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Total syntheses and *in vivo* quantitation of novel Phytofurans derived from α-linolenic acid

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Dedication ((optional))

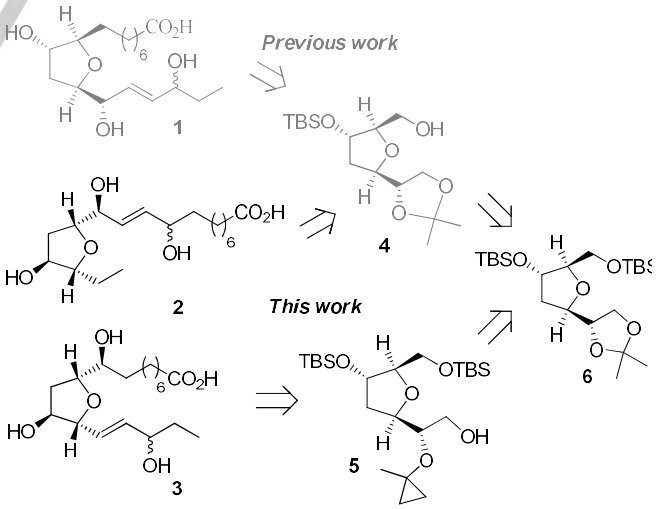
Abstract: Phytoprostanes (PhytoPs) are produced in plants and seeds by a non-enzymatic free radical pathway from α-linolenic acid (ALA). We recently highlighted the formation of a new class of compounds from ALA, named phytofurans (PhytoFs). Produced as a mixture in biological samples their analytical exploration remains challenging without their pure synthetic forms. The syntheses of phytofurans are thus described here, thanks to an enantiomerically enriched intermediate which allowed for the first time the access to both families of PhytoFs, the alkenyl and enediol. For the first time the quantitation of PhytoF metabolites was determined in liver tissue of rats treated with ALA rich flax seed or flax seed oil diet.

Introduction

Oxidative stress is responsible for the oxidation of phospholipid moiety in the living organisms. Under these conditions, arachidonic acid (AA, C20:4 n-6), adrenic acid (AdA, C22:4 n-6) and docosahexaenoic acid (DHA, C22:6 n-3) are oxidized and metabolized through non-enzymatic free radical pathways, forming isoprostanes (IsoPs),[1] dihomo-isoprostanes (Dihomo-IsoPs)[2] and neuroprostanes (NeuroPs)[3] respectively. In addition of being biomarkers for oxidative stress in human diseases, isoprotanoids have various biological activities such as vasoconstriction, pulmonary inflammation, neurovascular abnormalities[4] and anti-arrhythmic properties.[5] The major polyunsaturated fatty acid (PUFA) in plants is α-linolenic acid (ALA, C18:3 n-3) which can release phytoprostanes (PhytoPs) *via* free radical process,[6] and can mediate plant defense mechanisms [7] and neuroprotection in human cells[8].

In a similar manner, the biosynthesis of 2,3,5-trisubstituted tetrahydrofuran structures, named isofurans (IsoFs)[9] from AA, dihomo-isofurans (dihomo-IsoFs)[10] from AdA and neurofurans (NeuroFs)[11] from DHA was discovered. Recently, we investigated the presence of such mechanistic process in plants and we highlighted, for the first time, the existence of natural tetrahydrofuranic oxygenated products of ALA, the phytofurans (PhytoFs).[12] These new molecules were quantified in some nuts (pine and walnut) and seeds (chia and flax) by LC-MS/MS.

