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## Total syntheses of all tri-oxygenated 16-phytoprostane classes *via* a common precursor constructed by oxidative cyclization and alkyl-alkyl coupling reactions as the key steps†

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A unified strategy for the total synthesis of the methyl esters of all phytoprostane (PhytoP) classes bearing two ring-oxygen atoms based on an orthogonally protected common precursor is described. Racemic 16-F<sub>1t</sub>-, 16-E<sub>1</sub>-PhytoP and their C-16 epimers, which also occur as racemates in Nature, were successfully obtained. The first total synthesis of very sensitive 16-D<sub>1t</sub>-PhytoP succeeded, however, it quickly isomerized to more stable, but so far also unknown  $\Delta^{13}$ -16-D<sub>1t</sub>-PhytoP, which may serve as a more reliable biomarker for D-type PhytoP. The dioxygenated cyclopentane ring carrying the  $\omega$ -chain with the oxygen functionality in the 16-position was approached by a radical oxidative cyclization mediated by ferrocenium hexafluorophosphate and TEMPO. The  $\alpha$ -chain was introduced by a new copper-catalyzed alkyl-alkyl coupling of a 6-heptenyl Grignard reagent with a functionalized cyclopentylmethyl triflate.

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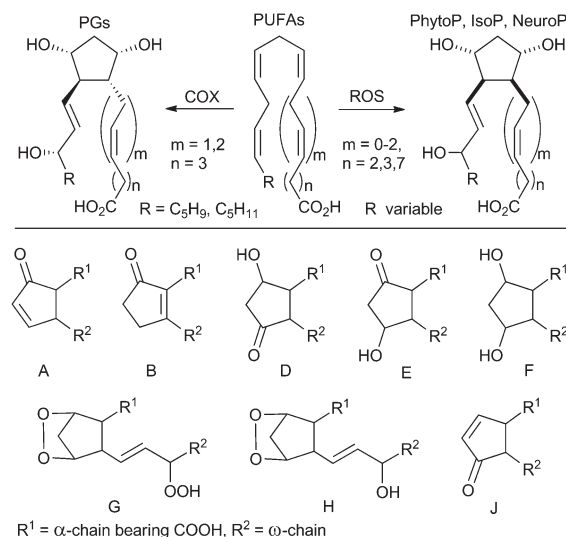
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### Introduction

Oxidative stress is one of the important and intensely studied topics in current medicine and life sciences. It describes a situation, where the redox equilibrium of a cell and its environment is imbalanced in favor of oxidants and by which reactive oxygen species (ROS) are unspecifically generated. This excess of ROS stabilizes by reaction with biologically important primary metabolites such as nucleic acids, proteins or lipids thus abrogating their functions.<sup>1,2</sup> Clear evidence has been gathered that increased levels of oxidative stress are related to many human diseases.

Prostaglandins (PGs) are enzymatically formed by a radical reaction cascade as single enantiomers from the most prominent polyunsaturated fatty acid (PUFA) arachidonic acid regulating a wide range of biological processes (Scheme 1).<sup>3–5</sup> However all PUFAs are essential parts of the cell membrane and react with ROS by radical reactions including peroxidation as well as fragmentation or cyclization cascades.<sup>6–9</sup> Cyclic products of these autoxidative transformations are structural analogs of PGs. The best known and studied representatives are isoprostanes (IsoPs) produced from arachidonic (C20:4  $\omega$ -6)<sup>6,10</sup> or eicosapentaenoic (C20:5  $\omega$ -3)<sup>11,12</sup> acids in animals



**Scheme 1** Formation of cyclic PUFA metabolites and classes based on their ring substitution. COX = cyclooxygenase for arachidonic acid, ROS = reactive oxygen species.

and humans. Recently metabolites of docosahexaenoic acid (C22:6  $\omega$ -3), named neuroprostanes (NeuroPs), were also discovered in the human brain.<sup>13</sup> A number of biological activities of IsoPs and NeuroPs were reported.<sup>14</sup>

In the plant kingdom phytoprostanes (PhytoPs) were found as metabolites of  $\alpha$ -linolenic acid (C18:3  $\omega$ -3).<sup>8</sup> PhytoPs are

