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Total Synthesis of the Four Enantiomerically Pure Diasteroisomers of the Phytoprostanes E_1Type II and of the 15-E_{2t}-Isoprostanes

Edith Pinot, Alexandre Guy, Anais Fournial, Laurence Balas, Jean-Claude Rossi, and Thierry Durand*

Institut des Biomolécules Max Mousseron, IBMM, UMR CNRS 5247, Université Montpellier I, Université Montpellier II, Faculté de Pharmacie, 15. Av. Ch. Flahault, F-34093 Montpellier cedex 05, France

Thierry.Durand@univ-montp1.fr

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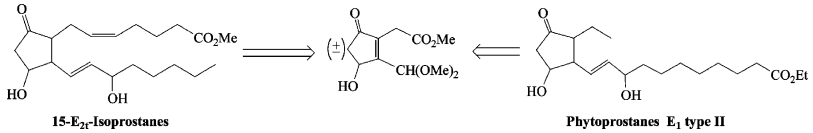

Syntheses of the four enantiomerically pure diastereoisomers of the phytoprostanes E_1 type II and 15-E_{2t}-isoprostanes (**1**−**4**) are described. The key steps included the preparation of the Freïmanis (±)-hydroxycyclopentenone **5**, enzymatic resolution of this racemic hydroxycyclopentenone, Wittig and Horner−Wadsworth−Emmons (HWE) coupling reactions and finally enantioselective reductions.

Introduction

Mammalian isoprostanes (IsoP) and plant based phytoprostanes (PP) are formed by a free radical mediated, nonenzymatic mechanism from arachidonic acid and α-linolenic acid, respectively (Figure 1).[1,2]

Most of the current knowledge concerning the biological actions of IsoPs is limited to the F_2-series where 15-F_{2t}-IsoP has been most studied, together, albeit to a lesser extent with 15-E_{2t}-IsoP.[3,4] In contrast to PGE_2 and PGF_2, which exhibit opposite biological effects, 15-E_{2t}-IsoP is also a vasoconstrictor and more potent than 15-F_{2t}-IsoP in systemic and pulmonary vessels. Its activity is mediated through the TP-receptor, and EP_3-receptor activation in the pulmonary vasculature.[5,6] Furthermore, 15-E_{2t}-IsoP may also induce relaxation through EP-receptors.[7]

In plants, several classes of PPs are constitutively present[8] and, notably, their levels increase in a variety of conditions with enhanced free radical generation. In 2005, Traidl-Hoffmann et al. proposed that pollen-derived PPEs act as regulators that modulate human dendritic cell (DC) function in a fashion that favors Th2 cell polarization.[9] Two recent studies by Mariani et al. and Gutermuth et al. confirmed that PPE_1 dose-dependently inhibited LPS-induced IL-12p70 of DCs and were identified to be one of the key factors leading to the Th2-polarizing potential of aqueous pollen extracts.[10,11]

To fully assess the physiological activities of each of the enantiomerically pure PPE_1 type II and 15-E_{2t}-IsoPs, we aimed to obtain sufficient quantities by chemical synthesis.

Over the past 10 years, we have developed a general strategy toward the synthesis of F-IsoP, neuroprostane (NeuroP) and PP, using a radical cyclization that serves to construct the required tetrasubstituted cyclopentane ring whereby the hydroxyl groups and the carbon side chains are either *syn*−*anti*−*syn* or all *cis*.[12,13] However, using this method, we were unable to access the E and D type because the protection of the hydroxyl groups was not orthogonal. We have recently reported a synthesis of the PPB_1 type I and II starting from 2-(8-carboxyoctyl)furan and 2-propylfuran.[14] We now wish to report the syntheses of other classes of IsoP and PP, namely the four diastereoisomers of

* Corresponding author. Tel: 33-4-67-54-86-23. Fax: 33-4-67-54-86-25.

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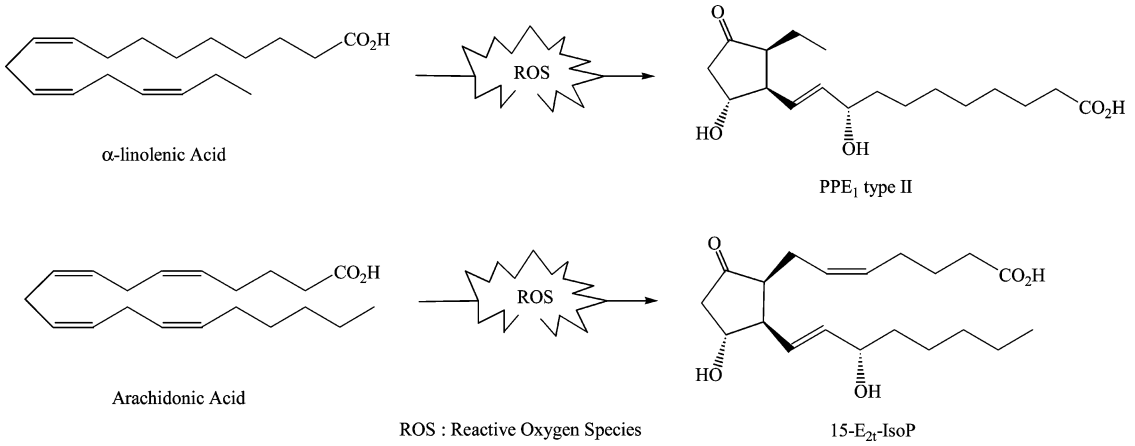
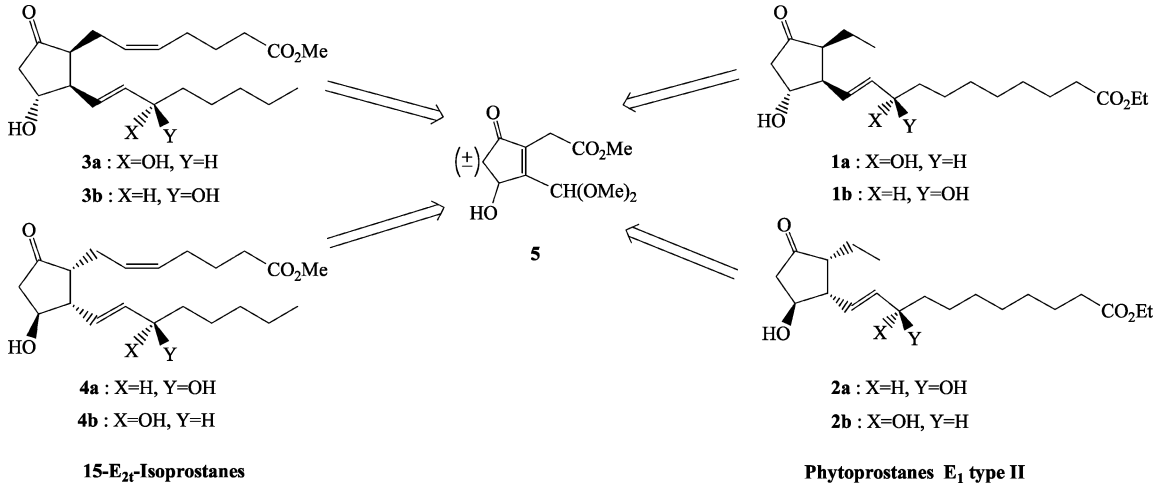


