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Stereoselective Synthesis of a *cis*-1,2-Dialkylcyclopentane Building Block and Its Application in Isoprostane Synthesis (5-*ent*-F_{2c}-IsoP)

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Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

Keywords: Natural products / Stereoselective synthesis / Wittig reaction / Total synthesis / Protecting groups

The all-*cis* substituted cyclopentane **3a**, an analogue of the Corey lactone, has been prepared from a readily available nortricyclanone derivative by a five-step sequence in an overall yield of 34 %. This chiral building block has been applied in total syntheses of two diastereomeric isoprostanes belonging to the 5-F_2 family: *ent*-5-F_{2c}-IsoP (*ent*-**1**) and 5-*epi*-*ent*-5-F_{2c}-IsoP (*ent*-**2**). Key features of the syntheses are the introduction of the two unsaturated alkyl side chains through an *E*-selective Horner–Wadsworth–Emmons reaction with the base-sensitive *syn*-aldehyde **10**, along with a *Z*-selective Wittig olefination.

Introduction

Isoprostanes (IsoPs) are a family of eicosanoids discovered in the early 1990s by Morrow et al.[1,2] These prostaglandin-like compounds are formed in vivo by free radical-initiated peroxidation of phospholipid-bound arachidonic acid. This process is independent of the cyclooxygenase enzyme system and can occur either by an endoperoxide mechanism or by a dioxetane/endoperoxide mechanism.[3] The key structural difference between isoprostanes and prostaglandins is the *cis* arrangement of the two carbon side chains on the five-membered ring in isoprostanes. Formulas of representative examples are collected in Figure 1. F_2-, D_2-, and E_2-IsoPs are directly formed, while A_2- and J_2-IsoPs are presumably derived from E- and D-IsoPs by dehydration.[4]

The all-*cis* isomers of the 5-F_2 series constitute the most abundant IsoPs discovered in human urine.[5] Given the all-*cis* configuration of the cyclopentane moiety, four stereoisomers are possible: 5-F_{2c}-IsoP (**1**) and its enantiomer *ent*-5-F_{2c}-IsoP (*ent*-**1**), as well as 5-*epi*-5-F_{2c}-IsoP (**2**) and its enantiomer 5-*epi*-*ent*-5-F_{2c}-IsoP (*ent*-**2**) (Figure 2).[6]

Thanks to the chemical stability of F_2-IsoPs, the quantification of these compounds constitutes a reliable method for assessing the status of oxidative stress in vivo.[7] This provides an important tool for the exploration of the role of oxidative stress in the pathogenesis of a variety of human diseases such as Alzheimer's disease,[8] arteriosclerosis,[9] and several lung diseases, such as asthma.[10] Besides their ability to act as biomarkers of oxidative stress, isoprostanes have also been shown to possess numerous biological activi-

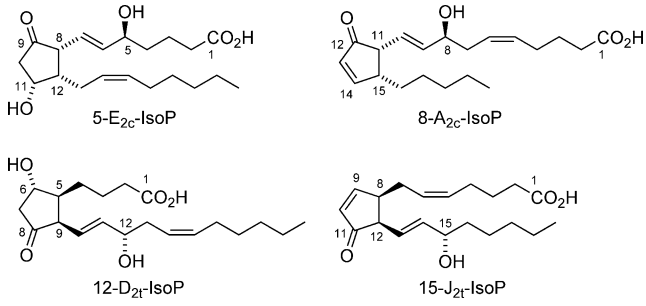

Figure 1. Important classes of isoprostanes.

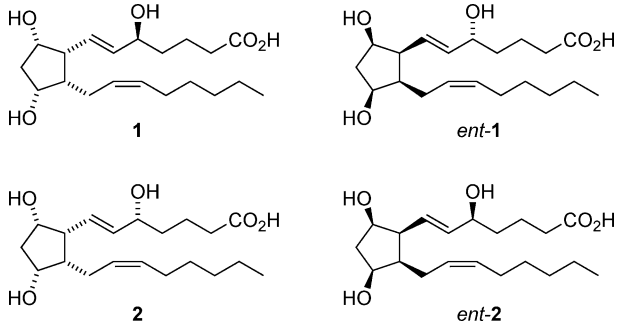

Figure 2. Stereoisomeric isoprostanes of the 5-F_2-IsoP series.