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† Electronic supplementary information (ESI) available: Experimental procedures, analytical characterization and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds. See DOI: 10.1039/c7ob02505j



assumed to play an essential role in the protection and detoxification of plant cells and serve as a part of their oxidative injury-sensing system.<sup>15–17</sup> A living cell is not required for their formation and the level and composition of PhytoP change during the processing of plant-originated raw materials in the food industry.<sup>18</sup> Thus, they are recommended as suitable biomarkers of oxidative degradation in plant-derived edibles.<sup>19–26</sup>

The structural similarity of PhytoPs to PGs and IsoPs suggests possible bioactivities in humans and animals. It was demonstrated that the level of PhytoPs in the human body depends on the diet and also increases after a high consumption of  $\alpha$ -linolenic acid.<sup>27,28</sup> However, only a few studies have been published in this field. Traidl-Hoffmann *et al.* reported that E<sub>1</sub>- and F<sub>1</sub>-PhytoPs act similarly to endogenous PGs and modulate human dendritic cell function and T-cell polarization.<sup>29,30</sup> The role of E<sub>1</sub>-PhytoP in pollen-caused allergies was subsequently studied in more detail.<sup>31,32</sup>

Because of the radical nature of their formation, PhytoPs occur *in vivo* as racemic mixtures of hardly separable regio- and diastereomers and the natural material is therefore not useful for a thorough study of their biological effects. The total synthesis of individual stereoisomers is the only appropriate way to provide a material for the study of their biological activity. Since the discovery of PhytoPs in 1998<sup>8</sup> more than ten total syntheses of individual PhytoPs have been published.<sup>6,33,34</sup>

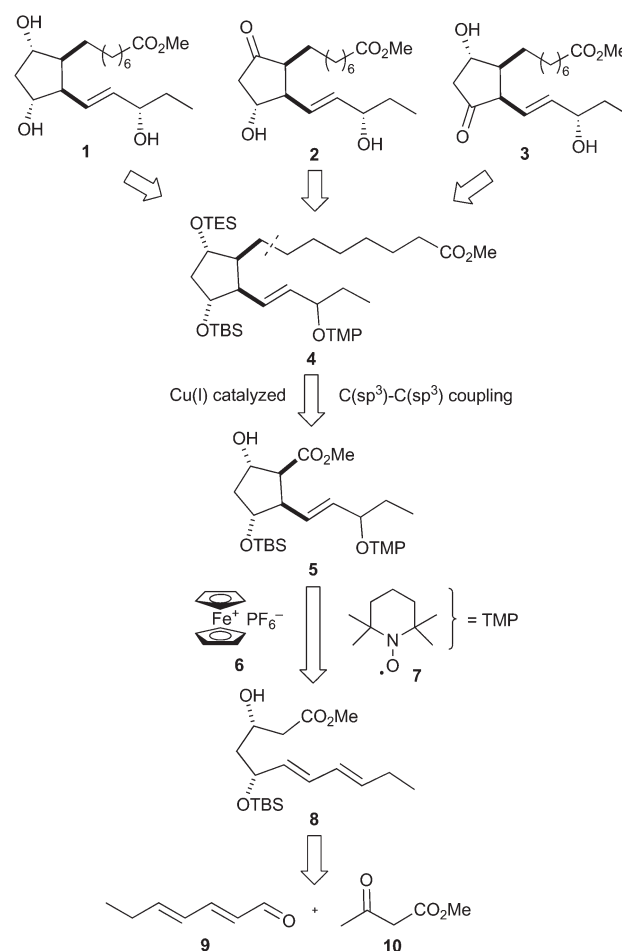
Diversity oriented syntheses of PhytoPs are especially attractive for many biological investigations. So far, such approaches aimed at accessing the different diastereomers or side chain isomers for a given ring substitution pattern. For example, all eight diastereomers of 16-F<sub>1t</sub> and 9-F<sub>1t</sub> PhytoPs were published by Durand *et al.*,<sup>35,36</sup> which is based on a radical 5-*exo* cyclization of a sugar-based precursor.<sup>37</sup> An analogous approach was recently applied to the total syntheses of B<sub>1</sub>-PhytoPs<sup>38,39</sup> and 9-D<sub>1t</sub>-PhytoP.<sup>40</sup> An individual total synthesis of 16-E<sub>1</sub>-PhytoP was also published, based on the Friedel–Crafts acylation of furan, followed by a Piancatelli rearrangement and attachment of the  $\omega$ -chain by 1,4-conjugate addition after enzymatic resolution.<sup>41</sup> The total syntheses of ring-isomeric cyclopentenone PhytoP, namely 9- and 16-B<sub>1</sub>- and L<sub>1</sub>-PhytoP as well as 9-A<sub>1</sub>- and 9-J<sub>1</sub>-PhytoP, were accomplished by the Vidari–Zanoni group,<sup>42,43</sup> whereas Riera's group developed an individual approach to 16-B<sub>1</sub>- and 9-L<sub>1</sub>-PhytoPs.<sup>44</sup> A total synthesis of 16-D<sub>1t</sub>-PhytoP was never accomplished. The only evidence for its occurrence stems from the transformation of a mixture of all possible F<sub>1</sub>-PhytoP isomers based on a procedure originally developed for an access to PGD<sub>2</sub>.<sup>45</sup> A 3 : 1 mixture of D<sub>1t</sub>- to E<sub>1</sub>-PhytoP isomers was obtained, which was not further separated and identified.<sup>46</sup> This further highlights the need for selective approaches to these natural products for meaningful biological investigations. Considering that the diversity of biological activities of cyclic PUFA metabolites rather rests on the differential substitution patterns at the cyclopentane ring than on the side chain structure, we hypothesized that a unified approach allowing a simple simultaneous access to most possible ring oxygenation patterns of PhytoP may constitute a

