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Total Synthesis of the Eight Diastereomers of the Syn-Anti-Syn Phytoprostanes F_1 Types I and II

Siham El Fangour, Alexandre Guy, Valérie Despres, Jean-Pierre Vidal, Jean-Claude Rossi, and Thierry Durand*

UMR CNRS 5074, Université Montpellier I, Faculté de Pharmacie, 3e Etage-15, Avenue Charles Flahault, F-34093 Montpellier Cedex 05, France

thierry.durand@univ-montp1.fr

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Syntheses of the eight enantiomerically pure diastereomers of the syn-anti-syn phytoprostanes F_1 types I and II are described starting from D- and L-glucose. Key steps include Wittig coupling, Horner Wadsworth Emmons (HWE) reactions, and enantioselective reduction of α,β-unsaturated ketones.

Introduction

Isoprostanes (IsoPs) represent a new family of biomarkers for oxidative stress generated from peroxidation of polyunsaturated fatty acids via a free-radical-catalyzed mechanism.[1,2] Higher plants generally do not synthesize the arachidonate precursor required for isoPs formation, but rather utilize α-linolenic acid for the formation of isoprostane F_2-like compounds which have been termed phytoprostanes F_1 (PPF_1).[3] Jasmonates are established plant signaling compounds inducing defense responses.[4] Preliminary data indicate that phytoprostanes also induce phytoalexins in a variety of plant species, suggesting a possible function of phytoprostanes as mediators of plant defense reactions in response to oxidative stress.[5,6] Since we were interested in assessing the physiological activities of each of the phytoprostanes F_1 types I and II, we found it more attractive to obtain sufficient quantities by chemical synthesis.

In 2003, we published a note describing the syntheses of *ent*-PPF_1 type I **1** and its 16-epimer **2**.[7] We now report the syntheses of all eight diastereomers of the syn-anti-syn PPF_1 types I and II starting from cyclopentane precursors **3** and **3′**, obtained from D- and L-glucose (Scheme 1).

Results and Discussion

The Phytoprostanes F_1 types I and II were identified from autoxidation of α-linolenic acid by Mueller.[3] To confirm the stereochemistry of the eight enantiomerically pure diastereomers of phytoprostanes F_1 types I and II, and also to screen the physiological activity of these phytoprostanes, we have developed a general and flexible strategy from our common intermediate syn-anti-syn cyclopentane precursors **3** and **3′** (Scheme 1).

Synthesis of *ent*-Phytoprostane F_1 Type I 1 and 2 from D-Glucose. The syntheses of *ent*-PPF_1 type I **1** and its 16(*S*) epimer **2** from the cyclopentane percursor **3** is shown in Schemes 2−4 and was published as a note.[7] The first 9 steps leading to cyclopentane alkoxyester **3** were achieved in 27% overall yield by using our iodo pathway.[8]

The phosphorus synthon **7** was selected for the introduction of the upper chain of the PPF_1 type I, and was prepared by using the procedure outlined in Scheme 2.

The first step is the opening of the ϵ-caprolactone under acidic conditions leading to the corresponding hydroxy methyl ester **5**. Subsequent halogenation gave iodo ester **6**, which was transformed into the phophonium salt **7** in 98% yield in the presence of PPh_3 and a catalytic amount of K_2CO_3.

The introduction of the upper chain (Scheme 3) was achieved by using the above phosphonium salt **7**, which

* Address correspondence to this author. Phone: 33-4-67-54-86-23. Fax: 33-4-67-54-86-25.