As like IsoFs, dihomo-IsoFs and NeuroFs, two biosynthesic pathways of PhytoFs coexist leading to two classes of PhytoFs specifically alkenyl and enediol for a total of 128 potential phytofuran isomers. To date, there are four main synthetic strategies of furanoids reported in the literature.[13] In 2004, Taber *et al.* proposed the first total synthesis of the alkenyl-type IsoFs (8-*epi*-SC-Δ^{13}-9-IsoF and 8,15-*diepi*-SC-Δ^{13}-9-IsoF)[14] by a diol epoxide benzenesulfonate cyclization.[15] After, some modifications of this strategy, the synthesis of the enediol type (15-*epi*-*ent*-SC-Δ^{13}-8-IsoF and *ent*-SC-Δ^{13}-8-IsoF) was allowed.[16] The first synthesis of NeuroF (7-*epi*-ST-Δ^{8}-10-NeuroF) using Trost asymmetric alkylation was described by Zanoni and *coll.* [17] In 2014, our group developed a strategy based on 5-*exo*-tet and 5-*endo*-tet Borhan's orthoester directed cyclization to successfully synthesize, alkenyl dihomo-IsoF (10-*epi*-17(*RS*)-SC-Δ^{15}-11-dihomo-IsoF), enediol dihomo-IsoF and NeuroF (7(*RS*)-ST-Δ^{8}-11-dihomo-IsoF and 4(*RS*)-ST-Δ^{5}-8-NeuroF).[10],[18] We then recently validated the first total synthesis of enediol PhytoF (*ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1**) by one-pot Payne rearrangement/epoxide opening/5-*exo*-tet cyclization (Scheme 1).[12] To highlight the divergence and flexibility of this strategy, we describe here the new total syntheses of one other enediol PhytoF, *ent*-9(*RS*)-12-*epi*-ST-Δ^{10}-13-PhytoF **2** and one alkenyl type, *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3**.



Scheme 1. Retrosynthetic analysis of enediol and alkenyl PhytoFs **1**, **2** and **3**.

In order to understand the metabolism of PhytoFs we supplemented with and without ALA rich flaxseed (FS) and flaxseed oil (FSO) to rodents (n=6) for 28 days.[19] The concentration of ALA in FSO and FS diets were consistent (1% per gram of diet).The liver tissues were analyzed for the PhytoFs including the newly synthesized *ent*-9(*RS*)-12-*epi*-ST-Δ^{14}-13-PhytoF **2** and *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3**, using the

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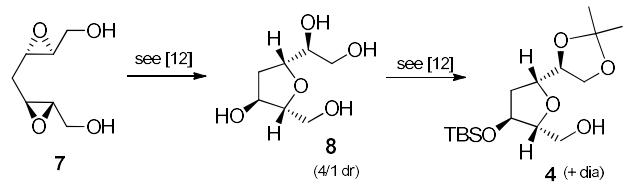
LC-MS/MS.[12] The liver was selected as it is the main organ for the synthesis, metabolism and storage for fats and lipids.

Results and Discussion

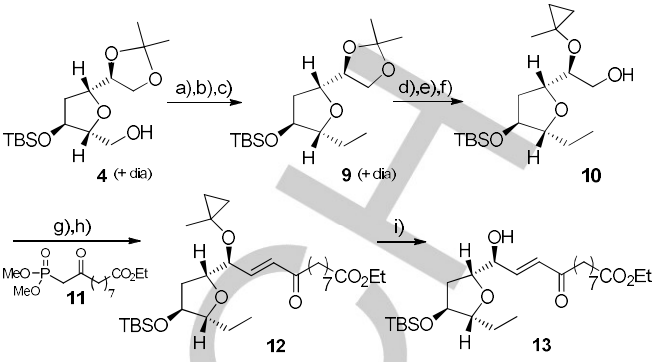
Synthesis of Phytofurans

The synthesis of the enediol-PhytoF **2** started from common mono-protected TBS-ether intermediate **4** in 4:1 mixture of diastereoisomer.[12] The synthesis of this intermediate involves a unprecedented C2-symmetric Payne rearrangement of (2S,2'S,3S,3'S)-*bis*-epoxide **7** followed by a 5-*exo*-tet cyclization to obtain the furan core **8**. Two orthogonal protections of the alcohol moieties and selective deprotection accessed compound **4** (Scheme 2).