FIGURE 1. Phytoprostane E_1 and isoprostane E_2 pathway.

SCHEME 1. Retrosynthetic Scheme of the PPE_1 Type II and 15-E_{2t}-IsoPs



PPE_1 type II **1**, **2** and 15-E_{2t}-IsoPs **3**, **4** starting from 4-hydroxycyclopentenone **5** (Scheme 1).

Results and Discussion

Currently, the synthesis of PPE_1 type II has not been reported in the literature. In contrast, two syntheses of 15-E_{2t}-IsoPs have been reported by Nakamura and Sakai,[15] and more recently the PPE_1 type I, the 15-E_{1t}- and 15-E_{2t}- IsoP were synthesized by Rodriguez and Spur.[16,17]

The key steps of our procedure rely on the regioselective fragmentation of the furan ring present in derivative **7** and its subsequent cyclization, leading to the 4-hydroxy-2-cyclopentenone **5** (Scheme 2).

Synthesis of 4-Hydroxycyclopentenones (*S*)-5 and (*R*)-5 from *trans*-3-(2-Furyl)acrylic acid. The preparation of the racemic 4-hydroxycyclopentenone **5**, was achieved from commercially available *trans*-3-(2-furyl)acrylic acid as starting material, using our previously described procedure.[18,19]

After a Pd-catalyzed alkenyl reduction under a hydrogen atmosphere, the introduction of the formyl group at C5 was achieved using a Vilsmeyer reaction thereby affording aldehyde **7**. The protection of the aldehyde in the presence of methyl orthoformate, followed by an electrophilic addition with MeOH/Br_2 under basic conditions afforded the bis-acetal **9**. This latter compound underwent an "aldol-type" cyclization under acidic hydrolysis and basic treatment leading to the 3-hydroxycyclopentenone **10**. Migration of the hydroxyl group with double bond formation using chloral under basic conditions led to the racemic 4-hydroxycyclopentenone **5** in 28% yield after four steps. Notably, all these reactions were performed on multigram scale (50−100 g) and ultimately afforded >20 g of *rac*-**5**.[20]

Using our previously optimized conditions (CAL-B, vinyl acetate in hexane)[18] for this enzymatic kinetic resolution, we obtained 45% (*R*)-acetate **11** and 49% alcohol (*S*)-**5** (94% ee, determined by NMR studies with the help of Mosher's method). In addition, enzymatic hydrolysis of the (*R*)-acetate **11**, with