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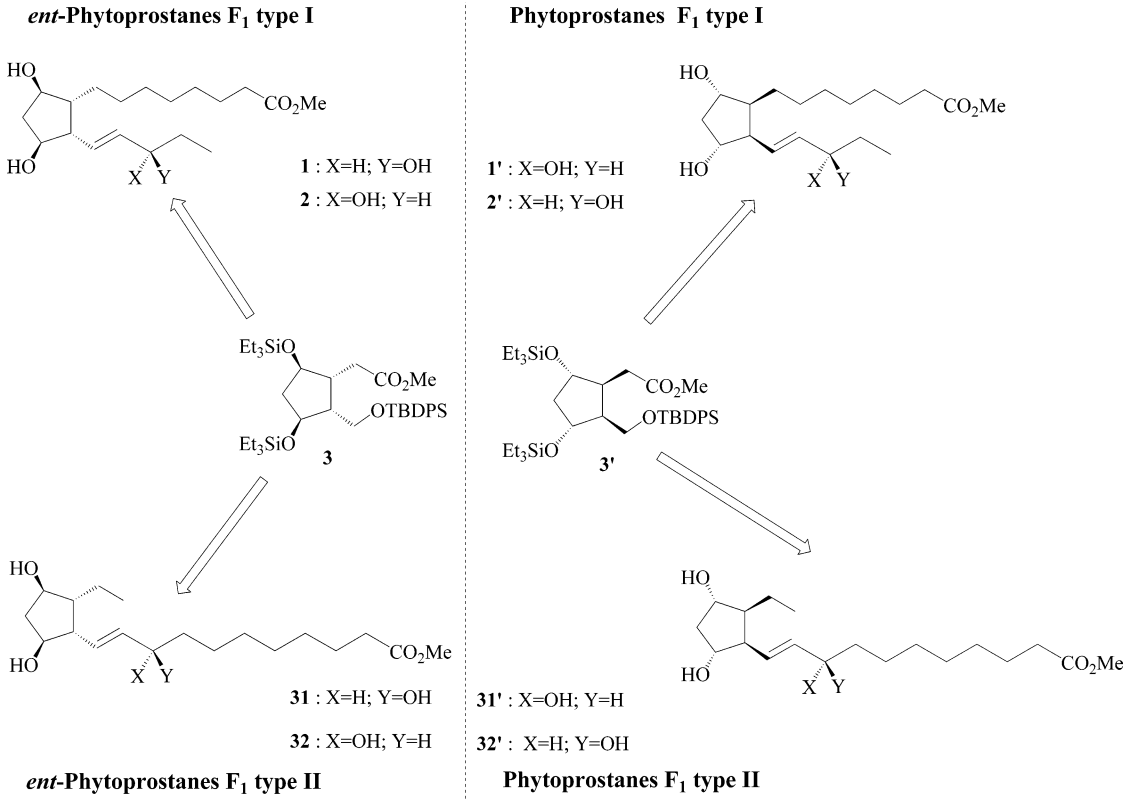
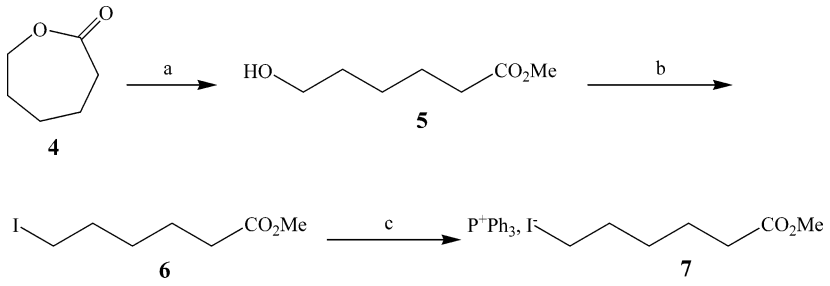
SCHEME 1. Retrosynthetic Scheme of the Phytoprostanes F_1 Types I and II and Enantiomers



SCHEME 2. Synthesis of Phosphonium Salt 7[a]



[a] Reagents and conditions: (a) MeOH, H_2SO_4, rt, 30 min, 94%. (b) I_2, PPh_3, imidazole, CH_2Cl_2 −10 °C, 2 h, 61%. (c) PPh_3, CH_3CN, 1% K_2CO_3, 18 h, 98%.

reacts with the aldehyde **8** to afford the pure (Z)-enic ester **9** in 70% yield. No trace of trans compound could be detected by ^{13}C and ^{1}H NMR analyses.

The following reduction of the cis double bond of **9** under hydrogen atmosphere gave the diol **10**, which was protected in the presence of benzoyl chloride in pyridine in 77% yield.