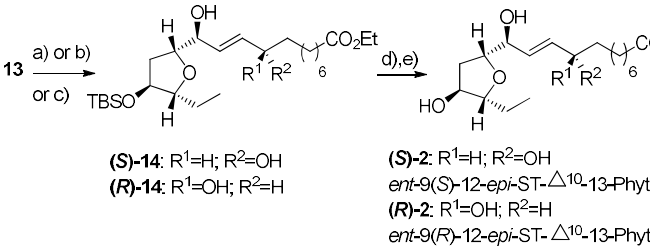
Scheme 2. Synthesis of intermediate **4**.

Primary alcohol **4** was transformed into the corresponding aldehyde with Dess-Marin periodinane (DMP) (Scheme 3). One-carbon homologation *via* a Wittig reaction using the commercially available methyltriphenylphosphonium bromide introduced the first side chain in 77% overall yield. The reduction by catalytic hydrogenation (Pd/C) of the terminal double bond gave intermediate **9** in 91% yield. Before introducing the second lateral chain, the primary alcohol was selectively deprotected following Rychnovsky method,[20] by converting 1,2-diol acetonide into secondary 1-methylcyclopropyl ether. By treatment with TMSOTf and *i*-Pr_2NEt, acetal **9** was cleaved into enol ether which was then directly stabilized by Simmons-Smith cyclopropanation prior to TMS cleavage in basic media to afford 1-methyl-1-cyclopropyl hydroxyl derivative **10** in 48% yield over 3 steps. Gratefully, the minor diastereoisomer of **10** (coming from the Payne reaction) was eliminated at this stage by a simple flash chromatography. Final introduction of the second side chain was achieved using DMP-oxidation of primary alcohol **10** followed by Horner-Wadsworth-Emmons olefination with previously described β-ketophosphonate **11**[21] in the presence of $Ba(OH)_2$,[22] and the enone **12** was obtained in 87% yield over two steps. It is important to note that the oxidation step needed to be performed in degassed DCM.[23] Selective deprotection of cyclopropyl group of **12** was realized by mild oxidation with *N*-bromosuccimide to give the compound **13** in 79% yield.[20]



Scheme 3. a) DMP, $NaHCO_3$, CH_2Cl_2/H_2O, 0°C to RT; b) $BrPh_3PCH_3$, NaHMDS, THF, -78°C to RT, 79% over 2 steps; c) H_2, Pd/C, MeOH, RT, 91%; d) *i*-PrNEt, TMSOTf, CH_2Cl_2, 0°C to RT then reflux; e) Et_2Zn, CH_2I_2, Et_2O, RT; f) K_2CO_3, MeOH, RT, 48% over 3 steps; g) DMP, CH_2Cl_2 degassed, 0°C to RT; h) **9**; $Ba(OH)_2$, THF/H_2O, 87% over 2 steps; i) NBS, THF/H_2O, RT, 79%. TMS: trimethylsilyl; Tf: trifluoromethansulfonyl; NBS: *N*-bromosuccinimide; DMP: Dess Martin Periodinane; NaHMDS: sodium *bis*(trimethylsilyl)amide.

