JOC*Article*

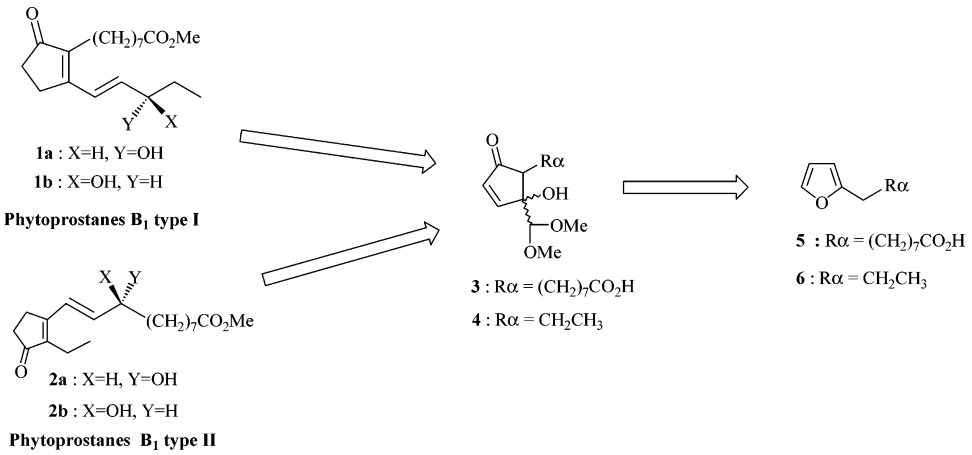
A Flexible Synthesis of the Phytoprostanes B_1 Type I and II

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

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

thierry.durand@univ-montp1.fr

Received October 15, 2004



Syntheses of the enantiomerically pure phytoprostanes B_1 type I and II are described starting from furfural and *n*-propylfuran. Key steps include the preparation of the Freimanis (±)-hydroxycyclopentenone and Wittig coupling using chiral phosphonium salts.

Introduction

Isoprostanes are formed in animals from arachidonic acid by a free-radical-catalyzed nonenzymatic mechanism.[1] Phytoprostanes are a novel family of plant effectors that are formed from α-linolenic acid via an identical mechanism (Figure 1).[2]

The nomenclature used to name different phytoprostane classes conforms with the general isoprostane/prostaglandin terminology.[3] In animals, isoprostanes not only are extremely reliable markers of oxidative stress but also display potent biological activities.[1,4]

In plants, several classes of phytoprostanes are constitutively present,[5] and notably, their levels increase in a variety of conditions with enhanced free-radical generation. Recently, Mueller et al. proposed that phyto-

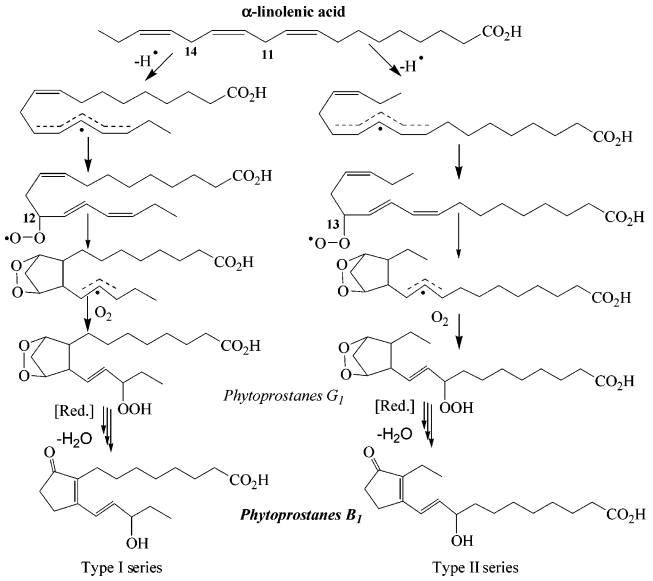


FIGURE 1. Phytoprostane B_1 pathway.

* To whom correspondence should be addressed. Tel: 33-4-67-54-86-23. Fax: 33-4-67-54-86-25.

(1) (a) Morrow, J. D.; Hill, K. E.; Burk, R. F.; Nammour, T. M.; Badr, K. F.; Roberts II, L. J. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9383−9387. (b) Roberts, L. J., II; Morrow, J. D. *Free Radic. Biol. Med.* **2000**, *28*, 505−513. (c) For a general review, see: *Chem. Phys. Lipids* **2004**, *128*, 1−193.

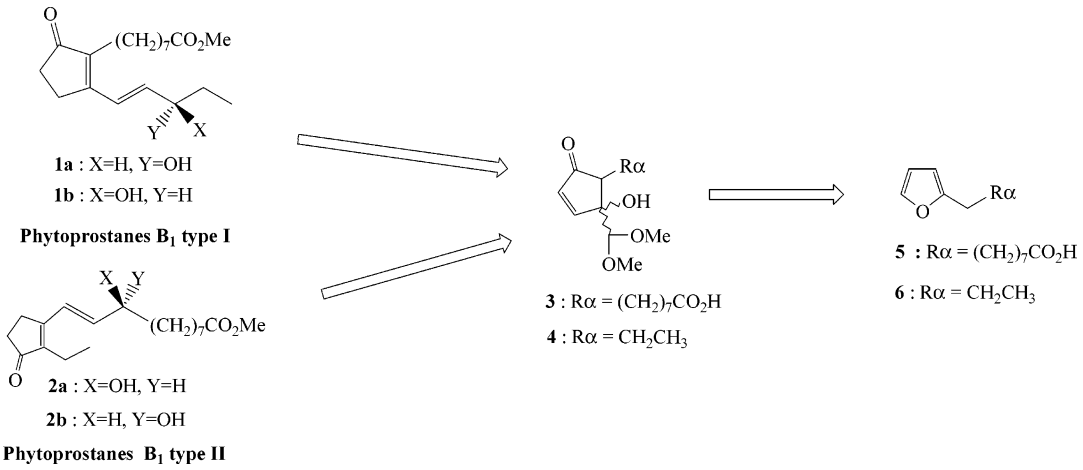
(2) Thoma, I.; Krischke, M.; Loeffler, C.; Mueller M. J. *Chem. Phys. Lipids* **2004**, *128*, 135−148.

(3) Imbusch, R.; Mueller, M. J. *Plant Physiol.* **2000**, *124*, 1293−12303.

(4) Cracowski, J. L.; Durand, T.; Bessard, G. *Trends Pharmacol. Sci.* **2002**, *23*, 360−366.

10.1021/jo048179+ CCC: $30.25
Published on Web 01/07/2005

SCHEME 1. Retrosynthetic Scheme of the Phytoprostanes B_1 Type I and II



prostanes are components of an oxidant-injury-sensing, archaic signaling system that induces several plant defense mechanisms.[5,6]

Indeed, in these articles, the authors show that PPB_1 display powerful biological activities including the activation of mitogen-activated protein kinase (MAPK) and the induction of glutathione-S-transferase (GST), defense genes, and phytoalexins.

To assess the physiological activities of each of the phytoprostanes B_1 type I and II, we found it more attractive to obtain sufficient quantities by chemical synthesis.

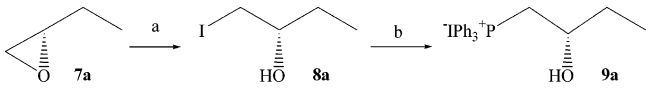
Earlier this year, we have published the syntheses of all eight diastereomers of the *syn-anti-syn* PPF_1 type I and II using our flexible strategy starting from D- and L-glucose.[7] We now report the syntheses of the phytoprostanes B_1 type I and II starting from 2-(8-carboxyoctyl)furan **5** and 2-propylfuran **6** (Scheme 1).

Results and Discussion

The phytoprostanes B_1 type I and II were identified from autoxidation of α-linolenic acid by Mueller.[3] Our interest was in developing a new and flexible route to phytoprostanes B_1 starting from two common Freimanis intermediates,[8] the 3-hydroxy-4-cyclopentenone precursors **3** and **4**, in order to confirm the stereochemistry of the enantiomerically pure phytoprostanes B_1 type I and II, and also to screen the physiological activity of these phytoprostanes. The key steps of this procedure rely on the selective splitting of the furan ring of the 5-formyl derivatives **12** and **24** and subsequent cyclization, leading to the 4-hydroxy-2-cyclopentenones **3** and **4** (Schemes 3 and 6).