The next steps were first a selective deprotection of the *tert*-butyldiphenylsilyl ether **11** with hydrogen chloride,[11] a Dess−Martin oxidation[12] of **12**, followed by a HWE coupling reaction in the presence of dimethyl-2-oxobutylphosphonate **14**,[10] yielding the trans-α,*β*-enone ester **15** in 60% overall yield from the alcohol **12**. The relative configurations of the chiral centers were confirmed by homonuclear ^{1}H steady-state-difference NOE spectroscopy (DNOES) experiments (vide infra).

The diastereoselective reduction of the C16 keto group in **15** with the chiral reducing agents[13] (*S*)- and (*R*)-BINAL-H gave the desired pure 16(*S*) derivative **16** and its 16(*R*) epimer **17** in 85% and 87% yield, respectively (Scheme 4).

Finally, saponification of ester functions, followed by treatment with an excess of CH_2N_2, afforded the desired *ent*-PPF_1 type I **1** and its 16 epimer **2** in 20% and 19% yields, respectively, from **3**, after 9 steps.

Synthesis of *ent*-Phytoprostanes F_1 Type II 31 and 32 from D-Glucose. Since the PPF_1 type II diaster-

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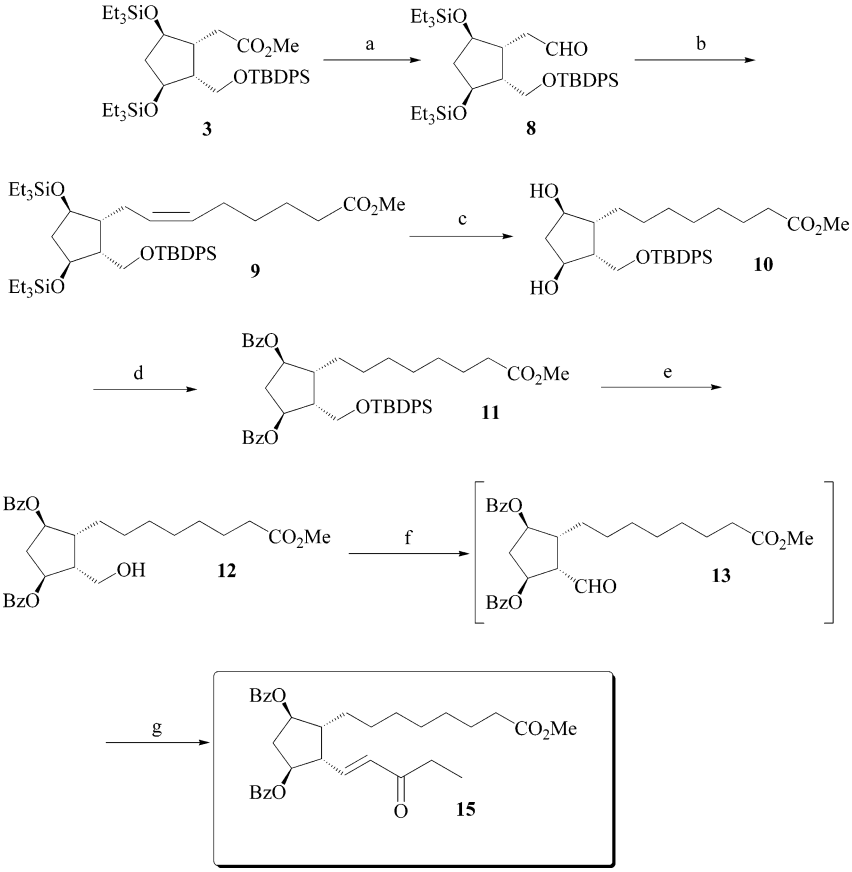
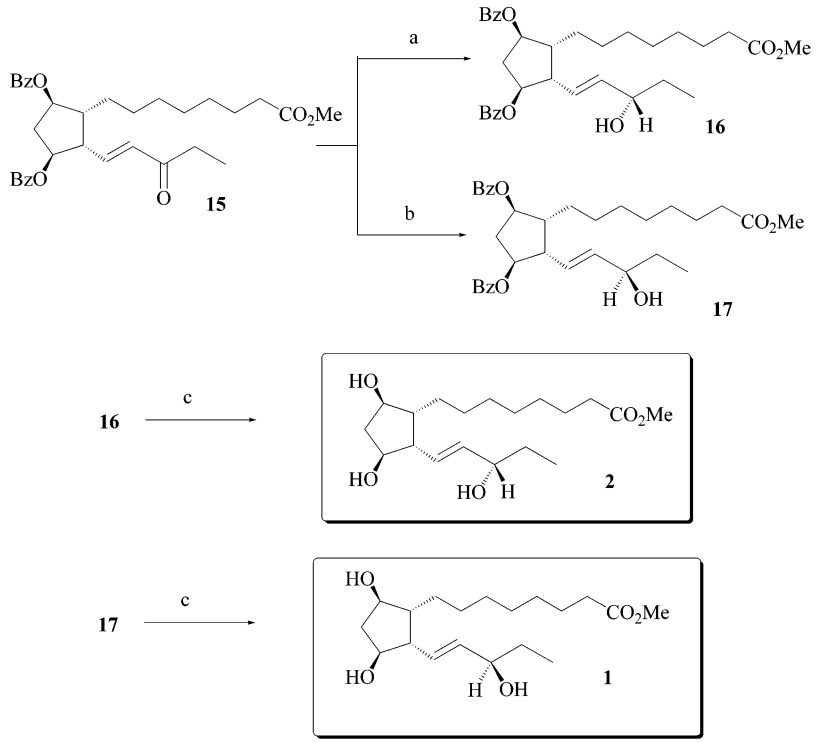
(13) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