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(19) Experimental procedures of compounds **7**−**10** mentioned in the text, were reported in the Supporting Information. In fact, these procedures were never published in English, but only in Russian (Loza, E.; Lola, D.; Freimanis, J.; Turovskis, I.; Gavars, M.; Liepipa, A. *Latvijas PSRZA vestis, Chem. Ser.* **1985**, *4*, 465−472).
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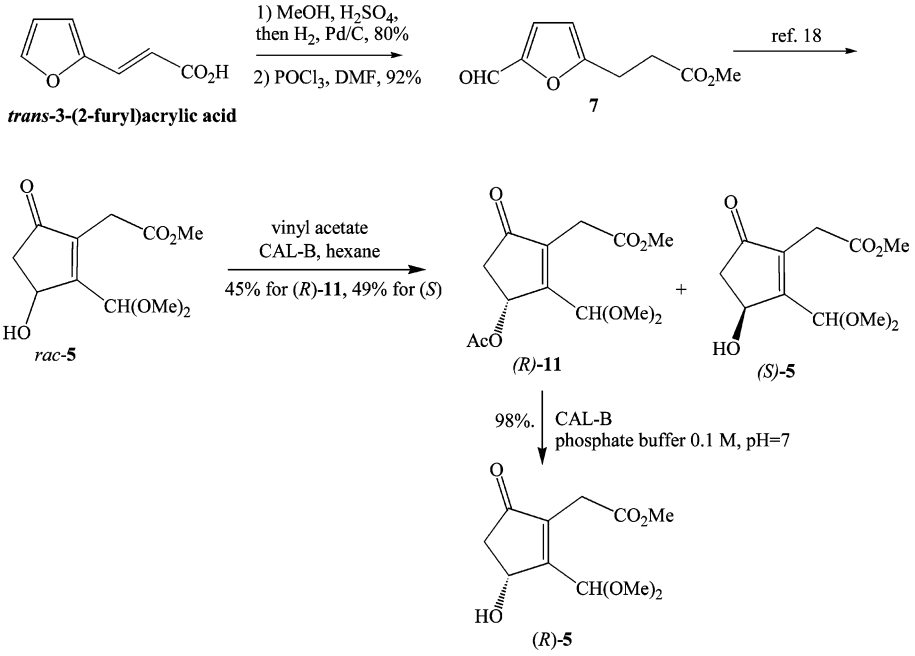
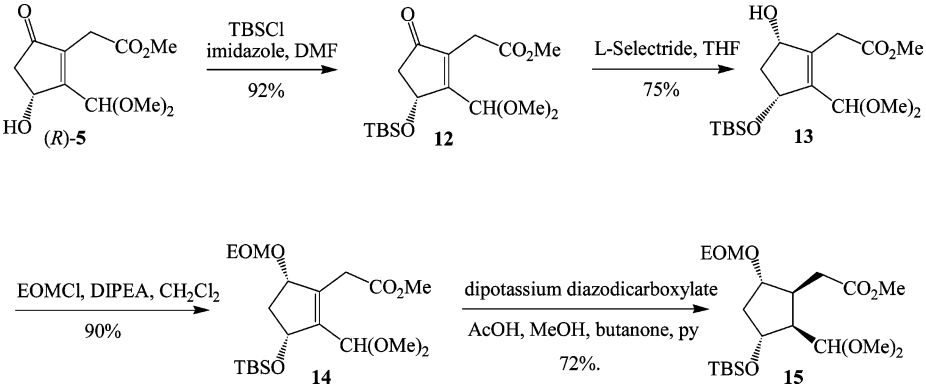
SCHEME 2. Synthesis of Precursor *rac*-5 and Enzymatic Kinetic Resolution of 4-Hydroxycyclopentenone *rac*-5



SCHEME 3. Synthesis of Tetrasubstituted Cyclopentane Precursor 15



the CAL-B in the presence of a phosphate buffer (0.1 M) at pH=7, led to the (*R*)-alcohol **5** with 94% ee in 98% yield.

Synthesis of PPE_1 Type II 1a,b and 2a,b from 4-Hydroxycyclopentenones (*R*)-5 and (*S*)-5. The syntheses of PPE_1 type II **1a,b** and **2a,b** were subsequently performed from 4-hydroxycyclopentenones (*R*)-**5** and (*S*)-**5** as shown in Schemes 3−5.

The protection of the hydroxyl group was accomplished with TBSCl, imidazole/DMF in 92% yield. Our first attempts to reduce the enone **12**, under the reaction conditions (H_2/Pd(C), MeOH) reported by Freïmanis[20] failed. We obtained a complex mixture of inseparable hydrogenation products, and traces of partial hydrogenolysis of the acetal group to the corresponding methyl ether. We, therefore, considered protection of the carbonyl functionality, in an attempt to decrease epimerization, using both a methyl thioacetal and an isopropylidene acetal. Unfortunately, all our attempts at hydrogenation, using palladium or rhodium catalysts, failed and we obtained inseparable hydrogenation products. Consequently, we decided to reduce the carbonyl group, using L-Selectride in THF. Under these conditions **13** was obtained with high stereoselectivity (95:5). These two diasteroisomers were separable by flash chromatography (cyclohexane/EtOAc, 1−10%, with 2% Et_3N). The orthogonal protection of the hydroxyl group with ethoxymethyl chloride (EOMCl), (diisopropylethyl)amine (DIPEA), in CH_2Cl_2 led to the protected derivative **14** in 90% yield. Another important challenge in this strategy proved to be the reduction of **14** to **15**. All our first attempts with palladium or rhodium catalysts failed again. However, we eventually obtained **15** in an excellent yield with complete diastereoselectivity using diimide, generated in situ from dipotassium diazodicarboxylate and acetic acid in MeOH. Interestingly, it has been reported that diimide[21] reacts only slowly with tetrasubstituted alkenyl derivatives. This led us to optimize the formation of **15** by controlling the addition speed and by adding butanone in the reaction mixture to remove the hydrazine formed in situ. Only under these controlled conditions could **15** be obtained in good yield with the required *syn-anti-syn* orientation. Theoretically the *syn*−*exo* reduction is favored,[21] but in our case, the *syn*−*anti*−*syn* orientation of **15** could be explained by electronic factors leading preferentially to an *anti*−*exo* reduction as reported in the literature.[22]

