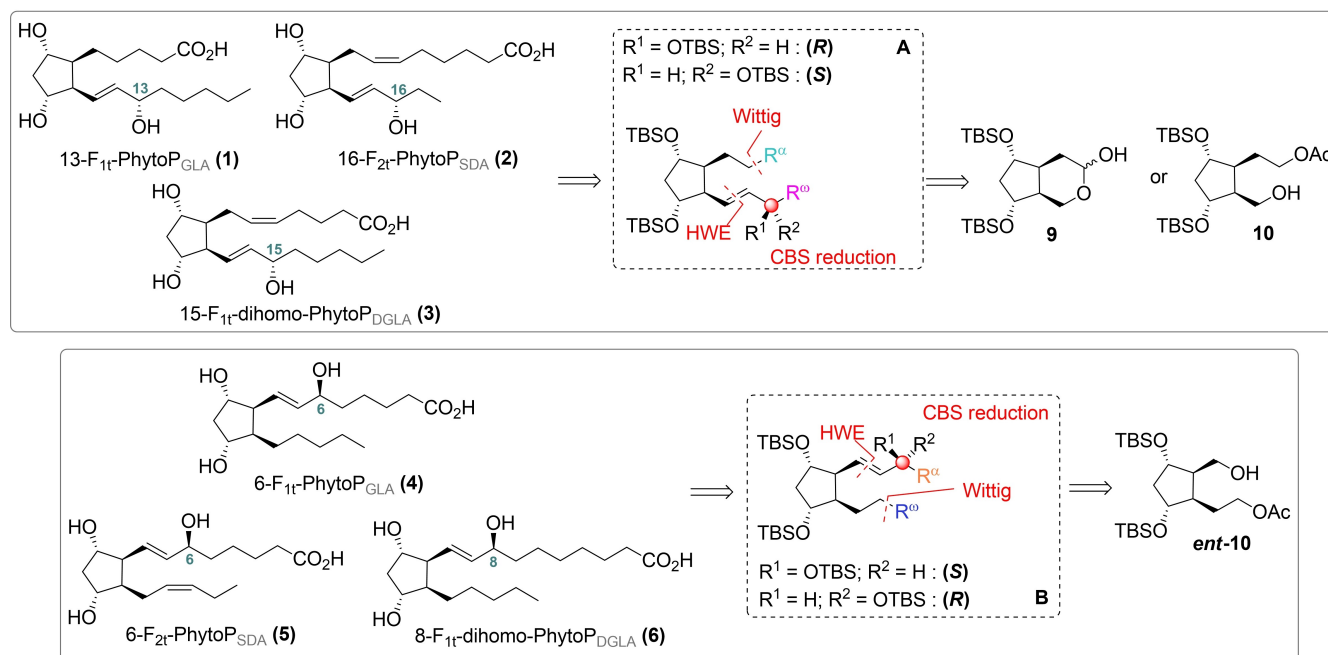
and ω -chain, in respect to the omega-6 or -3 family (on the bottom). As structural isomers of prostaglandins (PGs), the C18 non-enzymatic metabolites, derived from ALA, were named phytoprostanes (PhytoPs). The C20-metabolites derived from AA, isoprostanes (IsoPs) and neuroprostanes (NeuroPs) for the C22 derived from DHA. Finally, AdA-metabolites were called dihomio-isoprostanes (dihomo-IsoPs), as they contain two addi-

tional carbon compare to AA. As these nomenclatures are henceforth anchored, we proposed to name GLA and SDA non-enzymatic metabolites, PhytoPs, and DGLA metabolites: dihomio-PhytoPs. It should be noted that GLA and SDA-PhytoPs differentiate themselves by the number of double bonds, respectively one and two (in subscript in the nomenclature, compounds 1–6, Figure 2). Furthermore, for more clarity and simplicity for neophytes, we decided to add after PhytoP, in subscript, the name of the parent PUFA (Figure 2).

Fatty acids and their metabolites are known to exhibit valuable biological properties.^[19] Thus, to pursue these studies, we report herein the synthesis of the two series of GLA-PhytoPs (6- and 13-series), in addition to two series of SDA-PhytoPs (6- and 16-series out of the four series), and the two series of DGLA-dihomo-PhytoPs (8- and 15-series). Stereoselective strategies are used to access enantiopure metabolites with the aim to study the intrinsic biological properties of these derivatives.