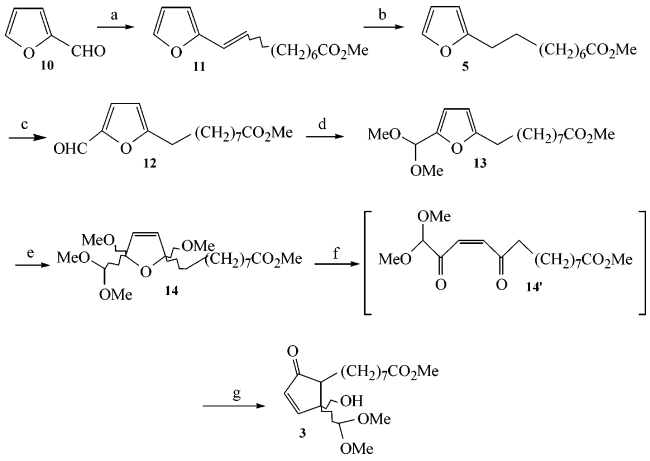
Synthesis of Phytoprostane B_1 Type I 1a and 1b from Furfural 10. The syntheses of PPB_1 type I **1a** and its enantiomer **1b** from the furfural **10** are shown in Schemes 2−4.

SCHEME 2. Synthesis of Chiral Phosphonium Salt 9a[a]



[a] Reagents and conditions: (a) NaI, NaOAc AcOH, AcOEt, 99%; (b) 2 equiv of PPh_3, THF, reflux, 7 days, 66%.

SCHEME 3. Synthesis of Precursor 3[a]



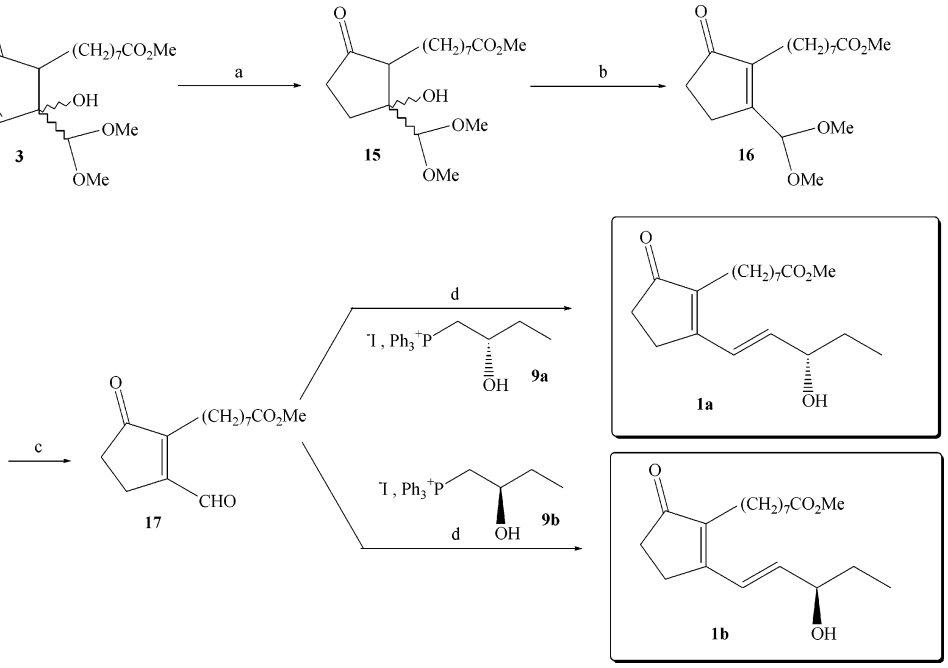
[a] Reagents and conditions: (a) 1 equiv of ^-Br, $^+PPh_3(CH_2)CO_2H$, 2 equiv of KHMDS (1 M in THF), THF, −78 to +20 °C, 1 h, then H_2SO_4 (0.34 N), MeOH, reflux, 20 h, 85% after two steps; (b) H_2, Pd/C 10%, MeOH, 20 min, 100%; (c) 1.3 equiv of DMF, 1.1 equiv of $POCl_3$, 70 °C, 3 h; (d) 1.6 equiv of $HC(OMe)_3$, 0.014 equiv of *p*-TsOH, MeOH, 0 °C to rt, 2 h; (e) 1.5 equiv of Na_2CO_3, 1.05 equiv of Br_2/MeOH (2.25 M), −30 °C, 2 h; (f) 0.1 N citric acid, 0.2 N Na_2HPO_4, dioxane, 55 °C, 4 h; (g) 0.2 N Na_2HPO_4, 75 °C, 4 h, 23% after six steps.

The chiral phosphorus synthon **9a** was selected for the introduction of the lower chain of the PPB_1 type I and was prepared using the procedure outlined in Scheme 2.

The first step is the opening of the chiral pool starting material, (*S*)-(−)-1,2-epoxybutane **7a**. Upon treatment with sodium iodide[9] in ethyl acetate, this epoxide gave the iodo compound (2*S*)-**8a** in 99% yield. Our first attempts to reach the phophonium salt **9a** in the presence

(5) Thoma, I.; Loeffler, C.; Sinha, A. K.; Gupta, M.; Krischke, M.; Steffan, B.; Roitsch, T.; Mueller, M. J. *Plant J.* **2003**, *34* (3), 363−375.
(6) Mueller, M. J. *Curr. Opin. Plant Biol.* **2004**, *7*, 441−448.
(7) El Fangour, S.; Guy, A.; Despres, V.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2004**, *69*, 2498−24503.
(8) (a) Loza, E.; Lola, D.; Freimanis, J.; Turovskis, I.; Gavars, M.; Liepipa, A. *Latvijas PSR ZA vestis, Chem. Series* **1985**, *4*, 465−472. (b) Loza, E.; Lola, D.; Freimanis, J.; Leipina, A. *Latv. Kim. Z.* **1998**, *1*, 76−82.
(9) Adamcyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron* **1999**, *55*, 63−88.

SCHEME 4. Synthesis of Phytoprostanes B_1 Type I 1a and 1b[a]



[a] Reagents and conditions: (a) H_2, Pd/C 10%, MeOH, 2 h; (b) HCl 3% in MeOH, 20 °C, 3 h, 93% after two steps; (c) 1 N HCl, THF−dioxane (1:1), rt, 3 h; (d) 1.9 equiv of LiHMDS (1 M in THF), THF, −78 °C, 20 min, 29% after two steps.

of PPh_3 in acetonitrile or benzene gave, respectively, no reaction and degradation. Finally, the iodo compound **8a** was transformed into the chiral phosphonium salt **9a**, in the presence of PPh_3 in refluxing THF in 66% yield.[10] Using the same strategy, the (*R*)-(+)-1,2-epoxybutane **7b** yielded the corresponding (*R*)-phosphonium salt **9b** in 67% after two steps.

The 3-hydroxy-4-cyclopentenone precursor **3** was prepared using the Freimanis procedure[8] outlined in Scheme 3. The first step was a Wittig reaction with the 7-carboxyheptyltriphenylphosponium salt which was prepared quantitatively from the commercially available 8-bromooctanoic acid and triphenylphosphine in dry acetonitrile as described by Dawson and Vasseur.[11] The condensation of **10** with 7-carboxyheptyltriphenylphosponium bromide, in the presence of potassium hexamethyldisilyl amide in dry THF, afforded **11** as a mixture of (*Z*/*E*) isomers. The carboxyl group was esterified in the presence of methanol under acidic conditions. The corresponding methyl ester **11** was obtained in 85% yield after two steps. The subsequent Pd-catalyzed reduction under hydrogen atmospheree led to the reduced compound **5** in 100% yield.

During the hydrogenation step, it was not possible to completely avoid the full reduction of the furan ring leading to the corresponding tetrahydrofuran derivative. This latter compound was removed after the formylation step. Compound **5** reacts with the Vilsmeier reagent ($POCl_3$/DMF) to give the corresponding crude 5-formyl derivative **12** which was protected in the presence of methyl orthoformate under acidic conditions. Oxidation of the furan ring **13** with bromine in methanol gave the bis-acetal **14** as a 1:1 mixture of diastereoisomers. Careful acidic hydrolysis of **14** in dioxane followed by basic treatment at 75 °C for 4 h resulted in an "aldol-type" cyclization to give the 3-hydroxy-4-cyclopentenone precursor **3** in 23% yield after six steps.