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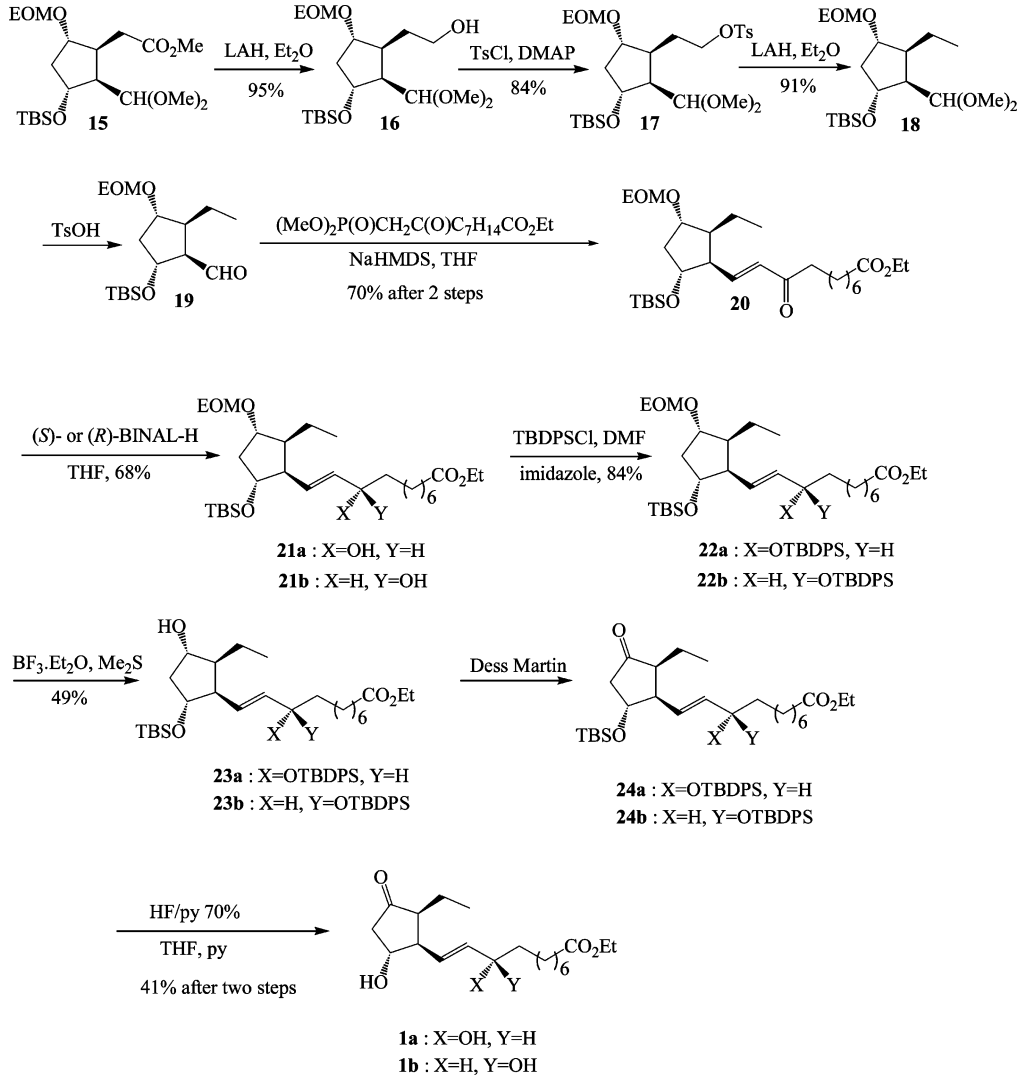
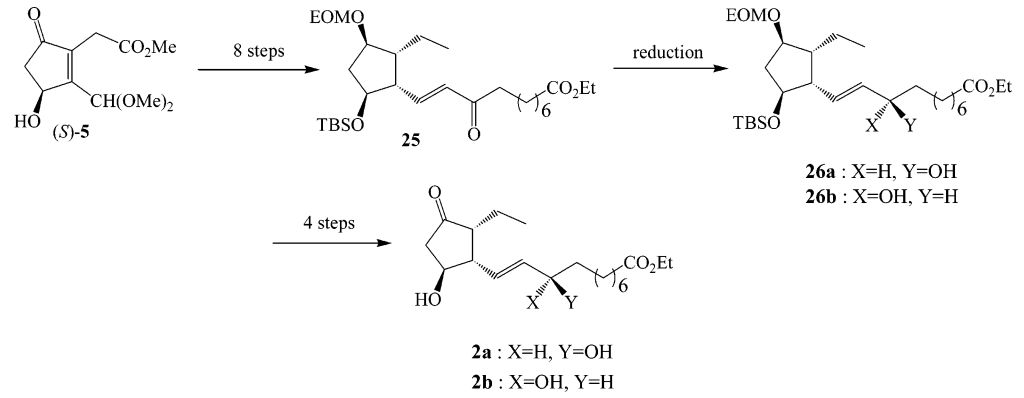
SCHEME 4. Synthesis of PPE$_1$ Type II 1a and Its 9-Epimer 1b