more promising and affordable approach than designing individual strategies to them (*vide supra*). Another benefit of such a unified approach is the possibility of attaching different types of  $\alpha$ -chains to the same  $\omega$ -chain-containing cyclic unit,<sup>47,48</sup> thus forming PhytoPs, IsoPs or NeuroPs with minimal effort.

We report here the total syntheses of 16-F<sub>1t</sub>-, 16-E<sub>1</sub>- and 16-D<sub>1t</sub>-PhytoP and provide evidence that 16-D<sub>1t</sub>-PhytoP will probably hardly be detectable in biological samples because of its facile isomerization to the so far unknown  $\Delta^{13}$ -16-D<sub>1t</sub>-PhytoP, which represents therefore a potentially better observable metabolite in biological materials.

## Results and discussion

The retrosynthesis of 16-F<sub>1t</sub>-, 16-E<sub>1</sub>- and 16-D<sub>1t</sub>-PhytoPs 1–3 is based on common precursor 4, which can be easily transformed to all target compounds by simple deprotection, protection and oxidation reactions (Scheme 2). This orthogonally protected PhytoP structure 4 was envisaged to be obtained by copper(i)-catalyzed C(sp<sup>3</sup>)–C(sp<sup>3</sup>) coupling<sup>49</sup> of a suitable  $\alpha$ -chain precursor and the substituted cyclopentane core 5. An



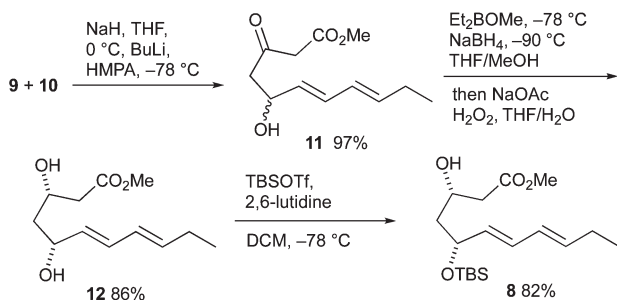
Scheme 2 Retrosynthetic analysis of F<sub>1t</sub>-, E<sub>1</sub>- and D<sub>1t</sub>-PhytoP.



oxidative radical anion cyclization using ferrocenium hexafluorophosphate **6** and the stable radical 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) **7** paves the way for construction of the central cyclic structure **5**. Cyclization substrate **8** should be easily prepared from commercially available (*E,E*)-2,4-heptadienal (**9**) and methyl acetoacetate (**10**).

The total syntheses commenced with the preparation of cyclization precursor **8** in analogy to published procedures in three steps (Scheme 3).<sup>47,48</sup> The vinylogous aldol addition of heptadienal **9** and acetoacetate **10** had to be performed with a somewhat larger excess of bases (1.3 equiv. NaH, 1.2 equiv. BuLi) than previously. Reduction of the carbonyl group at C-3 of hydroxy keto ester **11** proceeded with good yield and exclusive *syn* selectivity providing diol **12**. The formation of mono-protected diol **8** was accomplished with equimolar amounts of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine at low temperature.