The hydrogenation[12] of **3** gave quantitatively the 3-hydroxy-3-dimethoxymethyl-2-methoxycarbonylheptyl-4-cyclopentanone **15**, which underwent a dehydration upon treatment with a methanolic solution of dry hydrogen chloride giving 3-dimethoxymethyl-2-methoxycarbonylheptyl-4-cyclopentenone **16** in 93% yield (Scheme 4). The acetal **16** was converted by acidic hydrolysis to the aldehyde **17** which was used immediately in the next step. Finally, the introduction of the lower chain (Scheme 4) was achieved using the chiral phosphonium salts[13] **9a** and **9b**, which react with the aldehyde **17** to afford the enantiomerically pure (*E*)-enol **1a** and **1b** in 29% yield after two steps.

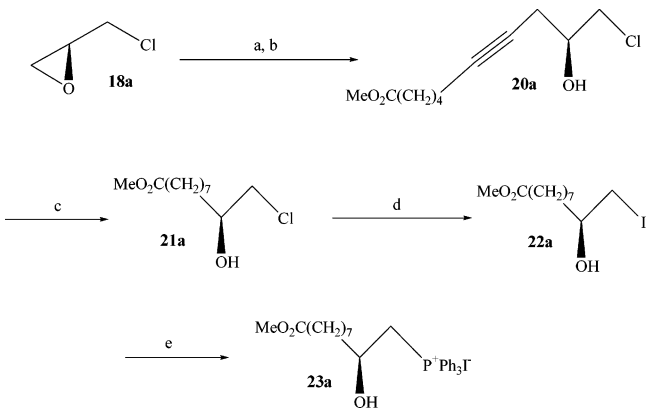
Synthesis of Phytoprostanes B_1 Type II 2a and 2b from *n*-Propylfuran. The phytoprostanes B_1 type II **2a** and **2b** were prepared following the same procedure as outlined in Schemes 5−7.

The phosphonium iodide **23** was selected and prepared using the following procedure and outlined in the Scheme 5.

(*S*)-(+)-epichlorohydrin **18a** was coupled with the hept-6-ynoic acid by following the Yamagushi method[14] (*n*-BuLi, BF_3·OEt_2, THF) leading to the 9(*S*)-hydroxy-10-chlorodeca-6-ynoic acid **19a** in 74% yield. Esterification of the carboxyl group in the presence of a methanolic solution of dry hydrogen chloride led to the corresponding

(10) Johnson, F.; Paul, K. G.; Favara, D.; Ciabatti, R.; Guzzi, U. *J. Am. Chem. Soc.* **1982**, *104*, 2190−2198.
(11) Dawson, M. I.; Vasser, M. *J. Org. Chem.* **1977**, *42*, 2783−2784.
(12) Loza, E.; Lola, D.; Freimanis, J.; Turovskis, I.; Rozite, S.; Bokaldere, R.; Sahartova, O. *Tetrahedron* **1998**, *44*, 1207−1219.
(13) Crombie, L.; Heavers, A. D. *J. Chem. Soc., Perkin Trans 1* **1992**, 2683−2687.
(14) Yamaguchi, M.; Hirano, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.

SCHEME 5. Synthesis of Phosphonium 23a[a]



[a] Reagents and conditions: (a) 1 equiv of $HC{\equiv}C(CH_2)_4CO_2H$, 2 equiv of *n*-BuLi, −78 °C, 1 h, 0.68 equiv of (*S*)-(+)-epichlorohydrin, 1 equiv of BF_3/Et_2O, −78 °C, 1 h, rt, 2 h, 74%; (b) HCl 3% in MeOH, reflux, 20 h, 68%; (c) H_2, Pd/C 10%, AcOEt, 70 psi, 10 h; (d) 2.2 equiv of NaI, *n*-butan-2-one, reflux, 48 h, 68% after two steps; (e) 2 equiv of PPh_3, THF, reflux, 7 days, 86%.

methyl ester **20a** in 68% yield. Reduction of the triple bond under an atmosphere of hydrogen led to the reduced compound **21a** in quantitative yield. Displacement of the chloride atoms of **21a** by sodium iodide in *n*-butan-2-one gave the desired iodo derivative **22a** in 68% yield. Finally, the iodo derivative was converted to the corresponding (*S*)-phosphonium iodide upon treatment with PPh_3 in THF over 7 days at reflux in 86% yield.

Using the same procedure, the (*R*)-(−)-epichlorohydrin **18b** gave the corresponding (*R*) phosphonium iodide **23b** in 26% overall yield.

TABLE 1. $[\alpha]^{20}_D$ (1×10^{-2}, MeOH) for All Chiral Phosphonium Salts and All Enantiomers of PPB_1 Type I and II

PPB_1 type I **1a**	+23	−23	*ent*-PPB_1 type I **1b**
PPB_1 type II **2a**	+24	−24	*ent*-PPB_1 type II **2b**
phosphonium salt **9a**	+59	−59	phosphonium salt **9b**
phosphonium salt **23a**	+35	−35	phosphonium salt **23b**

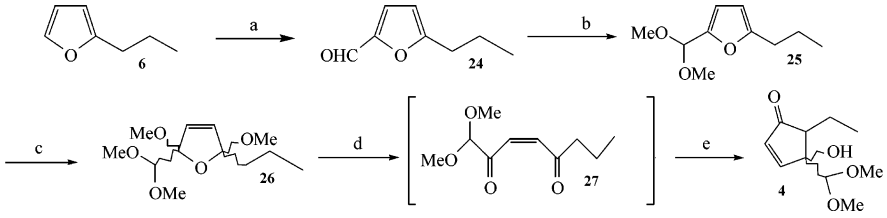
The synthesis of the 3-hydroxy-4-cyclopentenone **4** (Scheme 6) was achieved from the *n*-propylfuran **6** by using the same procedure as for precursor **3**. The Vilsmeier's formylation led to the 5-formyl derivative **24**, which was protected in the presence of methyl orthoformate under acidic conditions. Oxidation of the furan ring **25** with bromine in methanol gave the bis-acetal **26**, which underwent an acidic hydrolysis followed by base treatment to give the 3-hydroxy-4-cyclopentenone precursor **4** in 52% yield after five steps.

The hydrogenation[12] of **4** gave the crude 3-hydroxy-3-dimethoxymethyl-2-ethyl cyclopentanone **28**, which underwent dehydration upon treatment with a methanolic solution of dry hydrogen chloride giving 3-dimethoxymethyl-2-ethyl-2-cyclopentenone **29** in 69% yield (Scheme 7). The acetal **29** was converted by acidic hydrolysis to the aldehyde **30** which was used immediately in the next step.

The introduction of the upper chains (Scheme 7) was achieved using the chiral phosphonium salts **23a** and **23b**, which react with the aldehyde **30** to afford the enantiomerically pure (*E*)-enol **2a** and **2b** in 23% yield after two steps.

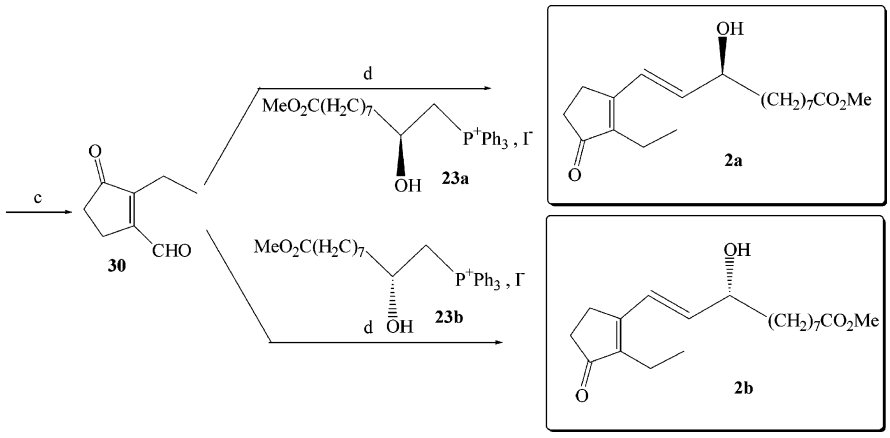
The physicochemical properties of the enantiomerically pure phosphonium salts **9a** and **23a** and the PPB_1 type

SCHEME 6. Synthesis of Precursor 4[a]



[a] Reagents and conditions: (a) 1.3 equiv of DMF, 1.1 equiv of $POCl_3$, 70 °C, 3 h, 75%; (b) 1.6 equiv of $HC(OMe)_3$, 0.014 equiv of *p*-TsOH, MeOH, 0 °C to rt, 2 h, 93%; (c) 1.5 equiv of Na_2CO_3, 1.05 equiv of Br_2/MeOH (2.25 M), −30 °C, 2 h; (d) 0.1 N citric acid, Na_2HPO_4, dioxane, 55 °C, 2 h; (e) 0.2 N Na_2HPO_4, 75 °C, 2 h, 75% after three steps.