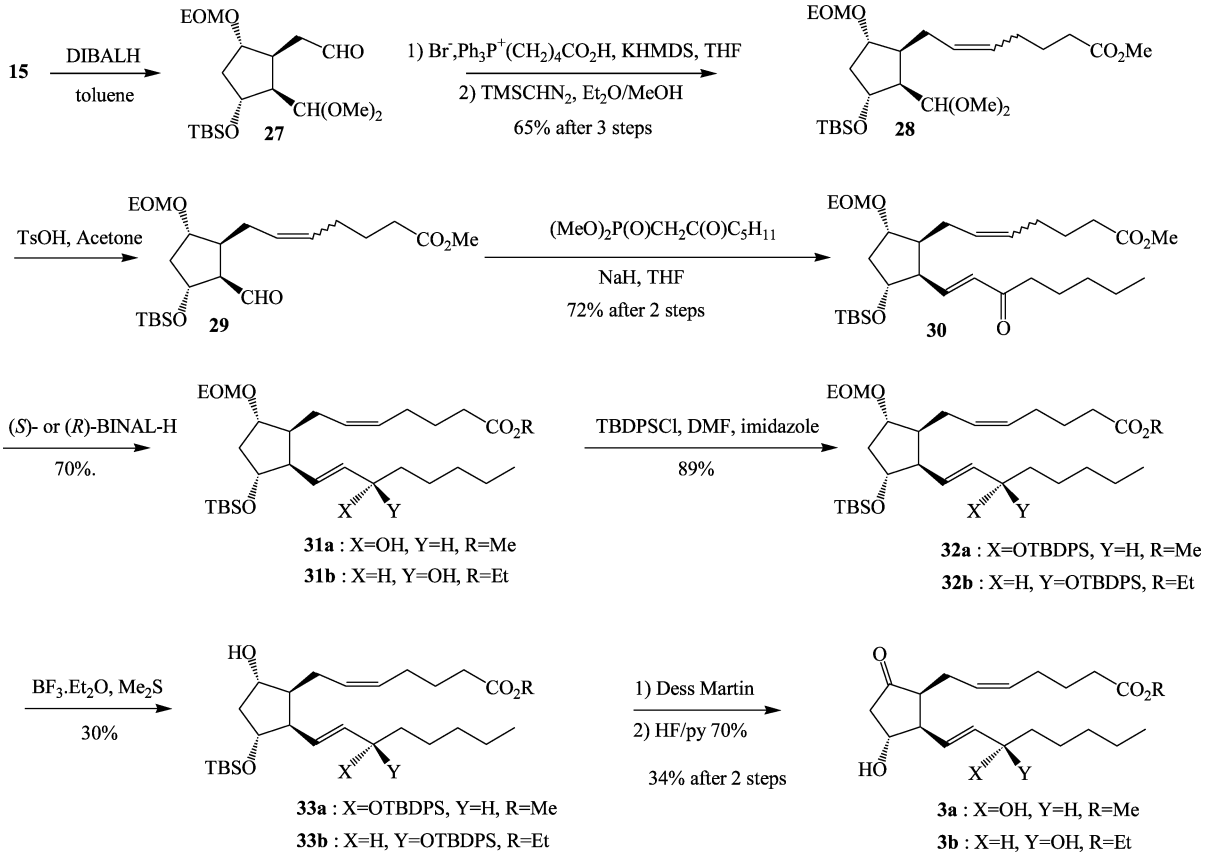


SCHEME 5. Synthesis of *ent*-PPE$_1$ Type II 2a and Its 9-Epimer 2b from 4-Hydroxycyclopentenones (*S*)-5



The methyl ester **15** was converted into the primary alcohol **16** (Scheme 4) in 95% yield by treatment with lithium aluminum hydride (LAH) in anhydrous ether at room temperature. Toluenesulfonyl chloride treatment led to the formation of tosylate **17** in 84% yield, which was subsequently reduced with LAH in anhydrous ether to afford the ethyl group constituting the α chain of the PPE$_1$ type II in 91% yield. The acetal **18** was converted by acidic hydrolysis with TsOH in acetone into the aldehyde **19**, which was used immediately in the next step. It was found that the reaction periods needed to be very short, to avoid the deprotection of the TBS group. The condensation of **19** with dimethyl[9-(ethoxycarbonyl)-2-oxononyl]phosphonate[13] in the presence of sodium (hexamethyldisilyl)amide, in anhydrous THF, afforded the *trans*-α,*β*-enone ester **20** in 70% yield

SCHEME 6. Syntheses of 15-E_{2t}-IsoP 3a and Its 15 Epimer 3b



after two steps. Neither detrimental elimination nor epimerization was observed during this HWE reaction, as reported previously in other series.[23]

The diastereoselective reduction of the C9 keto group in **20** with the chiral reducing agents[24] (*S*)- or (*R*)-BINAL-H gave the desired enantiopure 9(*S*) derivative **21a** and its 9(*R*) epimer **21b**, respectively, in 68% yield (Scheme 4). This type of diastereoselective reduction constitues a standard approach to the preparation of both isoprostanes and prostaglandins, and its stereochemical outcome is well understood. Protection of the hydroxyl groups **21a** and **21b**, using *tert*-butyldiphenylchlorosilane (TBDPSCl), imidazole in DMF afforded the corresponding protected alcohols **22a** and **22b** in 84% and 81% yields, respectively. Unfortunately, our preliminary attempts for the deprotection of the ethoxymethyl (EOM) group, using chlorocatecholborane[25] or bromocatecholborane[26,27] led to a mixture of inseparable hydroxyl derivatives. We then tried $TMSBr/CH_2Cl_2$,[28] $PPTS/MeOH/CH_2Cl_2$,[29] $InI_3/EtOAc$[30] and $FeCl_3/Ac_2O$[31] without any more success. Finally, the use of $BF_3{\cdot}Et_2O/Me_2S$[32] led to the corresponding deprotected derivatives **23a** and **23b** with an acceptable 49% yield. Dess-Martin[33] oxidation afforded quantitatively the ketones **24a** and **24b**, which were used immediately in the next step. Desilylation of **24a** and **24b** with HF/pyridine in THF at 0 °C at room temperature gave the desired PPE_1 type II **1a** and its C9 epimer **1b** in 41% yield. Interestingly, only under these reaction conditions, neither epimerization nor elimination was observed.

All reactions have been duplicated with the corresponding 4-hydroxycyclopentenone (*S*)-**5**, leading to the enantiomerically pure *ent*-PPE_1 type II **2a** and its 9-epimer **2b** as shown in Scheme 5.

Synthesis of 15-E_{2t}-IsoPs 3a,b and 4a,b from 4-Hydroxycyclopentenones (*R*)-5 and (*S*)-5, Respectively. 15-E_{2t}-IsoP **3a**, its C15 epimer **3b**, *ent*-15-E_{2t}-IsoP **4a** and *ent*-15-*epi*-15-E_{2t}-IsoP **4b** were prepared by using the same overall procedure as outlined in Schemes 6 and 7.