Results and Discussion

Our strategy relies on the preparation of two key structures (A and B, Scheme 2) that contain the cyclopentane-1,3-protected-diol bearing on one of the side chain the allylic alcohol functionality. Depending on the metabolites, the allylic alcohol can be on either the α -chain (oxylipins 1, 2 and 3) or ω -chain (oxylipins 4, 5 or 6). As highlighted in the retrosynthetic plan (Scheme 2), we envisioned to prepare these key structures using Horner-Wadsworth-Emmons (HWE) reactions and suitable β -ketophosphonates on either a hemiacetal compound (9)^[21] or on a monoacetylated-1,5-diol (10) or its enantiomer (*ent*-10),^[22] depending on the targeted oxylipins. These intermediates are



Scheme 2. Retrosynthetic analysis. R^α correspond to the α -chain (bearing the acid function) and R^ω to the ω -chain.

prepared in 9 or 10 consecutive steps,^[21,22] and permit to access the cyclopentane backbone of our compounds containing four out of the five stereogenic centers as well as the primers to assemble the side chains. The last stereogenic center is controlled by an enantioselective reduction of α,β -unsaturated ketones using Corey-Baski-Shibata (CBS) conditions and the appropriate oxazaborolidines.

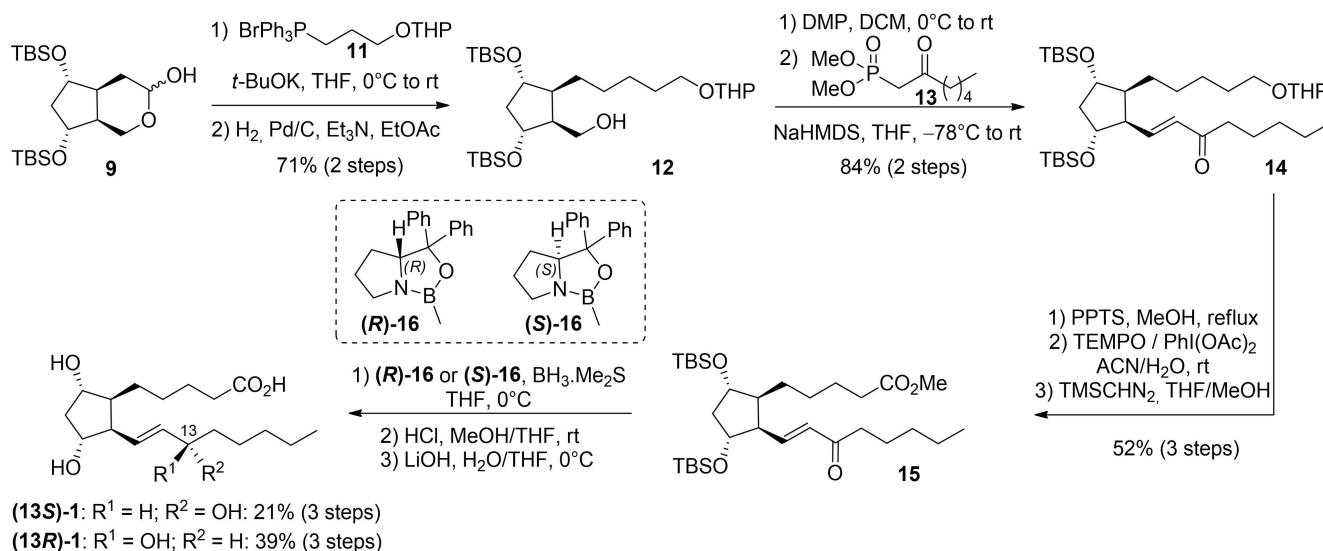
Oxylipins with the allylic alcohol on the ω -chain