SCHEME 7. Syntheses of Phytoprostanes B_1 Type II 2a and 2b[a]



[a] Reagents and conditions: (a) H_2, Pd/C 10%, MeOH, 30 min; (b) HCl 3% in MeOH, 20 °C, 3 h, 69% after two steps; (c) 1 N HCl, THF, rt, 5 h; (d) 1.9 equiv of LiHMDS (1 M in THF), THF, −78 °C, 20 min, 23% after two steps.

I and II diastereomers **1a** and **2a** were identical to those of **9b**, **23b**, **1b,** and **2b**, respectively, except for the sign of the specific optical rotation, as mentioned in Table 1.

Conclusion

In conclusion, the first synthesis of the pure enantiomers of the phytoprostanes B_1 type I and II has been accomplished starting from furfural **10** and 2-propylfuran **6**, using key intermediate Freimanis 3-hydroxy-4-cyclopentenone precursors **3** and **4** and two chiral phosphonium salts to introduce the chiral center in the side chains. Further studies of other phytoprostanes or analogues as well as the assessment of their individual biological activities are in progress and will be reported in due course.

Experimental Section

(*R*)-2-Hydroxypropyl Iodide (8b). To a solution of epoxide **7b** (2.5 g, 34.67 mmol, 1 equiv) in dry ethyl acetate (350 mL) were added sequentially NaI (6.76 g, 45.11 mmol, 1.3 equiv), anhydrous sodium acetate (3.13 g, 38.13 mmol, 1.1 equiv), and acetic acid (2.2 mL, 38.13 mmol, 1.1 equiv) at room temperature under nitrogen. After being stirred for 20 h, the mixture was diluted with water (200 mL) and brine (100 mL). The aqueous solution was separated, and the organic layer was washed with a 10% $Na_2S_2O_3$ solution (200 mL) and brine (2 × 100 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 600 mL), and the organic phase was dried and concentrated giving the crude material **8b** which was used in the next step. R_f: 0.80 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 3359 (OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.5 Hz, 3H), 1.59 (m, 2H), 1.85 (s, 1H), 3.24 (dd, J = 6.6 and 10.2 Hz, 2H), 3.42 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 9.9, 15.9, 29.5, 72.2.

(*S*)-2-Hydroxypropyl Iodide (8a). To a solution of epoxide **7a** (2.5 g, 34.67 mmol, 1 equiv) in dry ethyl acetate (350 mL) were added sequentially NaI (6.76 g, 45.11 mmol, 1.3 equiv), anhydrous sodium acetate (3.13 g, 38.13 mmol, 1.1 equiv), and acetic acid (2.2 mL, 38.13 mmol, 1.1 equiv) at room temperature under nitrogen. After being stirred for 20 h, the mixture was diluted with water (200 mL) and brine (100 mL). The aqueous solution was separated, and the organic layer was washed with a 10% $Na_2S_2O_3$ solution (200 mL) and brine (2 × 100 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 600 mL), and the organic phase was dried and concentrated giving the crude material **8a** which was used in the next step. R_f: 0.80 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 3359 (OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.5 Hz, 3H), 1.59 (m, 2H), 1.85 (s, 1H), 3.24 (dd, J = 6.6 and 10.2 Hz, 1H), 3.42 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 9.9, 15.9, 29.5, 72.2.

(*R*)-2-Hydroxypropylphosphonium Iodide (9b). A solution of the hydroxy iodide **8b** (6 g, 30 mmol, 1 equiv) and triphenylphosphine (18.2 g, 60 mmol, 2 equiv) in dry tetrahydrofuran (87 mL) was stirred at reflux over 7 days in the absence of oxygen. The precipitated phosphonium salt formed was filtered and washed with diethyl ether to give compound **9b** as a microcrystalline powder (9.2 g, 67%). R_f: 0.80 (dichloromethane/methanol 90:10). IR ν (cm^{-1}): 3359 (OH). ^{31}P NMR (81 MHz, $CDCl_3$, external ref H_3PO_4) δ: +24.5. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.5 Hz, 3H), 1.80−1.91 (m, 1H), 1.95−2.06 (m, 1H), 3.32−3.24 (m, 1H), 3.88−3.99 (m, 1H), 3.99−4.10 (m, 1H), 4.80−4.84 (m, 1H), 7.65−7.73 (m, 6H), 7.76−7.85 (m, 9H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 10.1, 29.1 (d, J = 50.5 Hz), 31.8 (d, J = 13.0 Hz), 67.7 (d, J = 7.5 Hz), 118.8 (d, J = 87.7 Hz), 130.3 (d, J = 12.2 Hz), 134.1 (d, J = 10.3 Hz), 134.8 (d, J = 2.9 Hz). $[\alpha]^{20}_D$ = −59 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{22}H_{24}IOP$: C, 57.16; H, 9.63. Found: C, 57.19; H, 9.68.

(*S*)-2-Hydroxypropylphosphonium Iodide (9a). To a solution of the hydroxy iodide **8a** (6 g, 30 mmol, 1 equiv) in dry tetrahydrofuran (87 mL) was added triphenylphosphine (18.2 g, 60 mmol, 2 equiv). The mixture was heated under reflux over 7 days in the absence of oxygen. The precipitated phosphonium salt was filtered and washed with diethyl ether to give compound **9a** as a microcrystalline powder (9.1 g, 66%). R_f: 0.80 (dichloromethane/methanol 90:10). IR ν (cm^{-1}): 3359 (C=O). ^{31}P NMR (81 MHz, $CDCl_3$, external ref H_3PO_4) δ: +24.5. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.5 Hz, 3H), 1.80−1.91 (m, 1H), 1.95−2.06 (m, 1H), 3.32−3.24 (m, 1H), 3.88−3.99 (m, 1H), 3.99−4.10 (m, 1H), 4.80−4.84 (m, 1H), 7.65−7.73 (m, 6H), 7.76−7.85 (m, 9H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 10.1, 29.1 (d, J = 50.5 Hz), 31.8 (d, J = 13.0 Hz), 67.7 (d, J = 7.5 Hz), 118.8 (d, J = 87.7 Hz), 130.3 (d, J = 12.2 Hz), 134.1 (d, J = 10.3 Hz), 134.8 (d, J = 2.9 Hz). $[\alpha]^{20}_D$ = +59 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{22}H_{24}IOP$: C, 57.16; H, 9.63. Found: C, 57.19; H, 9.64.

2-Methoxycarbonyl-8-octenylfuran (11). To a stirred suspension of 7-carboxyheptyltriphenylphosphonium bromide (5 g, 10.30 mmol, 1 equiv) in dry tetrahydrofuran (82 mL) under nitrogen at −60 °C was added dropwise a 1 M toluene solution of KHMDS (41.2 mL, 20.60 mmol, 2 equiv). The temperature was allowed to rise to 10 °C and then after 10 min was lowered again −78 °C. To this solution there was added during 10 min a solution of furfural (1.28 mL, 15.45 mmol, 1.5 equiv) in dry tetrahydrofuran (15.5 mL) at −78 °C. After slow warming to room temperature over 1 h, the reaction was quenched by addition of water (45 mL). The pH of the mixture was adjusted to 11 using 1 N aqueous NaOH (20 mL) and extracted with ethyl acetate (100 mL). The aqueous layer was separated and acidified with a 6 N HCl solution (10 mL) to pH 2 and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated giving the free acid which was used immediately in the next step. R_f: 0.74 (cyclohexane/ethyl acetate 60:40). IR ν (cm^{-1}): 3050−3450 (CO*OH*), 1710 (C=O).