The ester **15** was quantitatively converted into the aldehyde **27** by treatment with DIBALH in anhydrous toluene (Scheme 6). The introduction of the α-chain of the isoprostane was achieved by a Wittig reaction using the commercially available (4-carboxybutyl)triphenylphosphonium bromide and sodium (hexamethyldisilyl)amide as a base. The aldehyde **27** reacted with the ylide in anhydrous THF at room temperature, then a 2 M solution of (trimethylsilyl)diazomethane in ether was added. This afforded a mixture of inseparable (*Z*/*E*, 90:10) methyl esters

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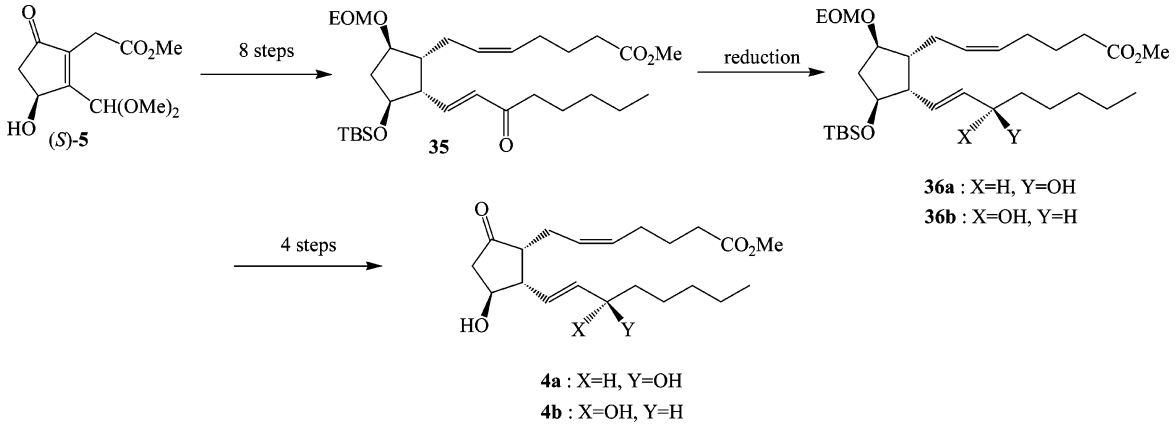
SCHEME 7. Syntheses of *ent*-15-E_{2t}-IsoP 4a and *ent*-15-*epi*-15-E_{2t}-IsoP 4b



28 in 65 yield after 3 steps. Due to difficulties in removing the unrequired alkenyl isomer the mixture of **28** was used for the next two steps. However, luckily, we were able to remove the (*E*)-stereoisomer after the diastereoselective reduction of the C15 keto group in **30**.

The acetal **28** was converted by acidic hydrolysis with TsOH in acetone into the aldehyde **29**, which was used immediately in the next step. As reported above (Scheme 4), the reaction time must be very short, to avoid loss of the TBS group. The condensation of **29** with the commercially available dimethyl-(2-oxoheptyl)phosphonate in the presence of sodium hydride, in anhydrous THF, afforded the *trans*-α,*β*-enone ester **30** in 72% yield after two steps. Neither elimination nor epimerization was observed during this HWE reaction, as for enone **20**.

The diastereoselective reduction of the C15 keto group in **30** with the chiral reducing agents[13] (*S*)- or (*R*)-BINAL-H gave the desired enantiopure 15(*S*) derivative **31a** and its 15(*R*) epimer **31b**, respectively, in 70% yield (Scheme 6). In our hands and for enone **30**, during the reduction process with (*R*)-BINAL-H and ethanol, we could not avoid the transesterification of the methyl ester to the ethyl ester.[34] Protection of the hydroxyl groups present in **31a** and **31b**, using TBDPSCl, imidazole in DMF afforded the corresponding protected alcohols **32a** and **32b** in 89% yield. As before, the EOM group was deprotected with $BF_3{\cdot}Et_2O/Me_2S$,[32] leading to the corresponding alcohols **33a** and **33b** with 30% yield and degradation. Dess-Martin[33] oxidation led quantitatively to the ketones **34a** and **34b**, which were used without purification in the next step. Desilylation of **34a** and **34b** with HF/pyridine under the same conditions as for **24a** and **24b** gave the desired 15-E_{2t}-IsoPs **3a** and its 15 epimer **3b** in 34% yield. All our data are in good agreement with those of Rodriguez and Spur.[16,17]

Furthermore, all reactions have been duplicated with 4-hydroxycyclopentenones (*S*)-**5** leading to the enantiomerically pure *ent*-15-E_{2t}-IsoP **4a** and *ent*-15-*epi*-15-E_{2t}-IsoP **4b**, as shown in Scheme 7.

Conclusion

In conclusion, the first synthesis of the optically pure diastereoisomers of the PPE_1 type II has been accomplished starting from *trans*-3-(2-furyl)acrylic acid **6**, using the key intermediate 4-hydroxycyclopentenone *rac*-**5**. Using the same strategy we were able to reach the pure diasteroisomers of the 15-E_{2t}-IsoP. Further syntheses of other phytoprostanes and isoprostanes, as well as the assessment of their individual biological activities, are in progress and will be reported in due course.

Experimental Section

(4*R*)-4-*O*-Acetoxy-3-(dimethoxymethyl)-2-(methylcarboxymethyl)cyclopent-2-enone, (*R*)-11, and (4*S*)-3-(Dimethoxymethyl)-4-hydroxy-2-(methylcarboxymethyl)cyclo-pent-2-enone, (*S*)-5. To a solution of compound *rac*-**5** (15 g, 60 mmol, 1 equiv) in hexane (540 mL) was added dry vinyl acetate (60 mL), followed by the *Candida antarctica* lipase B (3 g, 0.2 w/w). The reaction mixture was stirred at room temperature for 20 h. The reaction was monitored by HPLC using a chiral stationary phase (Chiralcel OD 250 × 4.6 mm, 5% 2-propanol in hexane). Once finished, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (10−50% ethyl acetate in cyclohexane) to give acetate (*R*)-**11** (7.79 g, 45%) and alcohol (*S*)-**5** (7.10 g, 49%).