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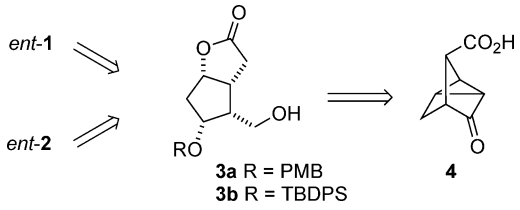
ties. Most of the knowledge available is based on the biological actions of 15-F_{2t}-IsoP, which is a potent vasoconstrictor.[11]

Many efforts towards the total synthesis of isoprostanes have been made in order to supply necessary amounts for their in vivo detection and identification, as well as for examination of their biological properties. The dominant key strategy in isoprostane synthesis is the stereocontrolled construction of a functionalized cyclopentane core into which the two alkyl side chains are introduced through olefination reactions.[12–18] Versatile building blocks should be the monoprotected bicyclic lactones **3** (Scheme 1), all-*cis* analogues of the well known Corey lactone, which has been applied successfully in the synthesis of numerous naturally occurring prostaglandins.[19] We have now developed a route allowing access to compounds of type **3** from the readily available nortricyclanone (**4**, see below).



Scheme 1. Lactones of type **3** as key intermediates for syntheses of isoprostanes.

Several syntheses of all-*cis* isoprostanes involve monoprotected lactones of type **3** as key intermediates. An early racemic approach based on a radical addition-acyl migration sequence of a bicyclic monoselenoacetal was reported by Renaud et al.[20] Most of the stereoselective syntheses are based on a biomimetic free-radical-induced cyclization as a key step to construct the bicyclic lactone moiety. Rokach's and Rossi's groups were the first to implement this strategy in the synthesis of all-*cis* isoprostanes, although, unfortunately, mixtures of diastereomeric bicyclic lactones were obtained in all cases. Nevertheless, bicyclic lactones isolated from these mixtures were used for syntheses of various isoprostanes.[3a,21] A highly stereoselective radical cyclization to provide the all-*cis* Corey lactone analogue **3b** was devised by Mulzer and co-workers in 2001.[12d] Recently, the Diels–Alder-based preparation of a precursor of lactone **3** with the CH_2OH group replaced by a vinyl group was reported.[22]

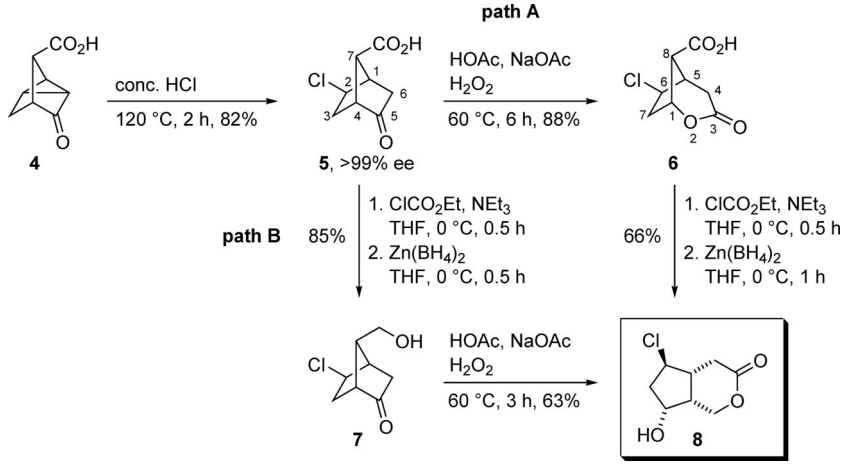
Apart from isoprostane synthesis, all-*cis* lactones **3** are also of interest for accessing highly substituted cyclopentanoids with biological significance. Their synthesis should be highly diastereoselective and provide both pure enantiomers. In this paper we describe a short synthesis of all-*cis* lactone **3a** starting from the tricyclic carboxylic acid **4** (Scheme 1). Enantiomerically pure **4** is readily available in large quantities (up to 50 g) from cheap starting materials, as shown previously by this group.[23] The all-*cis* lactone **3a** was used in total syntheses of two isoprostanes of the 5-F_2 series. As syntheses of isoprostanes **1** and **2** (see Figure 2) have been reported by Rokach et al.,[24] we decided to prepare the enantiomers *ent*-**1** and *ent*-**2** in order to complete the characterization of all all-*cis* isomers of the 5-F_2 series, which would be desirable for biological evaluation.