A solution of the free acid (3.4 g, 10.3 mmol, 1 equiv) in methanol (50 mL) and sulfuric acid (0.1 mL) was heated to a gentle reflux for 20 h and cooled at room temperature. The solvent was evaporated, and water (50 mL) was added. The mixture was neutralized with Na_2CO_3 (200 mg, to pH 9) and extracted with ethyl acetate (3 × 60 mL). The organic extracts were washed with a saturated $NaHCO_3$ solution (20 mL) and brine (15 mL), dried, and concentrated. The crude material was purified by column chromatography (cyclohexane/diethyl ether 95:5) to give compound **11** (2.46 g, 85% after two steps). R_f: 0.88 (cyclohexane/ethyl acetate 60:40). IR ν (cm^{-1}): 1734 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.29−1.41 (m, 4H), 1.43−1.51 (m, 2H), 1.59−1.67 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.39−2.47 (m, 2H), 3.64 (s, 3H), 5.47−5.56 (m, 1H), 6.18 (d, J = 12 Hz, 1H), 6.21−6.24 (m, 1H), 6.35−6.38 (m, 1H), 7.35 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 24.9, 28.9, 29.0, 29.1, 29.2, 33.9, 51.3, 108.7, 110.9, 117.4, 131.0, 141.1, 153.3, 174.0.

2-Methoxycarbonyloctylfuran (5). A mixture of compound **11** (1.93 g, 8.09 mmol, 1 equiv) and 10% Pd/C (58 mg) in methanol (33 mL) was hydrogenated at atmospheric pressure for 20 min. The mixture was filtered through Celite and the filtrate concentrated to provide **5** as a colorless oil (1.92 mg, 100%). R_f: 0.85 (cyclohexane/ethyl acetate 60:40).

2-Formyl-5-methoxycarbonyloctylfuran (12). To *N*,*N*-dimethylformamide (1.6 mL, 20.81 mmol, 1.3 equiv) was added dropwise freshly distilled phosphorus oxychloride (0.70 mL, 7.85 mmol, 1.1 equiv) at room temperature, under nitrogen. The mixture was stirred at 70 °C for 1 h and cooled at 10 °C. Then, a solution of compound **11** (1.6 g, 6.71 mmol, 1 equiv) in dry *N*,*N*-dimethylformamide (4 mL) was added dropwise by cannulation, and the resulting mixture was stirred for 3 h. A 14.5 mL portion of ice-cold water was then added, and the mixture was neutralized with 2.9 g of sodium hydrogenocarbonate and 2.9 mL of saturated sodium carbonate. The

aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were washed with brine (2 × 10 mL), dried, and concentrated giving the crude material **12** which was used immediately in the next step. R_f: 0.70 (cyclohexane/ethyl acetate 60:40).

2-Dimethoxymethyl-5-methoxycarbonyloctylfuran (13). To a solution of compound **12** (2.4 g, 6.71 mmol, 1 equiv) in methanol (2.24 mL) were added sequentially at 0 °C, under nitrogen, trimethyl orthoformate (1.18 mL, 10.74 mmol, 1.6 equiv) and *p*-toluenesulfonic acid hydrate (17.88 mg, 0.09 mmol, 0.014 equiv). The reaction mixture was stirred at room temperature for 2 h, neutralized with sodium hydrogenocarbonate (28.20 mg), and filtered, and solvent was removed under reduced pressure to give a crude material **13** which was used in the next step without further purification. R_f: 0.68 (cyclohexane/ethyl acetate 60:40, 2% triethylamine).

2-Dimethoxymethyl-5-methoxycarbonyloctyl)-2,5-dimethoxy-2,5-dihydrofuran (14). To a solution of compound **13** (3.2 g, 10.24 mmol, 1 equiv) in dry methanol (10.3 mL, 1 M) was added dry sodium bicarbonate (1.63 g, 15.37 mmol, 1.5 equiv). The mixture was cooled to −30 °C, and a solution of bromide (530 μL, 10.76 mmol, 1.05 equiv) in dry methanol (4.8 mL, 2.25 M) was added slowly over 10 min. After being stirred at the same temperature for 2 h, the mixture was allowed to warm to room temperature and methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), and 23.6 mL of 2% Na_2CO_3 and 74 mL of water were added. The aqueous layer was extracted with ethyl acetate (3 × 120 mL). The combined organic extracts were washed with water (2 × 40 mL), dried, and concentrated giving a crude material **14** which was used in the next step without further purification. R_f: 0.56 (cyclohexane/ethyl acetate 60:40).

3-Dimethoxymethyl-3-hydroxy-2-methoxycarbonylheptylcyclopent-4-en-1-one (3). To a solution of compound **14** (3.8 g, 10.15 mmol, 1 equiv) in dioxane (10.2 mL) were added sequentially 0.1 N aqueous citric acid (14.2 mL) and 0.2 N aqueous Na_2HPO_4 (0.90 mL). After the mixture was stirred at 55 °C for 4 h, 0.2 N aqueous Na_2HPO_4 (33.1 mL) and 20 mL of dioxane were added, and stirring was continued at 75 °C for 4 h. The reaction mixture was cooled and saturated with crystalline NaCl, and then it was extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were washed with water (30 mL), dried, and concentrated. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 75:25) to give a yellow oil **3** (1.07 g, 23% after six steps). R_f: 0.50 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 3476 (HO), 1734 (C=O), 1715 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.25−1.28 (m, 2H), 1.29−1.34 (m, 4H), 1.39−1.41 (m, 1H), 1.46−1.50 (m, 1H), 1.56−1.64 (m, 3H), 1.72−1.76 (m, 1H), 2.28 (t, J = 7.5 Hz, 2H), 2.31−2.35 (m, 1H), 3.34 (s, 6H), 3.64 (s, 3H), 4.32 (s, 1H), 6.23 (d, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 24.1, 24.8, 24.8, 28.9, 29.0, 29.6, 34.0, 51.4, 56.9, 57.5, 59.4, 83.3, 107.8, 134.6, 159.1, 174.3, 205.7. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.22; H, 8.65.

3-Dimethoxymethyl-3-hydroxy-2-methoxycarbonylheptylcyclopentan-1-one (15). A mixture of compound **3** (278 mg, 0.85 mmol, 1 equiv) and 10% Pd/C (27.8 mg) in methanol (1.7 mL) was hydrogenated at atmospheric pressure for 2 h. The mixture was filtered through Celite and the filtrate concentrated to provide **15** as a colorless oil which was used in the next step without further purification. R_f: 0.40 (cyclohexane/ethyl acetate 50:50).

3-Dimethoxymethyl-2-methoxycarbonylheptylcyclopent-2-en-1-one (16). Acetyl chloride (40 μL, 0.26 mmol, 0.66 equiv) was added dropwise to dry methanol (4.3 mL), and the 0.13 N hydrogen chloride solution obtained was cooled to 20 °C and was added to compound **15** (132 mg, 0.40 mmol, 1 equiv) at room temperature, under nitrogen. The reaction mixture was stirred for 3 h and neutralized with a 10% $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL) and water (10 mL), dried, and concentrated under reduced pressure. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 95:5) to give compound **16** (116 mg, 93% after two steps). R_f: 0.65 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 1734 (C=O), 1715 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.28−1.33 (m, 6H), 1.35−1.43 (m, 2H), 1.57−1.65 (m, 2H), 2.25 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.36−2.40 (m, 2H), 2.57−2.61 (m, 2H), 3.39 (s, 6H), 3.67 (s, 3H), 5.20 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 23.3, 24.9, 25.4, 28.5, 28.9, 29.0, 29.5, 34.0, 34.1, 51.4, 54.0, 100.9, 143.2, 165.9, 174.3, 210.1. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.40; H, 9.1.

3-Formyl-2-methoxycarbonylheptylcyclopent-2-en-1-one (17). To a solution of compound **16** (250 mg, 0.80 mmol, 1 equiv) in tetrahydrofuran (1 mL) and dioxane (1 mL) was added 1 N aqueous hydrochloric acid (1.7 mL). The mixture was stirred at room temperature for 3 h. The mixture was washed with water (4 × 8 mL, to pH 7), extracted with ethyl acetate (3 × 40 mL), and dried. The solvent was removed to give compound **17** which was used immediately in the next step. R_f: 0.84 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 1734 (C=O), 1715 (C=O), 1683 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.29−1.37 (m, 6H), 1.48−1.56 (m, 2H), 1.58−1.67 (m, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.49−2.52 (m, 2H), 2.59 (t, J = 7.7 Hz, 2H), 2.69−2.73 (m, 2H), 3.68 (s, 3H), 10.39 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 22.8, 23.3, 24.8, 28.8, 28.9, 29.3, 29.7, 34.0, 51.4, 153.9, 158.7, 174.2, 190.2, 210.1.