SCHEME 3. Synthesis of Precursor 15[a]



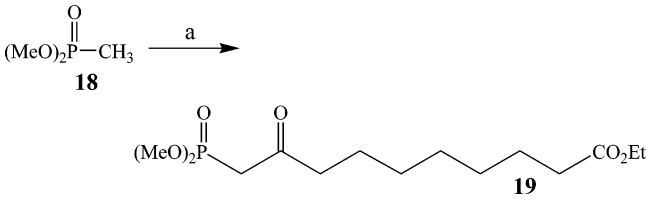
[a] Reagents and conditions: (a) 1.1 equiv of DIBAL-H (1 M in toluene), toluene, −80 °C, 30 min, 97%. (b) 2.25 equiv of methoxycarbonylpentyltriphenylphosphonium iodide, 2.2 equiv of $KN(SiMe_3)_2$, THF, −80 to 20 °C, 2 h, 70%. (c) H_2, Pd/C 10%, EtOH, 4 h, 98%. (d) 3 equiv of BzCl, pyridine, 20 °C, 1 h, 77%. (e) HCl 3% in MeOH, 20 °C, overnight, 80%. (f) Periodinane, CH_2Cl_2, rt, 2 h. (g) 3.3 equiv of dimethyl 2-oxobutylphosphonate **14**, 3 equiv of $NaN(SiMe_3)_2$, THF, 20 °C, 30 min, 60%.

SCHEME 4. Synthesis of *ent*-Phytoprostanes F_1 Type I 1 and 2[a]



[a] Reagents and conditions: (a) (*S*)-BINAL-H, −100 °C, 2 h, 85%. (b) (*R*)-BINAL-H, −100 °C, 2 h, 87%. (c) 1 N NaOH, THF−MeOH, rt, 1 h, then CH_2N_2 91% for **1** and 93% for **2**.

SCHEME 5. Synthesis of β-Ketophosphonate 19[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) diethylazelate, −78 °C, 3.5 h, 57%.

TABLE 1. $[\alpha]^{20}_D$ (1×10^{-2}, MeOH) for All Diastereomers of PPF_1 Types I and II

diastereomer	$[\alpha]^{20}_D$	$[\alpha]^{20}_D$	diastereomer
ent-PPF_1 type I (**1**)	−30	+25	PPF_1 type I (**1′**)
ent-16-*epi*-PPF_1 type I (**2**)	−13	+14	16-*epi*-PPF_1 type I (**2′**)
ent-PPF_1 Type II (**31**)	−26	+23	PPF_1 type II (**31′**)
ent-9-*epi*-PPF_1 type II (**32**)	−7	+7	9-*epi*-PPF_1 type II (**32′**)

eomers had never previously been prepared, we have performed the synthesis of these type II PPF_1 as shown in Schemes 6 and 7.