Results and Discussion

Preparation of the all-*cis* Lactone 3

In the first phase of the synthesis, carboxylic acid **4** was transformed into the bicyclic lactone **8** by route A or route B (Scheme 2).

Treatment of the carboxylic acid **4** with aqueous concentrated HCl at 120 °C proceeded with high selectivity to give the *exo*-chloronorbornane derivative **5** in a pure form and in 82% yield after recrystallization. Although racemization is unlikely in this step, the enantiomeric purity of **5** was determined and found to be >99% *ee*.[25] Baeyer–Villiger oxidation of ketone **5** with peracetic acid generated in situ at 60 °C gave the lactone **6** with perfect regioselectivity (Scheme 2, route A). This compound was obtained pure in 88% yield after removal of acetic acid by azeotropic distil-



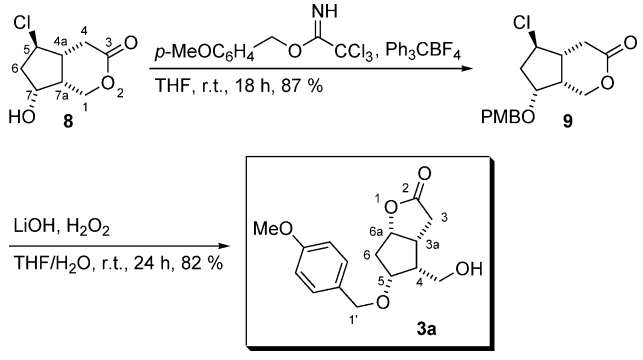
Scheme 2. Synthesis of the bicyclic lactone **8**.

lation with toluene and recrystallization. Lactone **6** displayed a characteristic ^{1}H NMR signal for C-1 at δ = 5.05–5.08 ppm. Reactions with other peracids such as performic acid, *m*CPBA/$NaHCO_3$, and *m*CPBA/*p*TSA proceeded with low selectivities of 2:1 to 4:1 for secondary vs. primary carbon migration. Chemoselective reduction of carboxylic acid **6** via a mixed anhydride, prepared in situ by treatment with ethyl chloroformate, gave the corresponding alcohol, which underwent intramolecular transesterification to afford bicyclic lactone **8** in 66% yield after column chromatography. Among a number of reducing agents investigated, zinc borohydride gave the highest chemoselectivity. This reducing agent was previously applied by Corey and co-workers in a synthesis of the Corey lactone.[26]

Reductions of mixed anhydrides derived from cyanuryl chloride (2,4,6-trichloro-1,3,5-triazine) and trifluoroacetic acid, as well as the acid chloride of **6**, were less effective in combination with zinc borohydride and sodium borohydride. Attempts to reduce the carboxylic acid **6** directly with borane/THF, borane/dimethyl sulfide, or borane generated in situ from sodium borohydride and iodine also resulted in lower yields. Lactone **8** was prone to decomposition during column chromatography on silica gel, though the use of dried silica gel reproducibly gave the yields stated above.

In an alternative route to the bicyclic lactone **8** (Scheme 2, route B) the order of reduction and rearrangement was reversed. Route B began with the chemoselective reduction of carboxylic acid **5** via the mixed anhydride, again formed with ethyl chloroformate. With zinc borohydride (0.25 equiv.) as reducing agent, the carbonyl group of the anhydride moiety was reduced in preference to the keto group. The alcohol **7** was obtained in 85% yield after column chromatography. Transformation of **7** into the lactone **8** by Baeyer–Villiger oxidation under the conditions described above gave an isolated yield of only 63%; the undesired regioisomer could not be detected. In general, both pathways are suitable to provide lactone **8** in multigram quantities.