Our first synthesis, toward the 13-F_{1t}-PhytoP_{GLA} started with a Wittig reaction on lactol **9** using THP-protected phosphonium salt **11**^[23,24] (Scheme 3), and provided after the hydrogenation of the resulting double bond using palladium on charcoal in the presence of trimethylamine, compound **12** in 71% yield (over two steps). The ω -chain was assembled by HWE olefination using β -ketophosphonate **13**, after a Dess-Martin oxidation of the corresponding alcohol. This reaction proceeded smoothly in 84% high yield (over two steps) and excellent stereoselectivity (only (*E*)-stereomer) to give enone **14**. Then, the cleavage of the THP-protection was followed by the oxidation of the resulting primary alcohol into carboxylic acid and a subsequent esterification using trimethylsilyldiazomethane, to provide intermediate **15** in 52% overall yield (over three steps). With compound **15** in hand, the last chiral center was introduced using CBS-

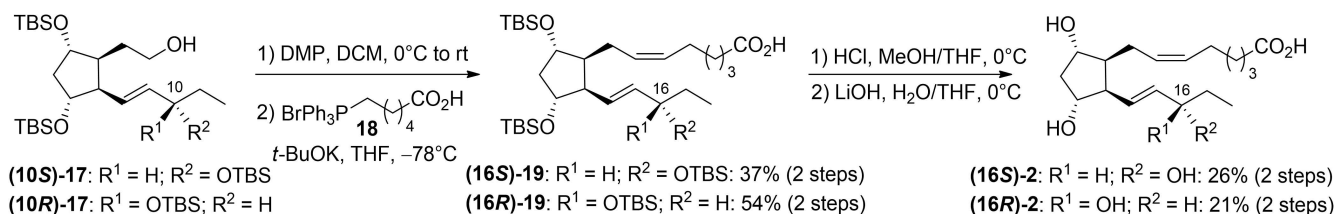
reductive conditions. Both (*R*)- and (*S*)-methyloxazaborolidines ((*R*)-**16** and (*S*)-**16**) were employed to access (*S*)- and (*R*)-epimers respectively. Good diastereomeric ratios of 9/1 ((13*S*)/(13*R*) using (*R*)-**16** and (13*R*)/(13*S*) (*S*)-**16**) for each CBS-reduction,^[25] as well as yields (86% and 69%) were obtained. The synthesis of 13-F_{1t}-PhytoP_{GLA} and its C13-epimer were achieved by the cleavage of the silylated ether under acidic condition (HCl/MeOH in THF) and final saponification using LiOH. Thereby, the 13-F_{1t}-PhytoP_{GLA} (**13S**)-**1** and its C13-epimer (**13R**)-**1** were obtained in 10 consecutive steps and 6.5% and 12.1% yield (starting from lactol **9**) respectively.

Buildings on precedents from our previous work,^[26] we began the synthesis of the 16-F_{2t}-PhytoP_{SDA} (Scheme 4) with compounds (**10S**)-**17** and (**10R**)-**17**. A tandem Dess-Martin oxidation/Wittig reaction using commercially available phosphonium salt **18**^[27] and *t*-BuOK (2 equiv./**18**) as a base provided (*Z*)-configured olefins (**16S**)-**19** and (**16R**)-**19** in 37% and 54% yields. Subsequent silyl ether deprotection using HCl in methanol and saponification of the methyl ester under basic condition delivered the desired 16-F_{2t}-PhytoP_{SDA} (**16S**)-**2** and its C16-epimer (**16R**)-**2** in 9.6% and 11.3% yield, starting from previously prepared intermediates (**10S**)-**17** and (**10R**)-**17** respectively.