The β-ketophosphonate **19** was selected and prepared by using the following procedure published by Miftakhov et al.[14] and outlined in Scheme 5. The lithio derivative of dimethyl methylphosphonate **18** reacts with the diethylazelate to afford the corresponding β-ketophosphonate **19** in 57% yield.

The alkoxyester **3** was converted into the primary alcohol **20** by treatment with lithium aluminum hydride (LAH) in anhydrous ether in 94% yield (Scheme 6). The following protection, using toluenesulfonyl chloride, led to the corresponding tosylate **21** in 97% yield, which was reduced, once again, by LAH in refluxing ether to afford the methyl group of the α chain in 91% yield.

The introduction of the ω chain of the PPF_1 type II started by the regioselective deprotection of the bistriethylsilyloxy ether in the presence of *tert*-butyldiphenylsilyl ether, using ammonium fluoride in MeOH/THF to afford the diol **23** in 82% yield. The protection of the hydroxyl functions of **23** with benzoyl chloride in dry pyridine gave the diester **24** in 94% yield.

The *tert*-butyldiphenylsilyl ether **24** was converted into the alcohol **25** by treatment with a solution of 3% hydrogen chloride[11] in methanol/diethyl ether (1:1). Oxidation of the alcohol **25** with the Dess−Martin periodinane[12] provided the unstable aldehyde **26**, which was immediately used in the next step without purification.

The condensation of **26** with dimethyl 9-(ethoxycarbonyl)-2-oxononylphosphonate **19**,[14] in the presence of sodium hexamethyldisilyl amide, in anhydrous THF at room temperature, afforded the trans-α,β-enone ester **27** in 79% overall yield from alcohol **25** (Scheme 7). During the HWE reaction, it was not possible to avoid the formation of compound **28** derived from the elimination of the benzoyl group at C13, as already observed in other

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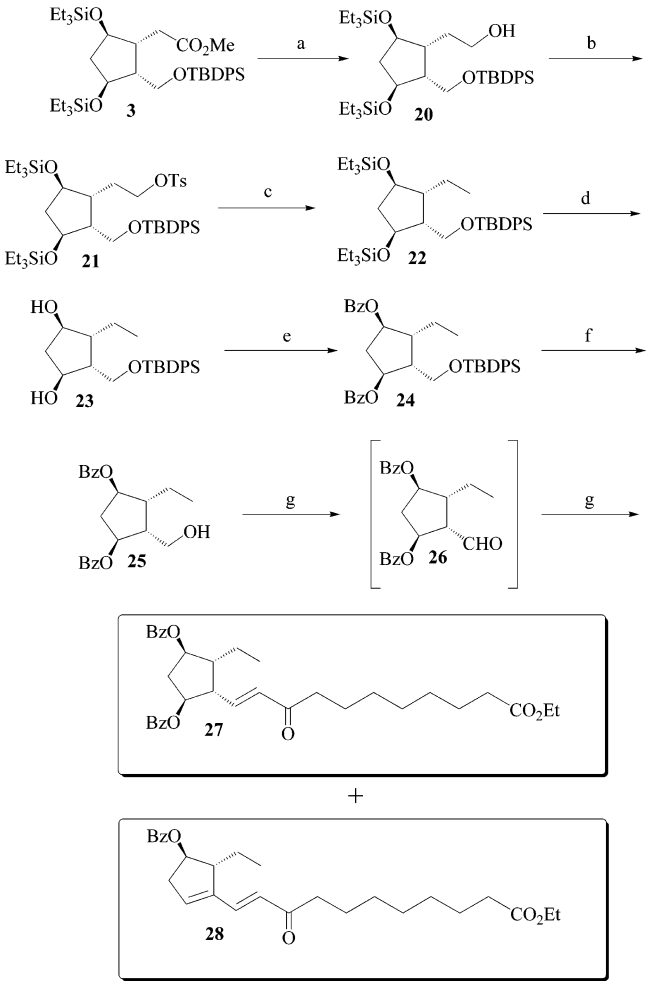
SCHEME 6. Synthesis of Precursor 27[a]