The preparation of an *O*-protected derivative of lactone **8** turned out to be more difficult than anticipated (Scheme 3). Due to the sensitivity of the lactone moiety towards base and nucleophiles, effecting either intermolecular nucleophilic substitution or C–O cleavage, respectively, many standard protocols for the protection of



Scheme 3. Synthesis of key intermediate **3a**.

alcohols gave low yields.[27] Finally, bicyclic lactone **8** was transformed into its *p*-methoxybenzyl (PMB) ether **9** in 87% yield by treatment with *p*-methoxybenzyl trichloroacetimidate in the presence of a catalytic amount of triphenylmethyl tetrafluoroborate.[28] Conversion of the lactone **9** into the targeted all-*cis* lactone **3** by lactone hydrolysis/nucleophilic displacement was achieved in 82% isolated yield by treatment with lithium hydroxide/hydrogen peroxide in a THF/water mixture as described previously in a synthesis of the Corey lactone.[26,29]

The five-step sequence starting from carboxylic acid **4** furnished lactone **3a** in an excellent overall yield of 34%. The presumed configuration was validated by nOe experiments. The proton 3a-H displayed nOes of 5.8% and 5.1% to protons 6a-H and 4-H, respectively; this confirms the *cis* relationship of these protons (Figure 3).

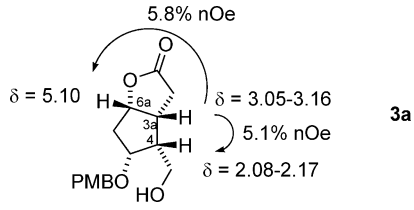
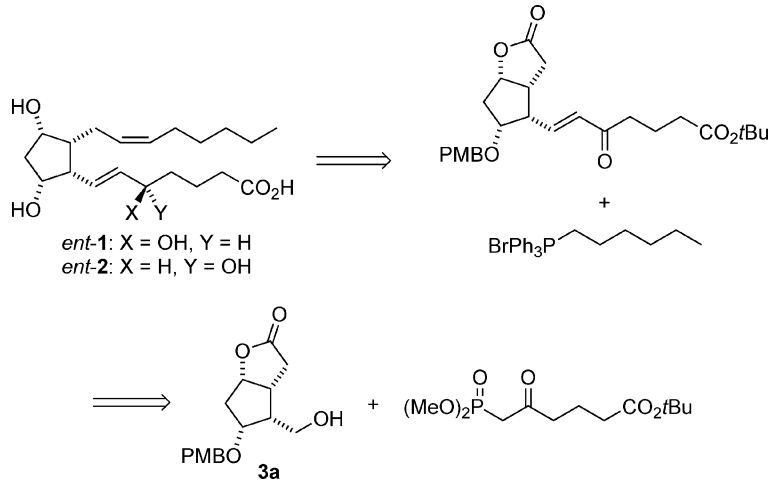


Figure 3. Nuclear Overhauser effects observed for lactone **3a**.

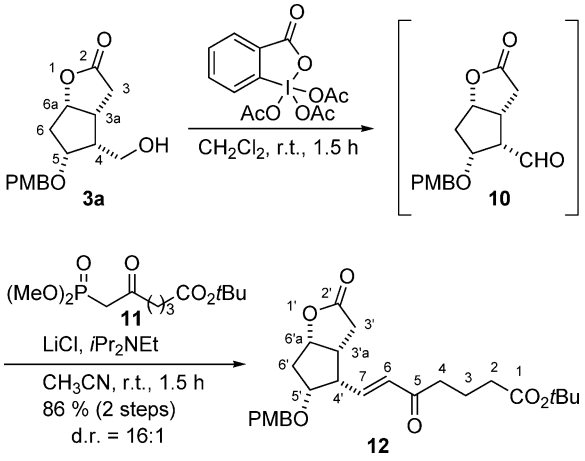
Total Syntheses of the Isoprostanes *ent*-1 and *ent*-2

With the chiral building block **3a** to hand, the syntheses of isoprostanes *ent*-**1** and *ent*-**2** were elaborated by the strategy displayed in Scheme 4. Stereoselective Wittig olefinations were the key steps.