The tandem radical cyclization/oxygenation was performed by deprotonating substrate **8** with an excess of base and the resulting 1,3-enediolate was subjected to single electron transfer (SET) oxidation, cyclization and oxygenation by treatment with ferrocenium hexafluorophosphate **6** and TEMPO **7**. Applying these conditions to the cyclization of **8** gave cyclopentanes **5** in 49% and 47% yield, respectively (Table 1, entries 1 and 2). The diastereomeric ratio of **5a** and **5b** is dependent on the applied base. The formation of PG-like structure **5b** is predominant when the deprotonation was caused by the stronger chelating magnesium species (Table 1, entry 2). Decreasing the chelating ability of magnesium by the addition of HMPA prior to deprotonation led to a reversed ratio being similar to that with LDA (Table 1, entry 3 vs. 1). Pentylzinc bromide induced an increase in the **5a/5b** ratio, but low conversion was observed when the deprotonation was conducted at  $-78\text{ }^{\circ}\text{C}$  (Table 1, entry 4). The conversion was better at higher temperature, but the stereoselectivity dropped (Table 1, entry 5). A noticeable improvement was observed when DME was used as the solvent and the amount of HMPA was increased (Table 1, entries 8 and 9). Other attempts to affect the reaction were unsuccessful. A recently developed catalytic version of the cyclization<sup>50</sup> proceeded with low yield and diastereoselectivity (not shown). Transmetalation of the dilithium 1,3-enediolate using  $\text{Ti}(\text{OiPr})_4$ ,  $\text{Al}(\text{OiPr})_3$  or  $\text{B}(\text{OMe})_3$  resulted in no cyclization, but  $\beta$ -elimination and transesterification products were identified.



Scheme 3 Preparation of cyclization precursor **8**.

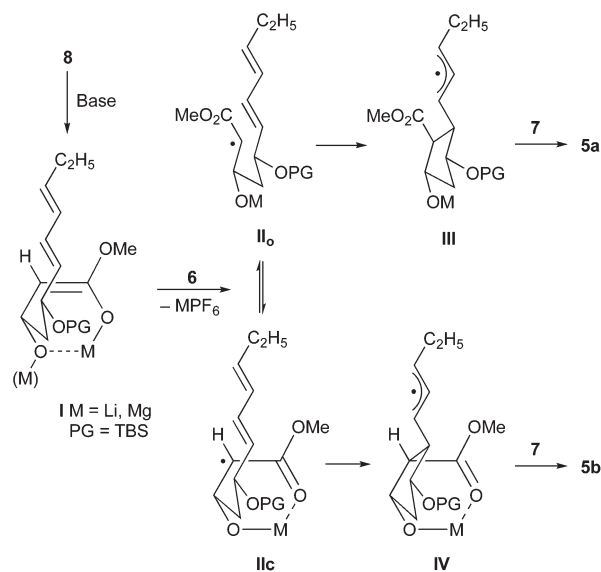
Table 1 Oxidative radical cyclization/oxygenation of dihydroxy ester **8**

Entry	Base	Additive <sup>a</sup> (equiv.)	Solvent	<b>5</b> (%)	<b>a</b> : <b>b</b> <sup>b</sup>
1	LDA	LiCl, HMPA (6)	THF	49	1.6 : 1
2	<i>t</i> BuMgCl, LDA	HMPA (6)	THF	47	1 : 5
3	<i>t</i> BuMgCl, LDA	HMPA (6) <sup>c</sup>	THF	30	1.3 : 1
4	PentZnBr, <sup>d</sup> LDA	HMPA (6)	THF	16	3 : 1
5	PentZnBr, <sup>e</sup> LDA	HMPA (6)	THF	42	1.5 : 1
6	LDA	LiCl, HMPA (12)	THF	48	1.5 : 1
7	LDA	LiCl, TMEDA (9)	THF	51	1.2 : 1
8	LDA	LiCl, HMPA (6)	DME	55	1.6 : 1
9	LDA	LiCl, HMPA (12)	DME	64	2 : 1

<sup>a</sup> LiCl is always 6 equiv. based on **8**. <sup>b</sup> dr determined from the <sup>1</sup>H NMR spectra of an inseparable mixture. <sup>c</sup> HMPA added prior to deprotonation. <sup>d</sup> Deprotonation at  $-78\text{ }^{\circ}\text{C}$ . <sup>e</sup> Deprotonation at  $25\text{ }^{\circ}\text{C}$ .