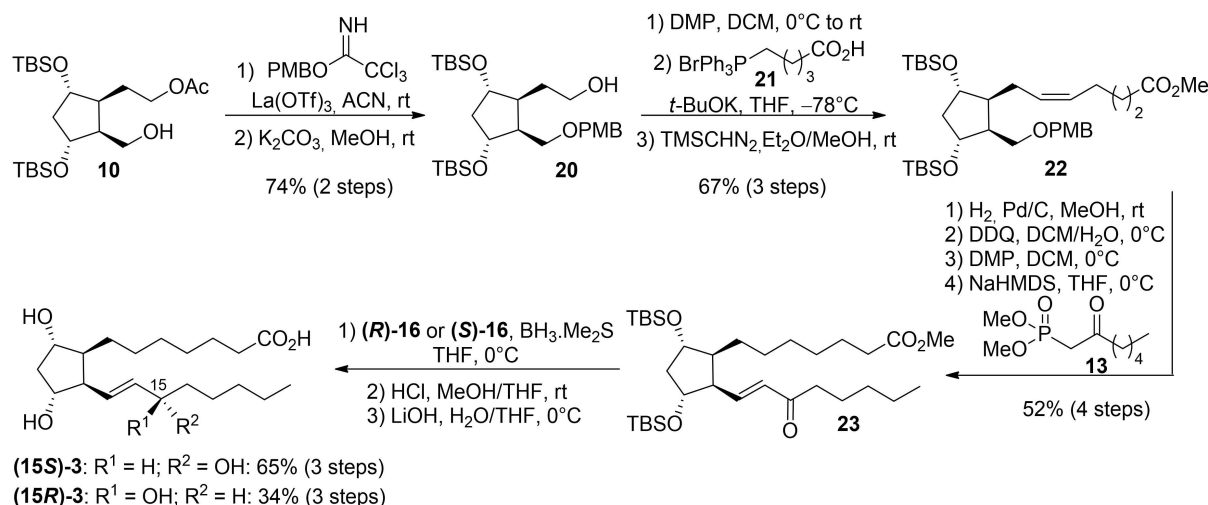
We next pursued with the synthesis of the first DGLA-metabolites (Scheme 5). Given that compound **10** is readily available in multigram quantities,^[21] our synthesis started with



Scheme 3. 13-F_{1t}-PhytoP_{GLA} synthesis.



Scheme 4. 16-F_{2t}-PhytoP_{SDA} synthesis.



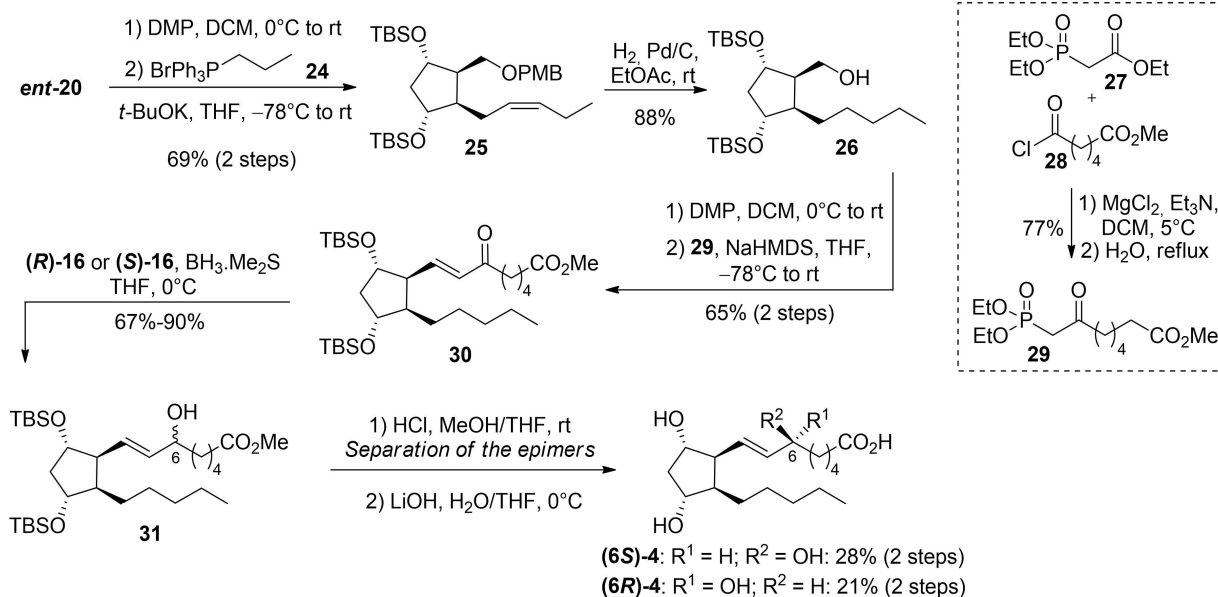
Scheme 5. 15-F_{1t}-dihomo-PhytoP_{DGLA} synthesis.