***ent*-Phytoprostane B_1 Type I Methyl Ester (1b).** A solution of (*R*)-phosphonium salt **9b** (518.6 mg, 1.12 mmol, 1.4 equiv) in dry tetrahydrofuran (6 mL) was cooled to −78 °C under nitrogen and treated with lithium dimethylsilylamide (1 M in tetrahydrofuran, 2.1 mL, 2.13 mmol, 2.65 equiv).

The temperature was allowed to rise to −25 °C and then after 15 min was lowered again to −78 °C. To this orange-red solution was added dropwise a solution of aldehyde **17** (156 mg, 0.80 mmol, 1 equiv) in dry tetrahydrofuran (3 mL) at −78 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched by addition of a 10% NH_4Cl solution (10 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and washed with 10% NH_4Cl solution (2 × 10 mL, to pH 7) and brine (10 mL). The organic extracts were dried and concentrated, and the crude material was purified by column HPLC (SI-60, 5 μm): cyclohexane/ethyl acetate 50:50; 3.0 mL/min at 254 nm t_R: 23 min (29% after two steps). R_f: 0.48 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 3457 (OH), 1734 (C=O), 1715 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.00 (t, J = 7.5 Hz, 3H), 1.27−1.33 (m, 6H), 1.57−1.64 (m, 2H), 1.37−1.45 (m, 2H), 1.65−1.71 (m, 2H), 2.25−2.32 (m, 4H), 2.41−2.44 (m, 2H), 2.63−2.68 (m, 2H), 3.68 (s, 3H), 4.25−4.32 (m, 1H), 6.26 (dd, J = 6.0 and 15.7 Hz, 1H), 6.82 (d, J = 15.7 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 9.6, 22.9, 24.8, 25.6, 28.7, 28.9, 29.0, 29.2, 30.2, 33.8, 34.0, 51.4, 73.6, 124.1, 139.9, 141.4, 163.1, 174.1, 209.5. $[\alpha]^{20}_D = -23$ (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.84; H, 9.43.

Phytoprostane B_1 Type I Methyl Ester (1a). A solution of (*S*)-phosphonium salt **9a** (518.6 mg, 1.12 mmol, 1.4 equiv) in dry tetrahydrofuran (6 mL) was cooled to −78 °C under nitrogen and treated with lithium dimethylsilyl amide (1 M in tetrahydrofuran, 2.1 mL, 2.13 mmol, 2.65 equiv).

The temperature was allowed to rise to −25 °C and then after 15 min was lowered again to −78 °C. To this orange-red solution was added dropwise a solution of aldehyde **17** (158 mg, 0.80 mmol, 1 equiv) in dry tetrahydrofuran (3 mL) at −78 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched by addition of a 10% NH_4Cl solution (10 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and washed with 10% NH_4Cl solution (2 × 10 mL, to pH 7) and brine (10 mL). The organic extracts were dried and concentrated, and the crude material was

purified by column HPLC (SI-60, 5μm): cyclohexane/ethyl acetate 50:50; 3.0 mL/min at 254 nm t_R: 23 min (29% after two steps). R_f: 0.53 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 3457 (O−H), 1734 (C=O), 1715 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.00 (t, J = 7.5 Hz, 3H), 1.28−1.33 (m, 6H), 1.57−1.64 (m, 2H), 1.37−1.45 (m, 2H), 1.65−1.72 (m, 2H), 2.23−2.33 (m, 4H), 2.42−2.45 (m, 2H), 2.64−2.68 (m, 2H), 3.68 (s, 3H), 4.26−4.31 (m, 1H), 6.27 (dd, J = 6.0 and 15.7 Hz, 1H), 6.82 (d, J = 15.7 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 9.6, 22.9, 24.8, 25.6, 28.7, 28.9, 29.0, 29.2, 30.2, 33.8, 34.0, 51.4, 73.6, 124.1, 139.9, 141.4, 163.1, 174.1, 209.5. $[\alpha]^{20}_D$ = +23 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.80; H, 9.42.

9(*S*)-Hydroxy-10-chlorodeca-6-ynoic Acid (19a). To a stirred solution of 8-heptynoic acid (4 g, 31.70 mmol, 1 equiv) in tetrahydrofuran (101 mL) at −78 °C was added 2.5 M *n*-BuLi in hexane (25.4 mL, 63.4 mmol, 2 equiv), and the mixture was stirred at −78 °C for 1 h. (*S*)-Epichlorhydrin (2 g, 21.61 mmol, 0.68 equiv) and $BF_3{\cdot}Et_2O$ (4.0 mL, 31.70 mmol, 1 equiv) were added, and the mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. After 2 h, the reaction was quenched with saturated NaCl (30 mL) and acidified with 1 N aqueous HCl (25 mL, to pH 2). The mixture was extracted with ethyl acetate (3 × 60 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), dried, and concentrated. The crude material was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give compound **19a** as a colorless oil (5.8 g, 74%). R_f: 0.66 (cyclohexane/ethyl acetate 60:40, 2% acetic acid). IR ν (cm^{-1}): 3050−3450 (COOH), 3453 (OH), 1715 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.52−1.60 (m, 2H), 1.71−1.78 (m, 2H), 2.18−2.24 (m, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.49−2.54 (m, 2H), 3.63 (dd, J = 6.0 and 11.2 Hz, 1H), 3.71 (dd, J = 4.6 and 11.2 Hz, 1H), 3.92−3.98 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 18.4, 23.8, 24.7, 28.1, 33.4, 48.2, 70.0, 75.1, 82.9, 179.3. $[\alpha]^{20}_D$ = −12 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{17}ClO_3$: C, 54.92; H, 6.91. Found: C, 54.99; H, 7.00.

9(*S*)-Hydroxy-10-chlorodeca-6-ynoic Acid Methyl Ester (20a). To a solution of compound **19a** (5.77 g, 31.69 mmol, 1 equiv) in methanol (63 mL) was added a solution of acetyl chloride (0.90 mL, 12.68 mmol, 0.4 equiv) in methanol (22.6 mL) at room temperature, under nitrogen. The reaction mixture was stirred at reflux for 20 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (100 mL) and neutralized with a 10% $NaHCO_3$ solution (60 mL). The organic layer was washed with brine (30 mL) and water (30 mL), dried, and concentrated under reduced pressure. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 80:20) to give compound **20a** (4.2 g, 68%). R_f: 0.72 (cyclohexane/ethyl acetate 60:40). IR ν (cm^{-1}): 3453 (OH), 1734 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.50−1.58 (m, 2H), 1.70−1.79 (m, 2H), 2.18−2.24 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.50−2.55 (m, 2H), 3.63 (dd, J = 6.2 and 11.3 Hz, 1H), 3.69 (s, 3H), 3.71 (dd, J = 4.5 and 11.4 Hz, 1H), 3.92−3.98 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 18.4, 24.0, 24.7, 28.2, 33.5, 48.3, 51.5, 70.0, 75.0, 83.0, 173.9. $[\alpha]^{20}_D$ = +13 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{17}ClO_3$: C, 54.78; H, 7.36. Found: C, 54.87; H, 7.45.

9(*S*)-Hydroxy-10-chlorodecanoic Acid Methyl Ester (21a). A mixture of compound **20a** (4 g, 20.38 mmol, 1 equiv) and 10% Pd/C (800 mg) in ethyl acetate (41 mL) was hydrogenated at 70 psi for 10 h. The mixture was filtered through Celite and the filtrate concentrated to provide **21a** as a colorless oil which was used in the next step without further purification. R_f: 0.65 (cyclohexane/ethyl acetate 70:30). IR ν (cm^{-1}): 3453 (OH), 1734 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.29−1.38 (m, 6H), 1.42−1.48 (m, 2H), 1.50−1.56 (m, 2H), 1.58−1.67 (m, 2H), 2.31 (t, J = 7.5 Hz, 2H), 3.48 (dd, J = 6.9 and 11.2 Hz, 1H), 3.63 (dd, J = 3.3 and 11.2 Hz, 1H), 3.67 (s, 3H), 3.76−3.83 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 24.9, 25.4, 28.9, 29.1, 34.0, 34.1, 50.5, 51.4, 71.4, 174.3. $[\alpha]^{20}_D$ = −8 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{21}ClO_3$: C, 55.81; H, 8.94. Found: C, 55.96; H, 8.99.