For the introduction of the α-side chain, a Horner–Wadsworth–Emmons (HWE) olefination was planned. From previous work by Weinges et al. and others[20,21,30] it was clear that a key problem would be epimerization of the aldehyde **10** formed from **3a** by oxidation (Scheme 5). Weinges et al. obtained the best results upon protection of 5-OH with a benzyl group. Mulzer et al.,[31] as well as Rokach et al.[32] and Rossi et al.,[21] showed that a 5-*O*-silyl-protected alcohol of type **3** can be oxidized to the corresponding aldehyde without significant epimerization. Additionally, Renaud et al. reported that 5-*O*-silyl-protected aldehydes of type **10** do not undergo unwanted side reactions during HWE olefination as had been observed for *p*-phenylbenzoyl-protected aldehydes of type **10**.[20] After considerable experimentation with **3a**, we obtained good results with Dess–Martin periodinane as oxidant. Attempted purification of **10** caused epimerization to a considerable degree, but the crude aldehyde **10** was sufficiently pure for the subsequent olefination with β-keto phosphonate **11**. In the event, a mild HWE olefination protocol devised by Masamune and Roush was used.[33] With ethyldiisopropylamine as base and lithium chloride as additive, the enone **12** was obtained in 86% overall yield with a high preference (*dr* = 16:1) for the desired all-*cis* enone **12**. Within the limits of detection (NMR), only the *E* isomer was formed.



Scheme 4. General strategy for the syntheses of isoprostanes *ent*-**1** and *ent*-**2**.



Scheme 5. Preparation of enone **12**.

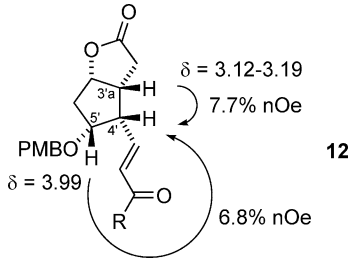


Figure 4. Nuclear Overhauser effects observed for enone **12**.

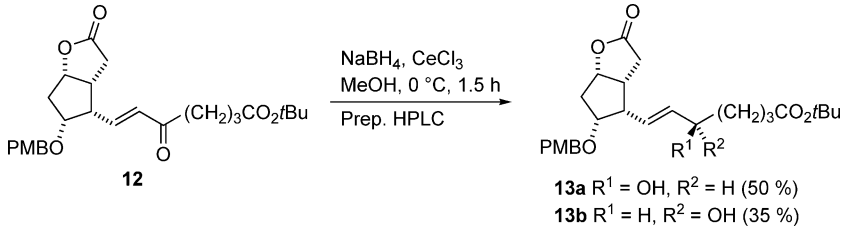
The *cis* relationship of the substituents on the cyclopentane ring of enone **12** was confirmed by nOe experiments (Figure 4).

For the next step the reduction of enone **12** to the allylic alcohols **13a** and **13b** was investigated. It was hoped that it would be possible to generate both diastereomers selectively using reagent control. However, the Itsuno–Corey procedure with *B*-methyl-oxazaborolidine catalyst[34] or with *B*-methoxy-oxazaborolidine catalyst[35] generated in situ with $H_3B{\cdot}THF$ or $H_3B{\cdot}SMe_2$ as reducing agents did not succeed. Treatment with catecholborane as stoichiometric reductant[36] suffered from low levels of conversion, reduction of enone **12** with BINAL-H[37] was accompanied by reduction of the lactone CO, and transfer hydrogenation[38] proceeded with predominant reduction of the double bond.[39]

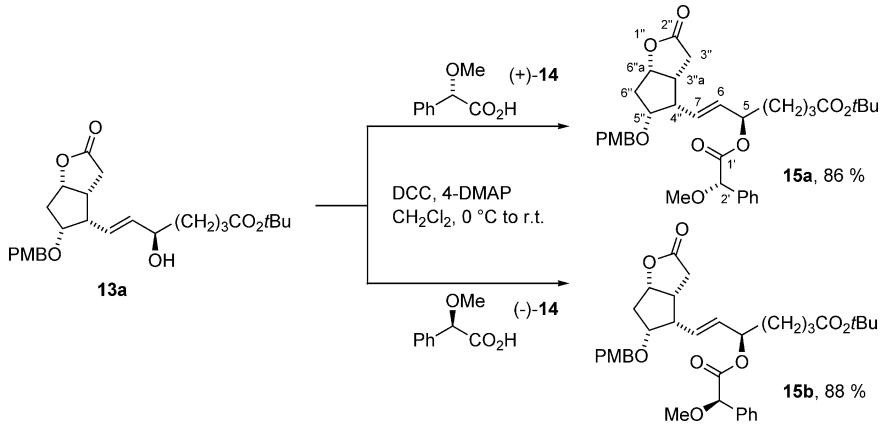
Finally, good chemoselectivity was obtained with a Luche reduction (Scheme 6). A mixture of the diastereomeric allylic alcohols **13a** and **13b** was formed, and these were separated by preparative HPLC to give alcohols **13a** and **13b** in 50 and 35% yields, respectively.