the preparation of compound **20**, in two steps, a PMB-protection using *p*-methoxybenzyltrichloroacetimidate and a methanolysis (K₂CO₃ in MeOH). Subsequent oxidation of the resulting alcohol and Wittig reactions using commercially available phosphonium salt **21**^[28] and *t*-BuOK (2 equiv./**21**) as a base, followed by an esterification provided compound **22** in 67% yield (over three steps). The resulting double bond was reduced using palladium on charcoal in methanol, prior to the cleavage of the PMB-group, and further oxidation/HWE reactions with β-ketophosphonate **13**. Compound **23** was obtained in an excellent 52% overall yield over these four steps and flawless stereoselectivity toward (*E*)-double bond. The reduction of the α,β-unsaturated ketone into allylic alcohol using CBS-reductive conditions, furnished the desired (15*S*)- and (15*R*)-

diastereomers with 9/1 diastereomeric ratios (on C15 center). Finally, the last two steps proceeded smoothly, providing the desired 15-F_{1t}-dihomo-PhytoP_{DGLA} (**15S**)-**3** and its C15-epimer (**15R**)-**3** in 65% and 34% yield respectively. These oxylipins were thus built in 10 steps starting from available compound **20** and respectively in 22.6% and 11.8% yield (over 10 steps).

Oxylipins With the Allylic Alcohol on the α-Chain

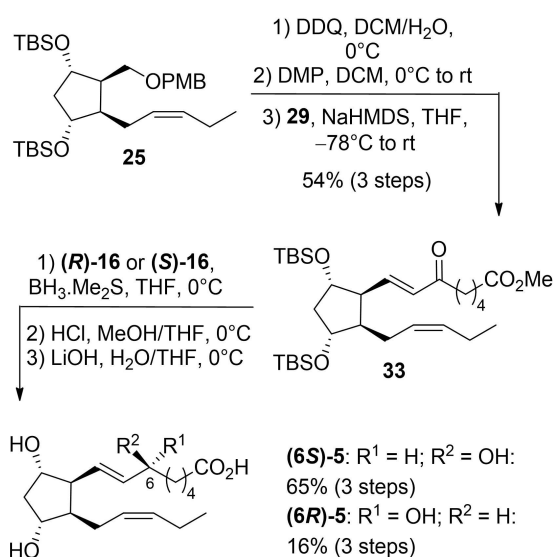
The synthesis of 6-F_{1t}-PhytoP_{DGLA} metabolite (Scheme 6) commenced with a Dess-Martin oxidation of the primary alcohol of intermediate **ent-20**, followed by a Wittig reaction using commercial phosphonium **24**^[29] (69% yield over two steps).



Scheme 6. 6-F_{1t}-PhytoP_{DGLA} synthesis.

Subsequent hydrogenation of **25** using Pd/C in EtOAc resulted in both the reduction of the (Z)-configured double bond and the PMB-deprotection, giving rise to compound **26** in 88% yield. With alcohol **26** in hands, the α -chain was assembled by oxidation and further HWE reaction using prepared phosphonate **29**^[30] and provided enone **30** in 65% (over two steps). Then, the treatment of enone **30** with (*R*)-**16** and (*S*)-**16** afforded the corresponding (6*S*)- and (6*R*)-allylic alcohols (**31**), however in an 1:1 diastereomeric (C6) ratio of inseparable compounds. Note that this ratio was observed for both chiral auxiliary and despite several attempts. Acetyl mandelic derivatives were prepared according to the work of Chataigner *et al.*,^[31] to induce a separation of the two C6 epimers. However, if the separation by column chromatography proceeded smoothly, after saponification of the acetyl-mandelates a mixture of the two C6-epimers was reobtained, nullifying both our epimer separation efforts as well as the determination of the absolute configurations. At this stage, we decided to keep going with the diastereomer mixture. The treatment of **31** with HCl in methanol permitted to separate the C6 epimers by chromatography. Final saponification of (6*S*)-**4** and (6*R*)-**4** provided the 6-*F*_{1t}-PhytoP_{GLA} and its C6 epimer. Thanks to our expertise and the syntheses of other phytoprostane structures, the (6*R*)- and (6*S*)-configurations were assigned by comparison of the ¹³C chemical shifts of the (9*R*)- and (9*S*)-epimers in the 9-*F*_{1t}-PhytoP and 9-*epi*-9-*F*_{1t}-PhytoP.