No reaction occurred and **8** was recovered when 12-crown-4 was used as an additive (not shown).

The significant effect of the metal cation can be traced to differentially strong chelation during the course of the cyclization (Scheme 4). Both, the dilithium and the magnesium 1,3-enediolate **I**, are likely strongly chelated, however on SET oxidation the resulting radical anions behave significantly different. The lithium radical anion apparently equilibrates between the open form **II<sub>o</sub>** and the chelated form **II<sub>c</sub>** prior to cyclization, so that a mixture of cyclic radicals **III** and **IV** with low diastereoselectivity results, which stabilizes by oxygenation with **7** to cyclic esters **5a** and **5b**. The magnesium radical anion is likely more stable in the chelated form **II<sub>c</sub>** and therefore cyclizes predominately to cyclopentancarboxylate **5b**.



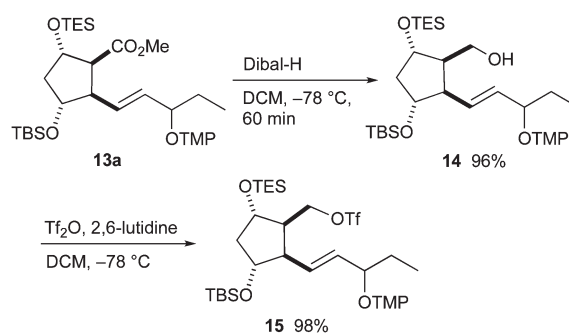
Scheme 4 Course of the radical cyclization/oxygenation of ester **8**.



In contrast to the previous IsoP syntheses,<sup>47,48</sup> where a free hydroxy group was mandatory, orthogonal protection was necessary to complete the unified approach to PhytoPs 1–3. Triethylsilyl (TES) protection of the free hydroxy group gave esters **13a** and **13b**, which were, however, only partially separable. Hypothesizing that the silylation of **5a** might be significantly faster than that of **5b** because of less steric interactions with the neighboring ester function, the amount of TESCl was reduced to the quantity of **5a** in the mixture (Table 2). Indeed, the hydroxy group of **5a** was preferably silylated and a separable mixture rich in diastereomer **13a** was obtained (entry 1). A decrease in the temperature further increased the selectivity for silylation of the desired ester **5a** (entries 2–4). In contrast, TES triflate reacted unselectively (not shown).

The ester group of **13a** was transformed to triflate **15** in two steps (Scheme 5). Dibal-H in dichloromethane was optimal for the reduction to alcohol **14**. In contrast, full deprotection of the TES group and partial deprotection of the TBS group occurred when LiAlH<sub>4</sub> in THF was used. Alcohol **14** was converted to triflate **15** using triflic anhydride and 2,6-lutidine in good yield.

The crucial introduction of the  $\alpha$ -chain was performed by copper(i)-catalyzed alkyl–alkyl coupling. Initial experiments were fruitless and therefore a series of model reactions was performed with cyclohexylmethyl triflate as a model substrate and several alkyl halides bearing functionality that could be later transformed to an ester group (for details, see the ESI†). Based on these results, the coupling reactions of  $\omega$ -alkenyl Grignard reagents **16** with triflate **15** were further studied (Table 3). 6-Heptenylmagnesium bromide **16a** gave surprisingly only a low yield of the desired PhytoP precursor **17** and bromide **18** was the main product, which was unreactive in the coupling reaction (Table 3, entries 1 and 2). A switch of the Grignard reagent to the less nucleophilic chloride **16b** prevented the triflate–halogen exchange largely and compound **17** comprising the complete skeleton was obtained in a reasonable yield (Table 3, entry 3). It was subsequently found that the addition of lithium halides<sup>51</sup> was beneficial to accelerate the coupling and to further reduce the formation of compound **18** (Table 3, entries 4 and 5). Surprisingly the bromide anion,



**Scheme 5** Preparation of alkyl–alkyl coupling partner **15** from ester **13a**.

**Table 3** Cu(i)-Catalyzed alkyl–alkyl coupling of triflate **15** and Grignard reagents **16**

Entry	<b>16</b>	Additive (equiv.)	<i>T</i> (°C)	<i>t</i> (h)	<b>17</b> (%)	<b>18</b> (%)
1	<b>a</b>	—	0	3	9	77
2	<b>a</b>	—	–78 to r.t.	24	15	78
3	<b>b</b>	—	–78 to 0	12	63	24 <sup>a</sup>
4	<b>b</b>	LiBr (5)	–78 to –50	3	66	7 <sup>a</sup>
5	<b>b</b>	LiCl (5)	–78 to –50	3	71	0

<sup>a</sup> Both chloride and bromide **18** were identified by NMR spectroscopy and ESI MS of the mixture.

stemming from LiBr, did not display the undesired substitution reactivity.