At this stage, subsequent Luche reduction of the enone **13** gave access to allylic alcohol epimer **(*S*)-14** and **(*R*)-14** as 1:1 mixture in 90% yield (named **(RS)-14** Scheme 4). Finally, the TBS group was removed using tetrabutyl ammonium fluoride prior to the ester saponification in the presence of lithium hydroxide to afford enediol *ent*-9-(*RS*)-12-*epi*-ST-Δ^{10}-13-PhytoF **(*RS*)-2** in 94% yield. We also synthesized both (9*R*) and (9*S*) epimers of the *ent*-9-(*RS*)-12-*epi*-ST-Δ^{10}-13-PhytoF **2** using Corey-Bakshi-Shibata oxazaborolidines for the stereoselective reduction of enone **13**. As a result, 9(*S*) derivative **14** and 9(*R*) derivative **14** were obtained in 89% and 76% yield respectively with a good diastereoisomeric ratio (dr : 9/1). Finally, the TBS cleavage-saponification sequence afforded the *ent*-9-(*S*)-12-*epi*-ST-Δ^{10}-13-PhytoF **(*S*)-2** and **(*R*)-2** in 64% and 90% yield respectively. As a consequence, we performed the total synthesis of 24 mg of *ent*-9-(*RS*)-12-*epi*-ST-Δ^{10}-13-PhytoF **(*RS*)-2**, 13 mg of the 9(*S*) epimer **(*S*)-2** and 15 mg of 9(*R*) epimer **(*R*)-2** in 20%, 14% and 16% yield respectively, in 12 steps starting from mono-protected TBS-ether **4**.

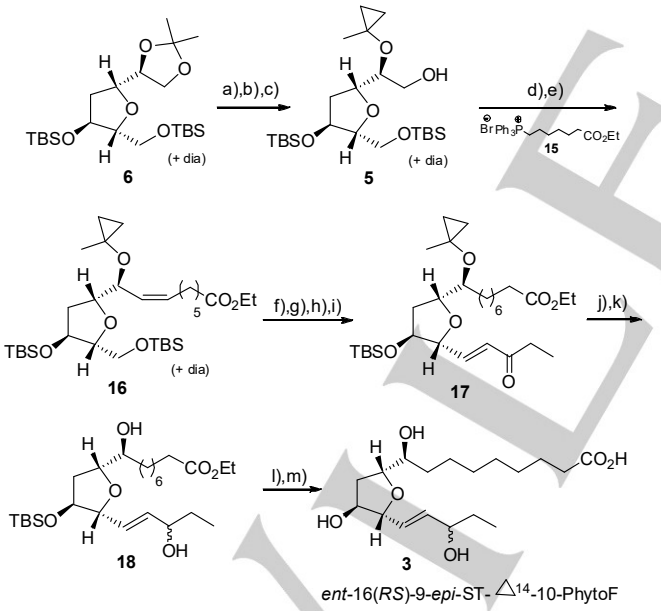


Scheme 4.a) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0°C to RT, 90% in **(*RS*)-14:** 1/1; b) *R*-methyl-CBS-oxazaborolidine, $BH_3.Me_2S$, THF, 0°C to RT, 89% in **(*S*)-14**, dr: 9/1; c) *S*-methyl-CBS-oxazaborolidine, $BH_3.Me_2S$, THF, 0°C to RT, 76% in **(*R*)-14**, dr: 9/1; d) TBAF, THF, RT; e) LiOH, THF/H_2O, RT, 94% in **(*RS*)-2**, 67% in **(*S*)-2**, 90% in **(*R*)-2** over 2 steps. CBS: Corey-Bakshi-Shibata;TBAF: tetrabutyl ammonium fluoride.

The synthesis of this enediol-PhytoF **2** confirmed the potential of our core structure **4** to obtain various enediol-PhytoFs. However, it remained to prove that the choice of our orthogonal protecting groups will provide access to alkenyl-PhytoFs. Indeed, by exchanging the order of primary alcohol

deprotection, the upper side chain can be introduced first (Scheme 1). To illustrate the flexibility of our strategy, we then turned our attention to the synthesis of alkenyl *ent*-9(*RS*)-12-*epi*-ST-Δ^{10}-13-PhytoF **3**, described below.