[a] Reagents and conditions: (a) 1.5 equiv of LAH (1 M in THF), diethyl ether, −78 °C, 1 h, 94%. (b) DMP, TEA, 1.5 equiv of TsCl, CH_2Cl_2, rt, 2 h, 97%. (c) 1.1 equiv of LAH (1 M in THF), diethyl ether, reflux, 91%. (d) 4 equiv of NH_4F, MeOH/THF (7:3), reflux, 2 h, 82%. (e) 3 equiv of BzCl, pyridine, rt, 1 h, 94%. (f) HCl 3% in MeOH/Et_2O (1:1), rt, overnight, 97%. (g) Periodinane, CH_2Cl_2, rt, 30 min. (h) 3 equiv of dimethyl 9-(ethoxycarbonyl)-2-oxononylphosphonate **19**, 2.8 equiv of $NaN(SiMe_3)_2$, THF, rt, 1 h, 79%.

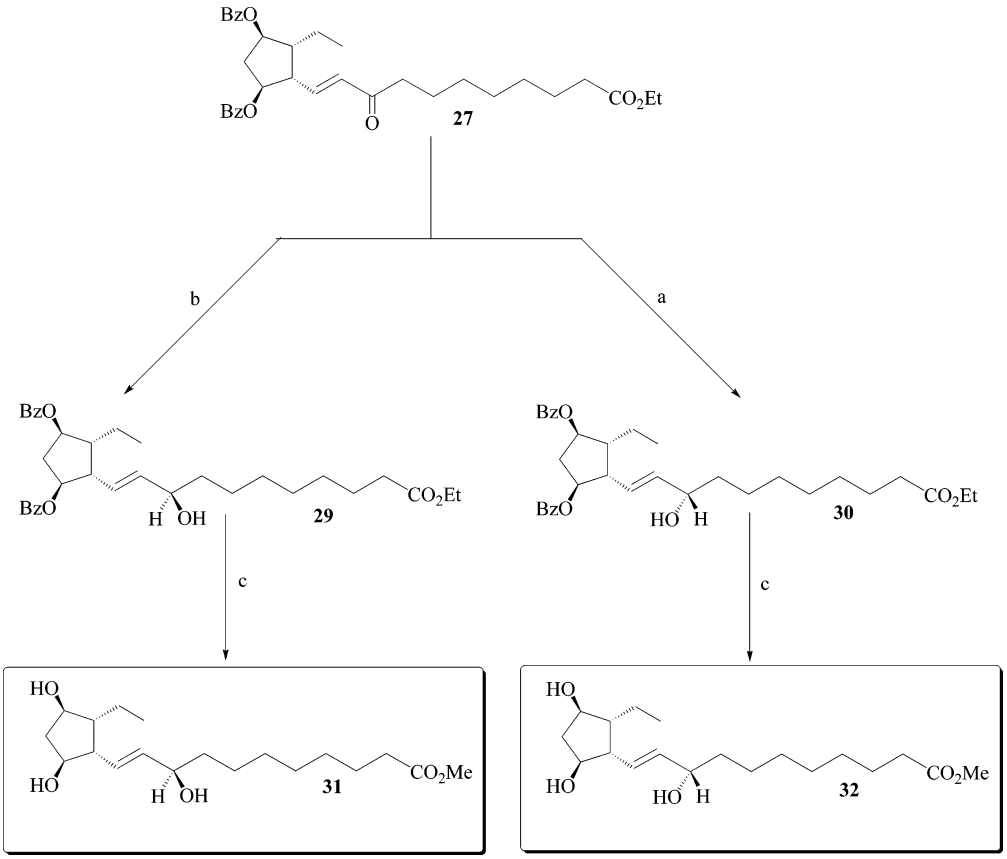
series. The relative configurations of the chiral centers were confirmed by homonuclear ^1H steady-state-difference NOE spectroscopy (DNOES) experiments (vide infra).