The central synthetic intermediate **4** was obtained from olefin **17** in four steps (Scheme 6). Hydroboration with 9-BBN using classical conditions or microwave heating provided the corresponding borane in almost quantitative yields, but the reaction time was reduced under microwave conditions. Its oxi-

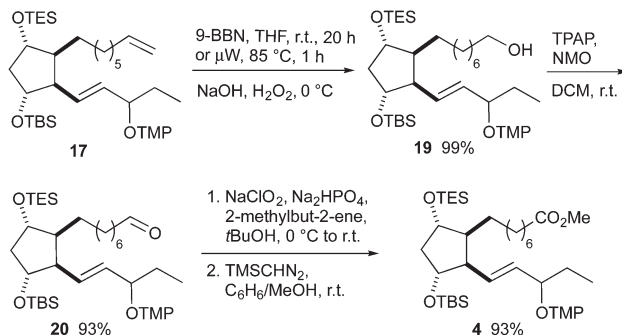
**Table 2** Diastereomer-selective TES protection of hydroxycyclopentanecarboxylates **5a** and **5b**

Entry	<b>5a</b> : <b>5b</b> <sup>a</sup>	TESCl (equiv.)	<i>T</i> (°C)	Yield <sup>b</sup> (%)	<b>13a</b> : <b>13b</b> <sup>a</sup>	Unreacted <b>5a</b> : <b>5b</b> <sup>a</sup>
1	1.5 : 1	0.60	25	75	4.6 : 1	1 : 1.15
2	1.5 : 1	0.53	0	90	5.4 : 1	1 : 1.9
3	2 : 1	0.66	–20	80	7.5 : 1	1 : 1.6
4	1.7 : 1	0.64	–60	95	6.2 : 1	1 : 1.8

<sup>a</sup> dr determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Yield based on the applied amount of TESCl.





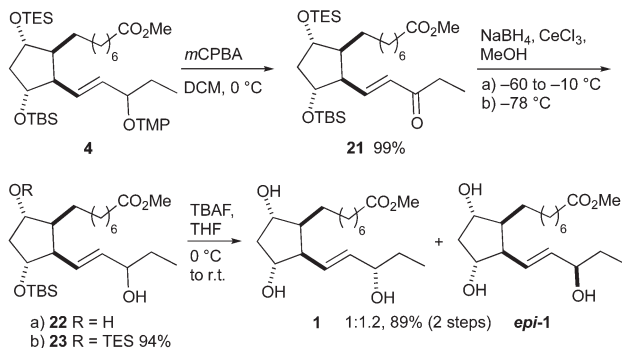


**Scheme 6** Transformation of olefin **17** to orthogonally protected ester **4**.

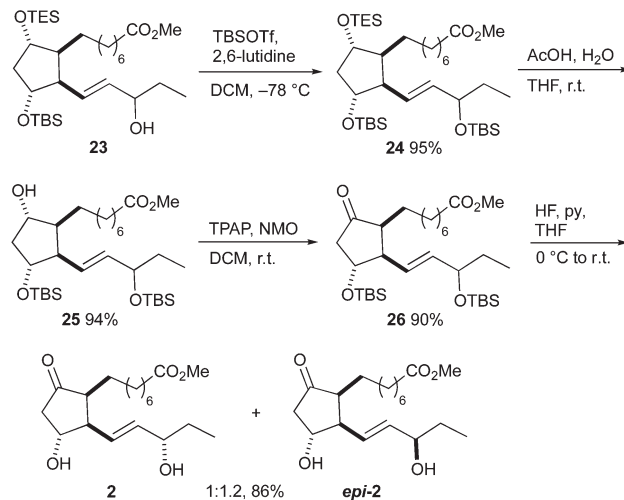
dation with basic hydrogen peroxide gave alcohol **19**, which was oxidized to the corresponding acid using a two-step protocol consisting of Ley–Griffith oxidation to aldehyde **20** and subsequent Pinnick oxidation. Methyl ester **4** was prepared from the crude acid with (trimethylsilyl)diazomethane.