Starting from di-protected TBS-acetal **6**[12] the 1,3-acetonide was transformed by Rychnovsky's three-step sequence into the free primary alcohol 1-methyl-1-cyclopropyl hydroxyl derivative **5** in 80% (Scheme 5). The insertion of the upper lateral chain (α-chain) was performed after DMP oxidation by Wittig reaction with phosphonium salt **15** and NaHMDS as a base. The Z-alkene **16** obtained in 40% yield over 2 steps was then hydrogenated using palladium over charcoal to give the corresponding alkane in 91% yield. The regioselective deprotection of the primary alcohol was realized using pyridinium *para*-toluene sulfonate in ethanol and at 0°C. This non-optimized step permitted to obtain the free alcohol in 46% yield (61% based on recovered starting material) and without the undesired minor diastereoisomer removed by flash chromatography. To pursue, the tandem oxidation-HWE reaction with commercially available diethyl(2-oxobutyl)-phosphonate gave the expected enone **17** in 20% yield. The methyl cyclopropyl group was then removed in the presence of N-bromosuccinimide, prior to the reduction of the enone. Finally, intermediate **18**, obtained in 64% yield allowed the synthesis of 1.6 mg of alkenyl *ent*-16*(RS)*-9-*epi*-ST-Δ^{14}-10-PhytoF **3** in 53% yield after TBAF-deprotection of silylated ether and LiOH-saponification of the ethyl ester. We therefore confirmed the flexibility of our strategy with the first synthesis of alkenyl-PhytoF *ent*-16*(RS)*-9-*epi*-ST-Δ^{14}-10-PhytoF **3**, starting from di-protected TBS-acetal **6** and achieved in 13 steps for 1.2% overall yield.



Scheme 5. a) *i*-PrNEt, TMSOTf, CH_2Cl_2, 0°C to RT then reflux; b) Et_2Zn, CH_2I_2, Et_2O, RT; c) K_2CO_3, MeOH, RT, 80% over 3 steps; d) DMP, CH_2Cl_2 , 0°C to RT; e) **15**, NaHMDS, THF, -78°C to RT, 40% over 2 steps; f) H_2, Pd/C, EtOH, RT, 91%; g) PPTS, EtOH, 0°C, 46%, 61% brsm; h) DMP, $NaHCO_3$, CH_2Cl_2/H_2O, 0°C to RT; i) diethyl(2-oxobutyl)phosphonate, $Ba(OH)_2$, THF/H_2O, 20% over 2 steps; j) NBS, THF/H_2O, RT, 83%; k) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0°C to RT, 77%; l) TBAF, THF, RT,74%; m) LiOH, THF/H_2O, RT, 72%. PPTS: pyridinium *para*-toluenesulfonate.

Measurement of phytofurans

To date, phytofurans have not been identified in mammalian samples. In our previous report,[12] the first synthesized *ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1** was found to be present in nuts and seeds (flax, chia, walnut, pine). Flax seed did not show the highest *ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1** level in the findings despite ALA level, the precursor, to be exceeding compared to chia and pine seeds, and walnut. For this reason, flax seed oil (FSO) and flax seed (FS) were chosen as the diet for this study. We report herein the first quantitation of PhytoFs in liver tissues of Sprague Dawley rats fed with FS and FSO.

As shown in Figure 1, substantial amount of PhytoFs were present but only *ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1** and *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3** were detectable, where concentration of PhytoF **3** was higher than PhytoF **1** (2.5:1 ratio) in liver of the control rat. Other PhytoFs **(*R*)-2** and **(*S*)-2** were not measureable in the same liver samples. The absence of the latter compounds is likely due to low abundance that is below the limiting level of detection by the LC-MS/MS. [19] Regardless to this limitation, we showed that the concentration of PhytoF **1** and PhytoF **3** were not elevated in the liver after 28 days of FSO and FS diet compared to control and instead, a lower PhytoF **1** concentration (p=0.009) was found for the FSO group. However, the concentration ratio of **1** to **3** was elevated after FSO diet (1:6.6) compared to FS diet (1:1.3).