We next investigated the synthesis of the 6-*F*_{2t}-PhytoP_{SDA} starting from previously described compound **25** (Scheme 7). The treatment of **25** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by Dess-Martin oxidation of the corresponding alcohol and Wittig reaction using phosphonium **29** produced (Z)-configured olefin **33** in 55% yield. CBS-reduction proceeded as expected with a diastereoselectivity of 9/1 to access the desired (6*S*)- or (6*R*)-allylic alcohols, prior to the final deprotections. The 6-*F*_{2t}-PhytoP_{SDA} (**6S**)-**5** and its epimer (6*R*)-**5**



Scheme 7. 6-*F*_{2t}-PhytoP_{SDA} synthesis.

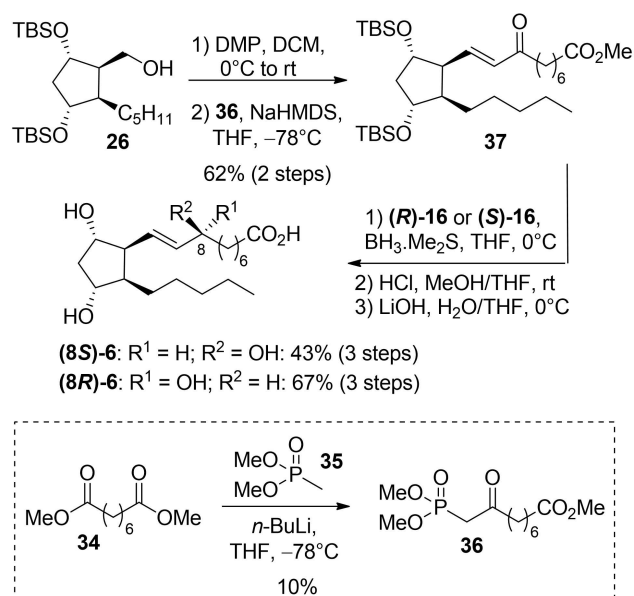
were obtained in six consecutive steps starting from intermediate **25** and in 35.8% and 8.8% yield (over 6 steps).

The completion of the total synthesis of the 8-*F*_{1t}-dihomo-PhytoP_{DGLA} is illustrated in Scheme 8. The oxidation of alcohol **26** followed by a HWE reaction with previously prepared β -ketophosphonate **36**, gave enone **37** in good 62% yield (over two steps). CBS-reduction and subsequent deprotections produced the 8-*F*_{1t}-dihomo-PhytoP (**8S**)-**6** and its C8-epimer in 26.7% and 41.5% yield from compound **26**.

Conclusion

The strategy developed in 2008 to access isoprostanoids one more time proved to be highly efficient and permitted straightforward routes to new PUFA metabolites. We herein described the total synthesis of six new series of non-enzymatic metabolites derived from three PUFAs (GLA, SDA and DGLA). Each synthesis was optimized in term of number of steps and time by using already prepared intermediates we had in reserve (**20** and *ent*-**20**), and/or through structures common for two metabolites (e.g. the 6-*F*_{2t}-PhytoP_{SDA} and the 8-*F*_{1t}-dihomo-PhytoP_{DGLA} syntheses took advantages of intermediates **25** and **26** prepared for the 6-*F*_{1t}-PhytoP_{GLA}). This allowed us to prepare between 13 mg to 51 mg of these metabolites starting with range of 330 mg to 800 mg of starting material.

With all these metabolites in hand, we will first prove that they are present in terrestrial and marine vegetal by using them as standards for targeted lipidomic. In addition, we will study their intrinsic biological properties to further understand their role in cells signaling.



Scheme 8. 8-*F*_{1t}-dihomo-PhytoP_{DGLA} synthesis.

Acknowledgements

The author would like to thank the university of Montpellier and CNRS for financial support. Credit for the graphical abstract picture to © Maria MATARD/LBI2M/CNRS Photothèque. Finally, the authors thank our collaborators for they interest in oxylipins.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Biomarkers · Fatty acids · Organic chemistry · Phytosteranes · Total synthesis

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Manuscript received: January 27, 2022
Revised manuscript received: March 21, 2022
Accepted manuscript online: March 24, 2022