9(*S*)-Hydroxy-10-iododecanoic Acid Methyl Ester (22a). A mixture of compound **21a** (5.4 g, 26.79 mmol, 1 equiv) and sodium iodide (9 g, 59.94 mmol, 2.2 equiv) in dry 2-butanone (70 mL) was refluxed for 2 days. After NaCl was removed by filtration, the filtrate was concentrated, and the oily residue was dissolved in ethyl acetate (300 mL) and washed with 10% $Na_2S_2O_3$ (3 × 80 mL), saturated $NaHCO_3$ (80 mL), and brine (80 mL). The organic layer was dried and concentrated. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 90:10) to give compound **22a** (5.89 g, 68%). R_f: 0.63 (cyclohexane/ethyl acetate 60:40). IR ν (cm^{-1}): 3453 (OH), 1734 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 1.25−1.34 (m, 6H), 1.37−1.44 (m, 2H), 1.48−1.56 (m, 2H), 1.56−1.63 (m, 2H), 2.28 (t, J = 7.5 Hz, 2H), 3.21 (dd, J = 6.4 and 10.1 Hz, 1H), 3.35 (dd, J = 3.9 and 10.1 Hz, 1H), 3.45−3.55 (m, 1H). 3.64 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 16.5, 24.9, 25.5, 28.9, 29.0, 34.0, 36.5, 51.5, 70.9, 174.3. $[\alpha]^{20}_D$ = −3 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{11}H_{21}IO_3$: C, 40.26; H, 6.45. Found: C, 40.32; H, 6.51.

2(*S*)-Hydroxy-10-carbonylnonyltriphenylphosphonium Iodide (23a). To a solution of the hydroxy iodide **22a** (4.9 g, 14.93 mmol, 1 equiv) in dry tetrahydrofuran (45 mL) was added triphenylphosphine (7.83 g, 29.87 mmol, 2 equiv). The mixture was heated under reflux for 7 days in the absence of oxygen and then concentrated at reduced pressure. The oily residue obtained was triturated and washed with dry diethyl ether to give the title compound **23a** as a yellow oil (7.2 g, 86%). R_f: 0.64 (dichloromethane/methanol 95:5). IR ν (cm^{-1}): 3359 (OH), 1739 (C=O). ^{31}P NMR (81 MHz, $CDCl_3$, external ref: H_3PO_4) δ: +24.4. ^1H NMR (360 MHz, $CDCl_3$) δ: 1.10−1.25 (m, 4H), 1.25−1.30 (m, 2H), 1.49−1.55 (m, 2H), 1.71−1.75 (m, 1H), 1.90−2.00 (m, 1-H), 2.29 (t, J = 7.5 Hz, 2H), 3.20−3.36 (m, 1H), 3.61 (s, 3H), 3.82−3.99 (m, 1H), 4.00−4.10 (m, 1H), 7.65−7.70 (m, 6H), 7.72−7.79 (m, 9H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 24.8, 25.5, 28.9, 29.0, 31.7 (d, J = 50.5 Hz), 34.0, 38.7 (d, J = 13.0 Hz), 51.4 (s, 3H), 66.5 (d, J = 7.5 Hz), 118.8 (d, J = 87.7 Hz), 130.3 (d, J = 12.2 Hz), 134.1 (d, J = 10.3 Hz), 134.8 (d, J = 2.9 Hz), 174.3. $[\alpha]^{20}_D$ = +35 (1 × 10^{-2}, MeOH). Anal. Calcd for $C_{22}H_{24}IOP$: C, 57.16; H, 9.63. Found: C, 57.19; H, 9.68.

2-Formyl-5-*n*-propylfuran (24). To *N*,*N*-dimethylformamide (52.3 mL, 703.58 mmol, 1.3 equiv) was added dropwise freshly distilled phosphorus oxychloride (23.3 mL, 249.66 mmol, 1.1 equiv) at room temperature, under nitrogen. The mixture was stirred at 70 °C for 1 h and cooled at 10 °C. Then, a solution of commercially 2-*n*-propylfuran **6** (25 g, 226.96 mmol, 1 equiv) in dry *N*,*N*-dimethylformamide (136.1 mL) was added dropwise by cannulation, and the resulting mixture was stirred for 3 h. Ice-cold water (491 mL) was then added, and the mixture was neutralized with 99.32 g of sodium hydrogenocarbonate and 97 mL of saturated sodium carbonate. The aqueous layer was extracted with diethyl ether (3 × 500 mL). The organic layers were washed with brine (2 × 200 mL), dried, and concentrated to give the crude material. Fractional distillation afforded compound **24** (23.10 g, 75%) as a colorless oil. Bp: 84 °C (8 mbar). R_f: 0.70 (cyclohexane/ethyl acetate 80:20). IR ν (cm^{-1}): 1683 (C=O). ^1H NMR (360 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.5 Hz, 3H), 1.62−1.72 (m, 2H), 2.64 (t, J = 7.5 Hz, 2H), 6.19 (d, J = 3.7 Hz, 1H), 7.13 (d, J = 3.3 Hz, 1H), 9.46 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.6, 20.9, 30.2, 108.7, 123.5, 151.8, 163.8, 176.8. Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.61; H, 7.39.

2-Dimethoxymethyl-5-*n*-propylfuran (25). To solution of compound **24** (23.1 g, 167.20 mmol, 1 equiv) in methanol (55.7 mL) were added sequentially at 0 °C, under nitrogen, trimethyl orthoformate (29.3 mL, 267.54 mmol, 1.6 equiv) and *p*-toluenesulfonic acid hydrate (445.3 mg, 2.34 mmol, 0.014 equiv). The reaction mixture was stirred at room temperature for 2 h, neutralized with sodium hydrogenocarbonate (702.4 mg), and filtered, and solvent was removed under reduced

pressure to give a crude material. Fractional distillation afforded compound **25** (29.60 g, 93%) as a colorless oil. Bp: 86 °C (8 mbar). R_f: 0.74 (cyclohexane/ethyl acetate 80:20, 2% triethylamine). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.96 (t, J = 7.5 Hz, 3H), 1.62−1.72 (m, 2H, 7-H), 2.61 (t, J = 7.5 Hz, 2H), 3.36 (s, 1H). 5.39 (s, 1H). 5.96 (d, J = 3.0 Hz, 1H), 6.31 (d, J = 3.0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.6, 21.3, 30.0, 52.8, 98.2, 105.2, 109.1, 148.8, 156.6. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.81.

2-Dimethoxymethyl-5-*n*-propyl-2,5-dimethoxy-2,5-dihydrofuran (26). To a solution of compound **25** (29 g, 157.11 mmol, 1 equiv) in dry methanol (158 mL, 1 M) was added dry sodium bicarbonate (25 g, 236.11 mmol, 1.5 equiv). The mixture was cooled to −30 °C, and a solution of bromide (8.1 mL, 165.28 mmol, 1.05 equiv) in dry methanol (74 mL, 2.25 M) was added slowly over 20 min. After being stirred at the same temperature for 2 h, the mixture was allowed to warm to room temperature and methanol was removed under reduced pressure. The residue was dissolved in diethyl ether (500 mL), and 300 mL of 2% Na_2CO_3 and 100 mL of water were added. The aqueous layers were extracted with diethyl ether (2 × 500 mL). The combined organic layers were washed with water (2 × 200 mL), dried, and concentrated giving a crude material **26** which was used in the next steps without further purification. R_f: 0.77 (cyclohexane/ethyl acetate 70:30). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.85 (t, J = 7.5 Hz, 3H), 1.27−1.45 (m, 2H), 1.54−1.71 (m, 1H), 1.82−1.97 (m, 1H), 3.20−3.25 (m, 6H), 3.42 (s, 6H), 4.18 (s, 1H), 5.83 (d, J = 6.2 Hz, 1H), 6.05 (d, J = 6.2 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 14.2, 17.5, 38.2, 49.7, 50.5, 56.6, 57.8, 106.5, 112.2, 113.2, 128.6, 135.0.