We anticipated that an increase in ALA diet would elevate the PhytoFs. Interestingly ALA level was not significantly increased by FSO and FS diet compared to control.[24] In fact, we observed a noticeable negative correlation (p=0.023) between ALA concentration and total PhytoFs (PhytoF **1** *plus* PhytoF **3**) concentration of the FSO group only.[19] This was largely attributed by the concentration of PhytoF **1** of the FSO group (p=0.026) further indicating the metabolism of the molecule is not ALA dependent.

Nonetheless, the low liver PhytoF concentrations were foreseen as the rodents were not under oxidative stress. The generation of PhytoFs *in vivo* occurs under high oxygen concentration or in the presence of excessive ROS. In addition, predisposed antioxidant capacity of FSO and FS may have contributed to the low levels of PhytoFs where a high antioxidant activity was observed in oil extract of flaxseed compared to other common nuts and seeds found in the human diet (data not shown). Overall, we have shown the presence of *ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1** and *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3** in rat liver tissues, and high ALA in the diet without great oxidative stress, did not induce the generation of these PhytoFs.

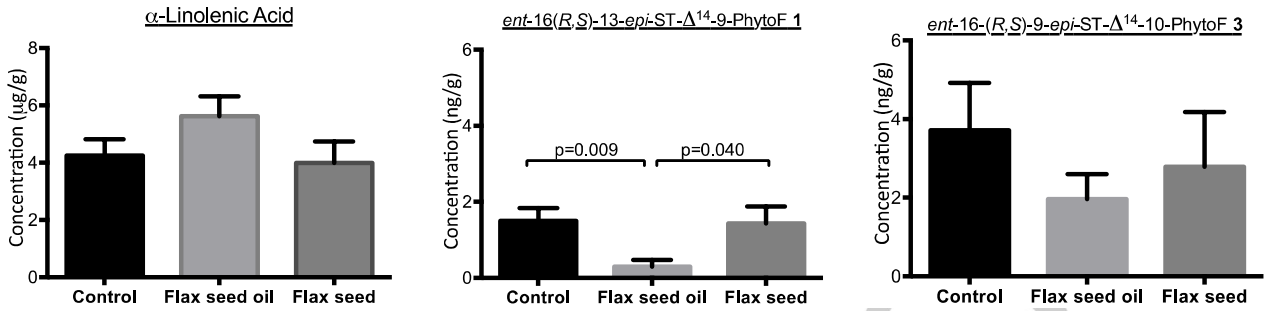


Figure 1. Concentration of α-linolenic acid and phytofurans in liver tissue of Sprague Dawley rats after supplementation. Values of each column are expressed as mean ± SEM, n=6.

Conclusion

In summary, we report the syntheses of *ent*-9(*RS*)-12-*epi*-ST-Δ^{14}-13-PhytoF **(*RS*)-2**, as well as both epimers **(*R*)-2** and **(*S*)-2**, and *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3**. The total syntheses were achieved thanks to a flexible and convergent strategy, and give access to enediol and alkenyl-type of PhytoFs for the first time. This strategy may be useful to complete the synthesis of other polyunsaturated fatty acids metabolites (isofurans, neurofurans and dihomo-isofurans). With these new metabolites in hand, we also highlighted the presence of *ent*-16(*RS*)-13-*epi*-ST-Δ^{14}-9-PhytoF **1** and *ent*-16(*RS*)-9-*epi*-ST-Δ^{14}-10-PhytoF **3** in mammalian liver. Moreover, these metabolites are presently in testing as oxidative stress biomarkers in disease models as well as for their potential role as bioactive compounds in pathogenesis.

Experimental Section

All the chemical experimental data, procedures and NMR spectra are found in the supporting information, as well as the details of the rodent feeding and analysis of liver samples for ALA and PhytoFs.