16- $F_{1t}$ -PhytoP methyl ester **1** was obtained from precursor **4** in three steps (Scheme 7). Oxidative removal of the tetramethylpiperidinyloxy group using *m*CPBA<sup>52</sup> gave ketone **21** in almost quantitative yield. Although not executed here, an advantage of this strategy is the potential opportunity to reduce the carbonyl group enantioselectively.<sup>35,36</sup> Since we focused on generating both C-16 diastereomers, the Luche reduction was applied, which gave both C-16 epimers in a 1:1.2 16- $F_{1t}$ -/16-*epi*-16- $F_{1t}$ -PhytoP ratio. Both silyl groups were conserved when the reduction was performed at  $-78$  °C, however, TES deprotection occurred on warming to  $-10$  °C. The remaining protected hydroxy groups were liberated by reaction with TBAF. The methyl esters of 16- $F_{1t}$ -PhytoP **1** and its 16-epimer *epi*-**1** were separable by standard column chromatography and the correct stereochemistry at C-16 was determined by the comparison of measured and published NMR spectra.<sup>35,36</sup> The overall yield amounted to 13% over 15 steps.

The synthesis of 16- $E_1$ -PhytoP methyl esters **2** started with alcohol **23** (Scheme 8). The hydroxy group was protected as TBS ether and the TES group was subsequently selectively



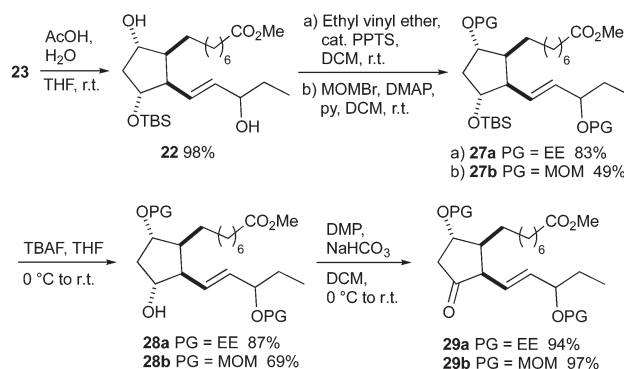
**Scheme 7** Completion of the total synthesis of 16- $F_{1t}$ -PhytoP **1** and 16-*epi*-16- $F_{1t}$ -PhytoP *epi*-**1** methyl esters.



**Scheme 8** Completion of the total synthesis of 16- $E_1$ -PhytoP **2** and 16-*epi*-16- $E_1$ -PhytoP *epi*-**2** methyl esters.

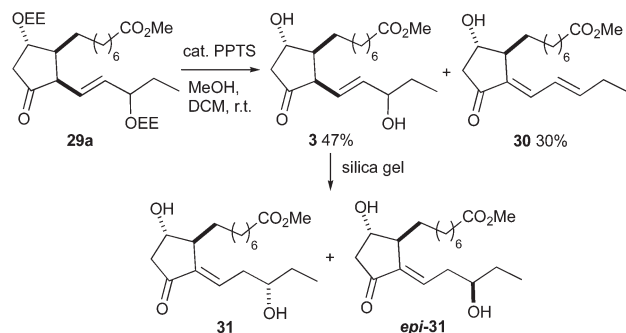
removed by acetic acid giving disilylated alcohol **25**. Ketone **26** was prepared by Ley–Griffith oxidation; using the Dess–Martin periodinane gave a slightly lower yield of 78%. Hydrogen fluoride/pyridine proved to be the reagent of choice for the deprotection of the TBS groups. Separation of 16- $E_1$ -PhytoP **2** and its 16-epimer *epi*-**2** by flash column chromatography was possible. The stereochemistry at C-16 was confirmed by comparison with the published NMR data.<sup>41</sup> The epimeric ratio is in agreement with that observed in the synthesis of  $F_{1t}$ -PhytoP methyl esters **1** and *epi*-**1**. The overall yield was 9% over 18 steps.