The relative configuration of C-5 was assigned by Mosher's method (Scheme 7).[40] Alcohol **13a** was esterified with (*S*)-*O*-methylmandelic acid [(+)-**14**] and (*R*)-*O*-methylmandelic acid [(–)-**14**] to give the esters **15a** and **15b**, respectively. Analysis of ^1H NMR spectra allowed an unambiguous assignment of the configuration at C-5 (Figure 5).

In a first attempt to prepare the target compounds, the OH group in alcohol **13a** was protected as a *tert*-butyldimethylsilyl (TBS) ether (Scheme 8). The ω-side chain was completed by reduction of **16a** with DIBAL-H to the lactol



Scheme 6. Preparation of the diastereomeric alcohols **13a** and **13b**.



Scheme 7. Esterification of alcohol **13a** with (*S*)- and (*R*)-*O*-methylmandelic acid.

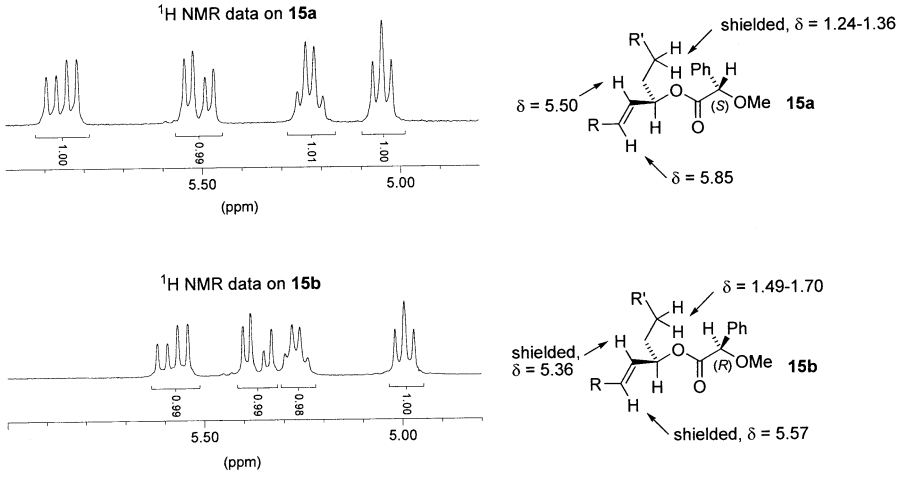
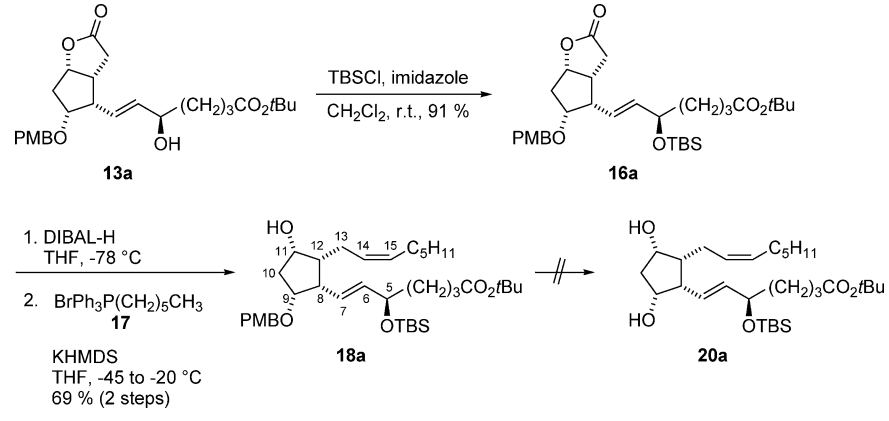