The diastereoselective reduction of the C9 keto group in **27** with the chiral reducing agents[13] (*R*)- and (*S*)-BINAL-H gave the desired pure 9(*R*) derivative **29** and its 9(*S*) epimer **30** in 82% and 89% yield, respectively (Scheme 7).

Finally, deprotection of the benzoyl groups in **29** and **30**, in the presence of 1 N NaOH at room temperature, followed by excess of CH_2N_2, afforded the desired *ent*-PPF_1 type II **31** and its 9 epimer **32** in 38% and 42% yields, respectively, from the cyclopentane alkoxyester **3**, in 10 steps.

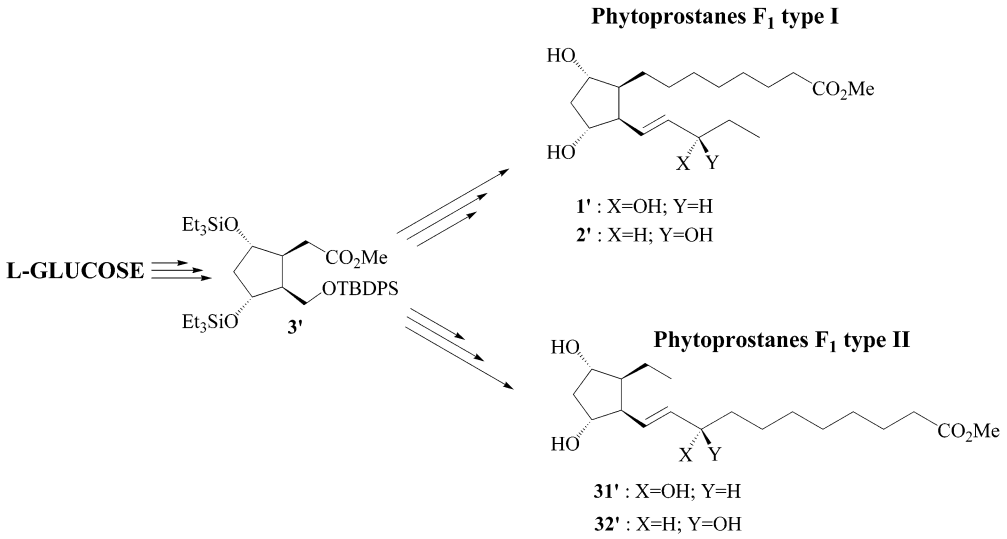
Syntheses of Phytoprostanes F_1 Types I and II 1′, 2′, 31′, and 32′ from L-Glucose. All reactions of D-glucose have been duplicated with L-glucose leading to

SCHEME 7. Syntheses of *ent*-Phytoprostanes F_1 Type II 31 and 32[a]



[a] Reagents and conditions: (a) (*S*)-BINAL-H, −100 °C, 2 h, 89%. (b) (*R*)-BINAL-H, −100 °C, 2 h, 82%. (c) 1 N NaOH, THF/MeOH, rt, 1 h, then CH_2N_2 96% for **31** and 94% for **32**.

SCHEME 8. Syntheses of Phytoprostanes F_1 Type I and Type II 1′, 2′, 31′, and 32′



the enantiomerically pure PPF_1 types I and II diastereomers **1′**, **2′**, **31′**, and **32′** as shown in Scheme 8.

The physicochemical properties of the enantiomerically pure PPF_1 types I and II diastereomers **1′**, **2′**, **31′**, and **32′** were identical with those of **1**, **2**, **31**, and **32** except for the sign of specific optical rotation, as mentioned in Table 1.

Structural Determination of α,β-Enones 15, 15′, 27, and 27′. The relative configurations of chiral centers were confirmed by homonuclear ^1H steady-state-difference NOE spectroscopy (DNOES) experiments as shown in Figure 1.