Typical procedure for the acetonide deprotection:

Preparation of (S)-2-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-ethyltetrahydrofuran-2-yl)-2-(1-methylcyclopropoxy)ethanol 10

To a solution of acetonide **9** (168 mg, 0.509 mmol, 1 eq) in 5 mL of DCM was added freshly distilled *i*-Pr_2NEt (173 µL, 1.18 mmol, 1 eq) and the mixture was cooled to 0 °C. Then, freshly distilled TMSOTf (157 µL, 0.87 mmol, 1.7 eq) was added dropwise and the mixture was warmed to rt and heated under reflux overnight. Then, the mixture was diluted with hexane, filtered through a plug of neutral alumina (activity III; 6% of water), rinsed with hexane/EtOAc: 9/1, and concentrated under reduced pressure.

To the resulting enol ether in 5 mL of Et_2O, with Et_2Zn (1.53mL, 1.53 mmol, 1 M in decane, 3 eq) was added and distilled CH_2I_2 (222 µL, 2.55 mmol, 5 eq) over 10 min. The mixture was stirred overnight at rt. The reaction mixture was diluted with 10 mL of NaOH 1N, extracted with Et_2O (3 x 7 mL), dried over $MgSO_4$, and concentrated under reduced pressure.

The crude oil was treated with 19 mg of K_2CO_3 in 5 mL of MeOH for 15 min at rt, to remove the remaining TMS group. The mixture was quenched with saturated NH_4Cl, extracted with Et_2O (3 x 4 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel was treated with 2% of Et_3N before elution with Pentane/EtOAc: 9/1) gave 1-methyl-1-cyclopropyl (MCP) hydroxyl derivative **10** free from its diastereoisomer (84 mg, 48%) as a colorless oil. $\mathbf{R_f}$= 0.43 (Cyclohexane/EtOAc: 7/3); $\mathbf{[\alpha]_D^{20}}$ ($CHCl_3$)= + 35.8 (c= 1.10^{-2}); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.13-4.06 (m, 1H, CH), 3.95-3.90 (m, 1H, CH), 3.74-3.66 (m, 2H, CH_2), 3.62-3.56 (m, 2H, CH), 2.47 (br, 1H, OH), 1.85-1.80 (m, 2H, CH_2), 1.55-1.34 (m, 5H, included (m, 2H, CH_2 + s, 3H, CH_3)), 0.94 (*t*, *J* = 7.5, 3H, CH_3), 0.89-0.84 (m, 11H, included (s, 9H, CH_3 + m, 2H, CH_2)), 0.45-0.37 (m, 2H, CH_2), 0.07-0.01 (m, 6H, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 88.3 (1C, CH), 79.5 (1C, CH), 78.6 (1C, CH), 75.9 (1C, CH), 63.8 (1C, CH_2), 58.4 (1C, Cq), 38.2 (1C, CH_2), 27.0 (1C, CH_2), 25.9 (3C, CH_3), 22.7 (1C, CH_3), 18.1 (1C, Cq), 14.5 (1C, CH_2), 13.5 (1C, CH_2), 10.6 (1C, CH_3), -4.4 (1C, CH_3), -4.6 (1C, CH_3); **IR** (ν_{max} cm^{-1}): 3448, 29567, 2858, 1463, 1384, 1254, 1110, 1044, 935, 833, 774; **ES+** : 367.23 $[M+Na]^+$; **HRMS** (ESI+): calculated for $C_{18}H_{36}O_4SiNa$ $[M+Na]^+$ 367.2281, found 367.2280.

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Keywords: total synthesis • oxidative stress • fatty acids • Phytofurans • biomarkers

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Phytofurans (PhytoFs) are produced in plants and seeds by non-enzymatic free radical mechanism from α-linolenic acid. The syntheses of phytofurans are described here as well as their quantitation for the first time in liver tissue of rats.

Claire Cuyamendous, Kin Sum Leung, Valérie Bultel-Poncé, Alexandre Guy, Thierry Durand, Jean-Marie Galano, Jetty Chung-Yung Lee,* Camille Oger**

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