The D-classes of IsoPs and PGs are known for their low stability caused by the sensitive  $\beta,\gamma$ -unsaturated ketone functionality,<sup>6,53–55</sup> therefore several protecting groups removable under mild conditions were tested for the synthesis of 16- $D_{1t}$ -PhytoPs. The 1-ethoxyethoxy (EE) group was the only fruitful choice besides the methoxymethoxy (MOM) group. Protected 16- $D_{1t}$ -PhytoP derivatives **29a, b** were synthesized in four steps from hydroxy ester **23** (Scheme 9). Selective removal of the TES group with acetic acid provided diol **22**. Introduction of the EE group using catalytic PPTS proceeded



**Scheme 9** Synthesis of EE- and MOM-protected 16- $D_{1t}$ -PhytoP derivatives **29a** and **29b**.





**Scheme 10** Access to 16-D<sub>11</sub>-PhytoP methyl ester **3** by deprotection and its isomerization to  $\Delta^{13}$ -16-D<sub>11</sub>-PhytoP methyl ester **31**.

smoothly to give **27a**, whereas MOM protection giving **27b** was less efficient. Removal of the remaining silyl group in **27a**, **b** was executed by TBAF and afforded free 12-alcohols **28a**, **b**. Their Dess–Martin oxidation to ketones **29a**, **b** worked almost quantitatively.

The final deprotection was performed by using catalytic amounts of PPTS (Scheme 10). Removal of the EE group of ketone **29a** was completed at room temperature over three hours and gave a 1.5 : 1 mixture of 16-D<sub>11</sub>-PhytoP methyl esters **3** and 16-deoxy- $\Delta^{13,15}$ -16-D<sub>11</sub>-PhytoP methyl ester **30**. The MOM deprotection of ketone **29b** proceeded very slowly at room temperature. Heating to reflux led to a hardly separable mixture, in which neither the expected D<sub>11</sub>-PhytoP **3** nor dienyl PhytoP **30** were identified. The C-16 epimers of **3** were not separable by column chromatography and moreover, partial isomerization to more stable  $\Delta^{13}$ -16-D<sub>11</sub>-PhytoP methyl esters **31** and *epi*-**31** occurred during chromatographic purification. The isomerization could be promoted by treatment with silica gel and C-16 epimers **31** and *epi*-**31** were isolated in overall 4% yield over 19 steps. The unequivocal assignment of the individual C-16 epimers was impossible. Nevertheless, we assume that the less polar epimer is  $\Delta^{13}$ -16-*epi*-16-D<sub>11</sub>-PhytoP (*epi*-**31**) in analogy to the polarities of 16-*epi*-16-F<sub>11</sub>-PhytoP and 16-*epi*-16-E<sub>1</sub>-PhytoPs. This hypothesis is supported by common signal patterns observed in the <sup>13</sup>C NMR spectra of compounds **29b**, **3** and **31** (for details see the ESI†). Moreover, *epi*-**3** is thus the major C-16 epimer of **3** being in agreement with the epimeric ratio obtained in the Luche reduction of **21** and observed in the total syntheses of 16-F<sub>11</sub>- and 16-E<sub>1</sub>-PhytoPs **1** and **2**.

## Conclusions

A new strategy for the diversity-oriented synthesis of all trioxo-generated 16-PhytoP classes, based on an orthogonally protected common precursor was developed. The key step for the formation of the dioxygenated cyclopentane ring was a radical oxidative cyclization mediated by ferrocenium hexafluorophosphate and TEMPO, which also introduced the oxygen functionality in the 16-position of the  $\omega$ -chain. The complete carbon skeleton was assembled by a copper-catalyzed alkyl-

alkyl coupling of a 6-heptenyl Grignard reagent and the properly functionalized cyclopentylmethyl triflate. 16-F<sub>11</sub>-PhytoP methyl ester **1** and its epimer *epi*-**1** were obtained in 13% yield over 15 steps. The synthesis of the methyl esters of 16-E<sub>1</sub>-PhytoP **2** and its C-16 epimer *epi*-**2** took 18 steps and the overall yield amounted to 9%. The first total synthesis of 16-D<sub>11</sub>-PhytoP methyl ester **3** resulted in an inseparable mixture of its C-16 epimers and their more stable isomerization products **31** and *epi*-**31**, which can be prepared by complete isomerization in 4% yield over 19 steps. The reported strategy will facilitate the simultaneous access to the majority of oxidatively formed cyclic metabolites derived from linolenic acid. Total syntheses of cyclopentenoic PhytoP can also be envisaged based on this approach. Moreover, the strategy will also be applicable to approach cyclic metabolites of the other major  $\omega$ -3 PUFAs, eicosapentaenoic or docosahexaenoic acids. Investigations along these lines are under way in these laboratories.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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