For compound **15**, the relative cis configuration of the protons 11-H, 1-H, 4-H, and 6-H was determined by

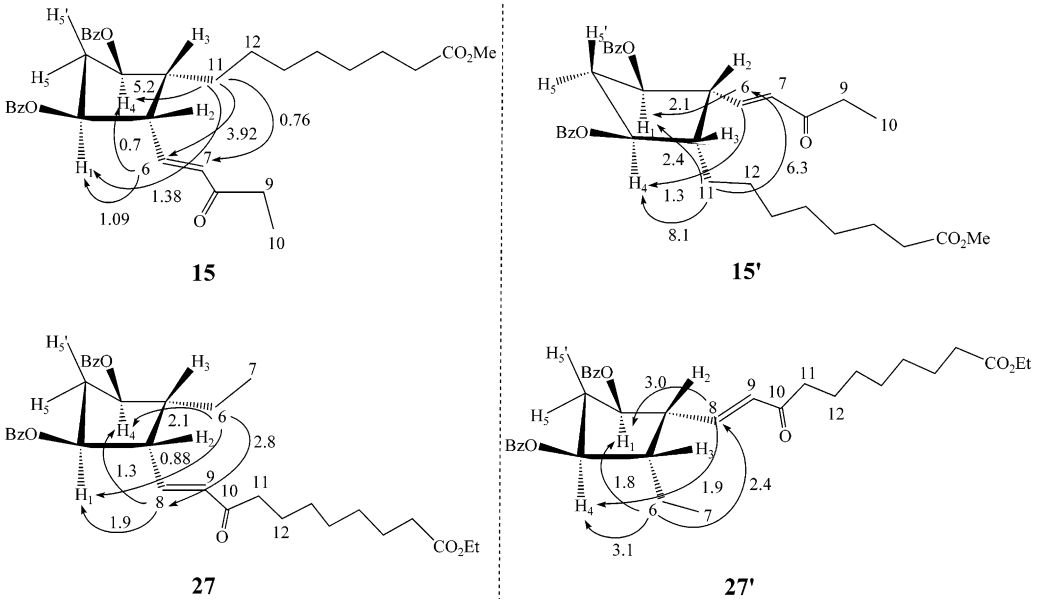


FIGURE 1. Observed NOEs resulting from irradiation of main protons are indicated with solid lines.

irradiation of 11-H, which induced NOEs of 1.3% on 1-H, 3.9% on 6-H, 5.2% on 4-H, and 0.7% on 7-H. Irradiation of 6-H induced NOEs of 1.0% on 1-H and 0.75% on 4-H. Similar results were observed for compound **15′**, the enantiomer of compound **15**.

Irradiation of 11-H induces a NOE of 6.3% on 6-H, 2.4% on 1-H, and 8.1% on 4-H, while irradiation of 6-H induces a NOE of 2.1% on 1-H and 1.3% on 4-H. These observations verify the relative cis configuration of the protons 1-H, 4-H, 6-H, and 11-H.

Concerning **27**, the irradiation of 6-H showed a NOE of 2.8% on 8-H, 2.1% on 4-H, and 0.88% on 1-H. Likewise, the irradiation of 8-H induces a NOE of 1.9% on 1-H and 1.3% on 4-H. These observations allow one to check the relative cis configuration of protons 1-H, 4-H, 6-H, and 8-H.

For compound **27′**, the enantiomer of compound **27**, the relative cis configuration of the protons 1-H, 4-H, 6-H, and 8-H was determined by irradiation of 6-H, which induced NOEs of 3.1% on 4-H, 1.8% on 1-H, and 2.4% on 8-H. Irradiation of 8-H induced NOEs of 3.0% on 1-H and 1.9% on 4-H.

Conclusion

In conclusion, the first synthesis of the eight enantiomerically pure diastereomers of the syn-anti-syn phytoprostanes F_1 types I and II has been accomplished starting form enantiopure alkoxyesters **3** and **3′**. Further studies of other phytoprostanes or analogues, as well as the assessment of individual biological activities in human and/or plant, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures for syntheses and ^{1}H NMR and ^{13}C NMR data for compounds **5**−**7**, **8**−**17**, **19**, **20**−**30**, and the target compounds **1**, **2, 31, 32, 1′**, **2′**, **31′**, and **32′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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