Compound (*S*)-5. R_f: 0.46 (cyclohexane/ethyl acetate: 70/30). HPLC (min): 37.2. IR ν (cm^{-1}): 3448 (OH), 1738 and 1711 (C═O), 1662 (C═C). ^1H NMR (300 MHz, $CDCl_3$), δ: 2.37 (dd, J = 6.3, 18.7 Hz, 1H), 2.78 (dd, J = 6.3, 18.7 Hz, 1H), 3.17 (brs, 1H), 3.32 (s, 3H), 3.33 (AB, J = 12.4 Hz, 1H), 3.34 (AB, J = 12.4 Hz, 1H), 3.39 (s, 3H), 3.65 (s, 3H), 5.00 (d, J = 5.7 Hz, 1H), 5.45 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ: 28.2, 42.6, 52.1, 52.6, 54.0, 69.0, 100.8, 137.2, 166.1, 170.0, 204.0. $[\alpha]_D^{20}$: −19.1 (10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.98; H, 6.71.

Compound (*R*)-11. R_f: 0.71 (cyclohexane/ethyl acetate: 30/70). HPLC (min): 26.4. IR ν (cm^{-1}): 1732 and 1718 (C═O), 1663 (C═C). ^1H NMR (300 MHz, $CDCl_3$), δ: 2.05 (s, 3H) 2.29 (dd, J = 1.6, 19.0 Hz, 1H), 2.78 (dd, J = 6.4, 19.0 Hz, 1H), 3.25 (s, 3H), 3.34 (s, 3H), 3.44 (AB, J = 20.1 Hz, 1H), 3.51 (AB, J = 20.1 Hz, 1H), 3.64 (s, 3H), 5.26 (s, 1H),5.85 (br d, J = 6.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ: 20.7, 28.6, 41.3, 51.9, 52.1, 54.2, 70.0, 99.8, 140.5, 162.6, 170.1, 203.2. $[\alpha]_D^{20}$: −50.0 (10^{-2}, MeOH).

(4*R*)-3-(Dimethoxymethyl)-4-hydroxy-2-(methylcarboxymethyl)cyclopent-2-enone, (*R*)-5. To a solution of acetate (*R*)-**11** (4.0 g, 14 mmol, 1 equiv) in acetonitrile (6.1 mL) were added a solution of a phosphate buffer (0.1 M, pH = 7.240 mL) and the enzyme CAL-B (3.2 g, 0.8 w/w), and the reaction mixture was stirred at room temperature for 48 h. The reaction was monitored by TLC. Once finished, the reaction mixture was saturated with crystalline

(34) We have done Noyori's reduction many times in the past without problems and, as reported in this manuscript, the reduction proceeded well for compounds **20**, **25**, **35** and only with (*S*)-BINAL-H for **30** leading to **31a**. Astonishingly, we observed a transesterification during the reaction with (*R*)-BINAL-H with **30** leading to **31b** ethyl ester instead of methyl ester. But the difference between a methyl ester and an ethyl ester is not important and **31b** was nicely used anyway.

NaCl then filtered. The filtrate was washed with an aqueous solution of sodium hydrogenocarbonate (75 mL). The aqueous layer was extracted three times with ethyl acetate (75 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 80/20) to give alcohol (*R*)-**5** (3.39 g, 98%). In chiral HPLC (min): 35.8. $[\alpha]_D^{20}$: +21.2 (10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.18; H, 6.80.

(1*S*,2*S*,3*R*,4*R*)-4-*O*-(*tert*-butyldimethylsilyl)-3-(dimethoxymethyl)-1-*O*-(ethoxymethyl)-2-(methylcarboxymethyl)cyclopentane-1,4-diol, 15. To a solution of alkene **14** (7.3 g, 17.5 mmol, 1 equiv) in dry methanol (71.6 mL) were added butanone (50 mL), pyridine (21.2 mL, 262 mmol, 15 equiv) and dipotassium diazodicarboxylate (17.0 g, 87.3 mmol, 5 equiv) at room temperature under nitrogen. The reaction mixture was refluxed of methanol. Then a solution of acetic acid (10.0 mL, 174.6 mmol, 10 equiv) in MeOH (64.9 mL) was added dropwise over 2 h. Once the addition was finished, this procedure was repeated twice, then water (400 mL) was added, and the aqueous layer was extracted three times with diethyl ether (400 mL). The combined organic layers were washed twice with water (250 mL) and brine (250 mL), then dried over $MgSO_4$, and concentrated under reduced pressure. The same reaction was repeated four times until the consumption of the starting product was completed. The crude material was purified by column chromatography on silica gel (0−10% ethyl acetate in cyclohexane) to give compound **15** (5.3 g, 72%). R_f: 0.68 (cyclohexane/ethyl acetate: 70/30). IR ν (cm^{-1}): 1738 (C═O), 1463 (C−Si). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H), 1.45−1.55 (m, 1H), 2.32−2.52 (m, 4H), 2.55−2.72 (m, 1H), 3.27 (s, 3H), 3.29 (s, 3H), 3.49−3.60 (m, 2H), 3.64 (s, 3H), 3.69 (q, J = 7.4 Hz, 1H), 4.09−4.19 (m, 2H), 4.61 (AB, J = 10.8 Hz, 1H), 4.63 (AB, J = 10.8 Hz, 1H. ^{13}C NMR (75 MHz, $CDCl_3$), δ: −4.8, −4.9, 14.9, 18.2, 25.6 (3C), 33.1, 41.6 (2C), 49.5, 51.4, 54.0, 55.1, 63.0, 71.5, 80.7, 94.3, 105.4, 177.0. $[\alpha]_D^{20}$: +17 (10^{-2}, MeOH). Anal. Calcd for $C_{20}H_{40}O_7Si$: C, 57.11; H, 9.59. Found: C, 57.30; H, 9.47.