3-Dimethoxymethyl-3-hydroxy-2-ethylcyclopent-4-en-1-one (4). To a solution of compound **26** (18.8 g, 76.5 mmol, 1 equiv) in dioxane (76.5 mL) were added sequentially 0.1 N aqueous citric acid (107.5 mL) and 0.2 N aqueous Na_2HPO_4 (6.8 mL). After the mixture was stirred at 55 °C for 2 h, 0.2 N aqueous Na_2HPO_4 (249 mL) was added, and stirring was continued at 75 °C for 2 h. The reaction mixture was cooled and saturated with crystalline NaCl, and then it was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine (200 mL), dried, and concentrated. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 70:20) to give a yellow oil **4** (11.6 g, 75% after two steps). R_f: 0.47 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 3476 (H−O), 1715 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.05(t, J = 7.5 Hz, 3H), 1.34−1.46 (m, 1H), 1.62−1.76 (m, 1H), 2.17 (t, J = 7.0 Hz, 1H), 3.34 (s, 3H), 3.54 (s, 3H), 4.25 (s, 1H), 6.13 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 6.0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.3, 17.4, 57.2, 58.9, 59.4, 83.2, 107.7, 134.4, 159.4, 206.0.

3-Dimethoxymethyl-3-hydroxy-2-ethylcyclopentan-1-one (28). A mixture of compound **4** (3.65 mg, 18.23 mmol, 1 equiv) and 10% Pd/C (365 mg) in methanol (37 mL) was hydrogenated at atmospheric pressure for 30 min. The mixture was filtered through Celite and the filtrate concentrated to provide **28** as a colorless oil which was used in the next steps without further purification. R_f: 0.58 (cyclohexane/ethyl acetate 50:50).

3-Dimethoxymethyl-2-ethylcyclopent-2-en-1-one (29). Acetyl chloride (0.86 mL, 12.03 mmol, 0.66 equiv) was added dropwise to dry methanol (92 mL), and the 0.13 N hydrogen chloride solution obtained was cooled to 20 °C and was added to compound **28** (3.6 mg, 18.23 mmol, 1 equiv) at room temperature, under nitrogen. The reaction mixture was stirred for 3 h and neutralized with a 10% $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed with brine (40 mL) and water (40 mL), dried, and evaporated under reduced pressure. The crude material was purified by column chromatography (cyclohexane/ethyl acetate 90:10) to give compound **29** (1.9 mg, 69% after two steps). R_f: 0.73 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 1715 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.00 (t, J = 7.5 Hz, 3H), 2.28 (q, J = 7.5 Hz, 2H), 2.31−2.39 (m, 2H), 2.53−2.70 (m, 2H), 3.38 (s, 3H), 5.20 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.1, 16.5, 25.4, 33.9, 28.9, 53.9, 100.9, 144.5, 165.5, 209.1. Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.26; H, 8.81.

3-Formyl-2-methoxycarbonylheptylcyclopent-2-en-1-one (30). To a solution of compound **29** (200 mg, 1.08 mmol, 1 equiv) in tetrahydrofuran (1.1 mL) was added 1 N aqueous hydrochloric acid (2.3 mL). The mixture was stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate (10 mL) and washed with water (4 × 8 mL, to pH 7). The aqueous layer was extracted with ethyl acetate (4 × 40 mL) and dried. The solvent was removed to give compound **30** which was used immediately in the next step. R_f: 0.70 (cyclohexane/ethyl acetate 50:50). IR ν (cm^{-1}): 1734 (C=O), 1683 (C=O).

***ent*-Phytoprostane B$_1$ Type II Methyl Ester (2b).** A solution of (*R*)-phosphonium salt **23b** (261.5 mg, 0.46 mmol, 1.4 equiv) in dry tetrahydrofuran (1.5 mL) was cooled to −78 °C under nitrogen and treated with lithium dimethylsilylamide (1 M in tetrahydrofuran, 0.87 mL, 0.87 mmol, 2.65 equiv).

The temperature was allowed to rise to −25 °C and then after 20 min was lowered again to −78 °C. To this orange-red solution there was added dropwise a solution of aldehyde **30** (45 mg, 0.32 mmol, 1 equiv) in dry tetrahydrofuran (0.7 mL) at −78 °C. After being stirred at the same temperature for 15 min, the reaction mixture was quenched by addition of a 10% NH_4Cl solution (6 mL). The mixture was extracted with ethyl acetate (3 × 8 mL), and the combined extracts were washed with 10% NH_4Cl solution (2 × 3 mL, to pH 7) and brine (4 mL). The organic extracts were dried and concentrated. The crude material was purified by column HPLC (SI-60, 5 μm): cyclohexane/ethyl acetate 50:50; 3.0 mL/min at 270 nm t_R: 30 min, 23% after two steps. R_f: 0.43 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 3457 (OH), 1734 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.01 (t, J = 7.5 Hz, 3H), 1.27−1.49 (m, 8H), 1.56−1.66 (m, 4H), 2.23−2.34 (m, 4H), 2.40−2.45 (m, 2H), 2.62−2.66 (m, 2H), 3.66 (s, 3H), 4.33 (m, J = 6.0 and 12 Hz, 1H), 6.26 (dd, J = 6.0 and 15.0 Hz, 1H), 6.81 (d, J = 15.0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.5, 16.3, 24.8, 25.3, 25.6, 29.0, 29.1, 29.3, 33.9, 34.0, 37.2, 51.5, 72.3, 123.7, 140.3, 142.7, 162.8, 174.3, 209.6. $[\alpha]^{20}_D = -24$ (1×10^{-2}, MeOH). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.82; H, 9.44.

Phytoprostane B$_1$ Type II Methyl Ester (2a). A solution of (*S*)-phosphonium salt **23a** (1.31 g, 2.28 mmol, 1.4 equiv) in dry tetrahydrofuran (9.6 mL) was cooled to −78 °C under nitrogen and treated with lithium dimethylsilyl amide (1 M in tetrahydrofuran, 4.24 mL, 4.24 mmol, 2.65 equiv).

The temperature was allowed to rise to −25 °C and then after 15 min was lowered again to −78 °C. To this orange-red solution was added dropwise a solution of aldehyde **30** (1.60 mmol, 1 equiv) in dry tetrahydrofuran (3.2 mL) at −78 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched by addition of a 10% NH_4Cl solution (15 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with 10% NH_4Cl solution (2 × 10 mL, to pH 7) and brine (10 mL). The organic extracts were dried and concentrated, and the crude material was purified by column HPLC (SI-60, 5 μm): cyclohexane/ethyl acetate 50:50; 2.25 mL/min at 270 nm t_R: 30 min, 29% after two steps. R_f: 0.48 (cyclohexane/ethyl acetate 40:60). IR ν (cm^{-1}): 3457 (O−H), 1734 (C=O), 1715 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.00 (t, J = 7.5 Hz, 3H), 1.26−1.45 (m, 8H), 1.52−1.64 (m, 4H), 2.22−2.30 (m, 4H), 2.42−2.45 (m, 2H), 2.62−2.68 (m, 2H), 3.67 (s, 3H), 4.32 (q, J = 6.0 and 12 Hz, 1H), 6.26 (dd, J = 6.0 and 15.0 Hz, 1H), 6.80 (d, J = 15.0 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.5, 16.3, 24.8, 25.3, 25.6, 29.0, 29.1, 29.2, 33.9, 34.0, 37.2, 51.4, 72.3, 123.7, 140.3, 142.7, 162.8, 174.3, 209.6. $[\alpha]^{20}_D = +24$ (1×10^{-2}, MeOH). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.84; H, 9.43.

Acknowledgment. We gratefully acknowledge the Ministère de l'Education Nationale et de la Recherche for financial support for S.E. We thank Prof. Janis Freimanis and Prof. Vladimir Bezuglov for helpful discussions. We are grateful to Dr. Agnes Vidal for carefully reading the manuscript.

Supporting Information Available: ^{1}H and ^{13}C NMR data for compounds **3**, **4**, **8a**, **9a**, **11**, **16**, **17**, **20a**–**23a**, **24**–**26**, and **29** and the target compounds **1a**, **2a**, **1b**, and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048179+