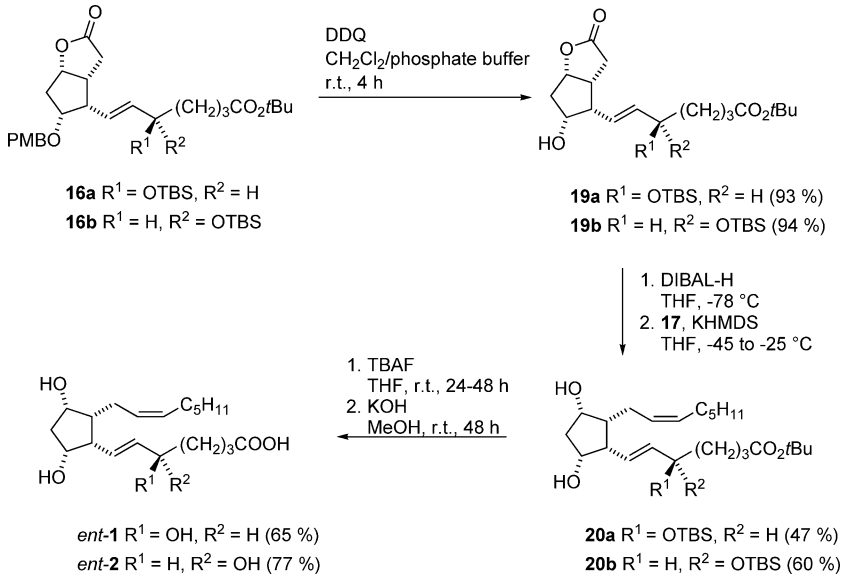
Figure 5. Assignment of the relative configuration at the stereogenic center C-5.

stage and subsequent Wittig olefination; it was important to mix the pre-cooled lactol with the cold (–45 °C) Wittig reagent derived from phosphonium salt **17**. The *Z* olefin **18a** was obtained in 69% isolated yield. Unfortunately, all attempts to remove the PMB group either furnished the diol **20a** in very low yield or resulted in decomposition (DDQ, cerium ammonium nitrate, $CeCl_3/NaI$,[41] $ZrCl_4$,[42] CF_3COOH, 1 M HCl or $Me_2S/MgBr_2{\cdot}OEt_2$[43]).

It could be argued that steric crowding within **18a** might be responsible for this failure, so it was decided to carry out



Scheme 8. First attempt to synthesize compounds **20**.



Scheme 9. Completion of the synthesis of isoprostanes *ent*-**1** and *ent*-**2**.

the deprotection at the stage of the less bulky lactones **16a** and **16b**. Indeed, treatment of these with DDQ in a CH_2Cl_2/phosphate buffer gave clean formation of alcohols **19a** and **19b** in 93–94% yields (Scheme 9). Introduction of the ω-side chain was then accomplished by reduction/Wittig olefination as described above. The *Z* olefins **20a** and **20b** were obtained in 47–60% isolated yields.

The total synthesis was completed as follows. The silyl groups was removed by treatment with nBu_4NF, and the resultant esters, **21a** or **21b** (see Exp. Section and Supporting Information), were saponified with KOH/methanol. The isoprostanes *ent*-**1** and *ent*-**2** were obtained in 65 and 77% yields, respectively. The ^{13}C NMR chemical shifts of *ent*-**1** recorded in [D_6]acetone are listed in the Supporting Information; data are in good agreement with those of Rokach et al.[24] For the assignment of all resonances of *ent*-**1** and *ent*-**2**, NMR spectra were recorded in [D_6]DMSO in order to avoid overlapping resonances.

Conclusions

A short and efficient stereoselective synthesis of the all-*cis* substituted cyclopentane building block **3a** has been developed. This compound is a versatile starting compound for the synthesis of cyclopentanoid natural products. As examples, total syntheses of two diastereomeric isoprostanes belonging to the 5-F_2 family – *ent*-5-F_{2c}-IsoP (*ent*-**1**) and 5-*epi*-*ent*-5-F_{2c}-IsoP (*ent*-**2**) – have been carried out. Key steps of the syntheses were the introduction of the two unsaturated alkyl side chains through an *E*-selective Horner–Wadsworth–Emmons reaction with the base-sensitive *syn*-aldehyde **10** and a *Z*-selective Wittig olefination. The syntheses each required 12 isolated linear steps and each gave an overall yield, from carboxylic acid **4**, of 4%.