For *ent*-15, the characteristics are the same with $[\alpha]_D^{20} = -17$ (10^{-2}, MeOH).

Phytoprostane E_1 Type II Methyl Ester 1a. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.90 (t, J = 7.1 Hz, 3H), 1.19−1.29 (m, 12H), 1.43−1.73 (m, 5H), 2.23−2.32 (m, 3H), 2.47−2.56 (m, 2H), 2.95 (t, J = 8 Hz, 1H), 4.00−4.13 (m, 3H), 4.30−4.32 (m, 1H), 5.25 (dd, J = 10.0, 15.2 Hz, 1H), 5.64 (dd, J = 6.8, 15.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 11.9, 14.2, 18.5, 24.8, 25.1, 28.9, 29.0, 29.1, 34.3, 37.2, 44.9, 51.4, 51.8, 60.1, 72.0, 72.6, 127.0, 137.1, 173.8, 217.2. $[\alpha]_D^{20}$: +60.8 (2.5×10^{-3}, MeOH). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.89; H, 9.54.

For 2a (*ent*-PPE$_1$ type II methyl ester), the characteristics are the same with $[\alpha]_D^{20} = -61.2$ (2.5×10^{-2}, MeOH). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.59; H, 9.46.

9-*epi*-Phytoprostane E_1 Type II Methyl Ester 1b. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.92 (t, J = 7.4 Hz, 3H), 1.20−1.39 (m, 12H), 1.42−1.75 (m, 5H), 1.85 (brs, 1H), 2.24−2.32 (m, 3H), 2.48−2.60 (m, 2H), 2.97 (t, J = 7.9 Hz, 1H), 4.03−4.14 (m, 3H), 4.32 (brs,1H), 5.29 (dd, J = 9.7, 15.3 Hz, 1H), 5.68 (dd, J = 6.2, 15.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 12.0, 14.2, 18.4, 24.8, 25.1, 28.9, 29.0, 29.1, 34.3, 37.2, 44.9, 51.3, 51.8, 60.1, 72.1, 72.3, 126.3, 137.2, 173.8, 217.0. $[\alpha]_D^{20}$: +66.5 (2.5×10^{-3}, MeOH). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.58; H, 9.59.

For 2b (*ent*-9-*epi*-PPE$_1$ type II methyl ester), the characteristics are the same with $[\alpha]_D^{20}$ = - 66.5 (2.5×10^{-2}, MeOH). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.63; H, 9.80.

15-E_{2t}-IsoP Methyl Ester 3a. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.86 (t, J = 6.6 Hz, 3H), 1.20−1.36 (m, 6H), 1.43−1.53 (m, 2H), 1.56−1.69 (m, 5H), 1.87−2.09 (m, 4H), 2.26 (t, J = 7.4 Hz, 3H), 2.28−2.35 (m, 1H), 2.36−2.46 (m, 1H), 2.51 (dd, J = 5.8 and 19.2 Hz, 1H), 2.68−2.75 (m, 1H), 2.93−3.00 (m, 1H), 3.64 (s, 3H),4.05 (q, J = 6.1 Hz, 1-H), 4.32−4.36 (m, 1H), 5.25−5.39 (m, 3H), 5.66 (dd, J = 6.4 and 15.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 13.9, 22.5, 23.2, 24.6, 25.0, 26.7, 31.6, 33.3, 37.3, 44.7, 50.6, 51.4, 51.5, 72.1, 72.2, 126.2, 127.5, 130.0, 137.6, 174.1, 216.5. $[\alpha]_D^{20}$: +70.5 (2×10^{-3}, MeOH). Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 66.69; H, 9.17.

For *ent*-15-E_{2t}-IsoP methyl ester 4a, the characteristics are the same with $[\alpha]_D^{20} = -70.3$ (2×10^{-3}, MeOH). Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 66.98; H, 9.50.

15-*epi*-15-E_{2t}-IsoP Ethyl Ester 3b. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.87 (t, J = 6.7 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H),1.24−1.32 (m, 6H), 1.40−1.57 (m, 4H), 1.59−1.70 (m, 2H), 1.91−2.07 (m, 3H), 2.27 (t, J = 7.3 Hz, 2H), 2.33−2.34 (m, 1H), 2.38−2.46 (m, 1H), 2.51 (dd, J = 5.8 Hz, 19.2 Hz, 1H), 2.68−2.77 (m, 1H), 2.93−3.00 (m, 1H), 4.01−4.14 (m, 3H), 4.31−4.34 (m, 1H), 5.28 (ddd, J = 1.0, 9.7, and 15.3 Hz, 1H), 5.35−5.38 (m, 2H), 5.66 (dd, J = 6.4 and 15.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ: 14.0, 14.2, 22.6, 23.1, 24.7, 25.1, 26.8, 31.7, 33.7, 37.3, 44.8, 50.7, 51.4, 60.4, 72.3, 72.4, 126.3, 127.7, 130.2, 138.0, 173.9, 216.4. $[\alpha]_D^{20}$: +46 (10^{-2}, MeOH). Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.68; H, 9.38.

For *ent*-15-*epi*-15-E_{2t}-IsoP methyl ester 4b, the characteristics are the same with $[\alpha]_D^{20} = -46$ (10^{-2}, MeOH). Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 66.93; H, 9.51.

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Supporting Information Available: Experimental procedures for selected compounds, a table of optical rotations, and ^{1}H NMR and ^{13}C NMR spectra for compounds **6**, **7**, **8**, ***rac*-5**, **(*R*)-11**, **12**−**18**, **20**, **21a**, **21b**, **22a**, **22b**, **23a**, **23b**, **28**, **30**, **31a**, **31b**, **32a**, **32b**, **33a**, **33b**, and the target compounds **1a**, **1b**, **3a**, **3b**. This material is available free of charge via the Internet at http://pub.acs.org.

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