Experimental Section

General Remarks: Melting and boiling points are uncorrected. NMR spectra were recorded on a Bruker Avance DRX 300 (300.13 MHz and 75.47 MHz for ^1H and ^{13}C, respectively) or a Bruker Avance DRX 500 (500.13 MHz and 125.75 MHz for ^1H and ^{13}C, respectively) spectrometer. The assignments of the resonances are based on ^1H,^1H COSY, HMQC, and HMBC experiments. Chemical shifts are reported in δ units relative to $CHCl_3$ (δ_H = 7.24), acetone (δ_H = 2.04), or DMSO (δ_H = 2.49) for ^1H NMR spectra and relative to the central $CDCl_3$, [D_6]acetone, or [D_6]-DMSO resonance for ^{13}C NMR spectra. The following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, m_c = centered, symmetric multiplet. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Mass spectra were recorded on a JOEL JMS 700 (FAB) or a ZAB 2F (EI) instrument. Analytical thin-layer chromatography was performed on precoated TLC plates (Polygram Sil G/UV_{254}, Macherey–Nagel); bromocresole green or molybdatophosphoric acid solutions were used for visualization. For column chromatography Macherey–Nagel silica gel grade 60 (0.032–0.062 mm) was used. For chromatography of sensitive compounds, silica gel was dried by heating for ca. 24 h at 200 °C under vacuum (0.01 mbar). Preparative HPLC was carried out with a LATEK silica gel column (250 × 21 mm, 5μ). Reagents were purchased from Aldrich or Fluka. Ethyl chloroformate was distilled prior to use and stored at 5 °C over molecular sieves (4 Å). Zinc borohydride was prepared as described in the literature[44] and stored under argon at –30 °C. *p*-Methoxybenzyl trichloroacetimidate was prepared as described in the literature[45] and stored under argon at 5 °C. Ketophosphonate **11**[46] and Dess–Martin periodinane[47] were prepared as described in the literature. THF was distilled from sodium/benzophenone ketyl, and dichloromethane was distilled from calcium hydride under argon. Reactions in dry solvents were carried out under argon with use of standard Schlenk techniques.

(–)-2-Chloro-5-oxobicyclo[2.2.1]heptane-7-carboxylic Acid (5): A mixture of the tricyclic acid (+)-**4** (1.00 g, 6.60 mmol) and concentrated hydrochloric acid (15 mL) was heated at reflux at 120 °C for

2 h in a 50 mL three-necked flask fitted with a reflux condenser and a thermometer. After the mixture had cooled to room temp., water (15 mL) was added, and the mixture was extracted with ethyl acetate (5 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was recrystallized from ethyl acetate/petroleum ether to yield chlorocarboxylic acid (–)-**5** (1.01 g, 82%) as colorless rod-like crystals. R_f = 0.16 (petroleum ether/ethyl acetate/acetic acid, 65:35:0.5). M.p. 134–136 °C. $[\alpha]_D^{20}$ = –27.0 (*c* = 3.0, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.89 (dd, *J* = 2.5, *J* = 18.6 Hz, 1 H, 6-H_A), 2.16 (dt, *J* = 3.8, *J* = 15.1 Hz, 1 H, 3-H_A), 2.28 (dd, *J* = 7.2, *J* = 14.9 Hz, 1 H, 3-H_B), 2.47 (dd, *J* = 4.9, *J* = 18.5 Hz, 1 H, 6-H_B), 2.87 (d, *J* = 4.7 Hz, 1 H, 4-H), 3.06 (d, *J* = 4.5 Hz, 1 H, 1-H), 3.44 (br. s, 1 H, 7-H), 4.10 (dd, *J* = 3.0, *J* = 7.2 Hz, 1 H, 2-H), 10.80 (br. s, 1 H, COOH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 36.2, 39.0 (2 × t, C-3 and C-6), 48.3, 49.5, 51.4 (3 × d, C-1, C-4, and C-7), 58.1 (d, C-2), 177.2 (s, C-8), 211.3 (s, C-5) ppm. $C_8H_9ClO_3$ (188.60): calcd. C 50.94, H 4.81, Cl 18.80; found C 50.99, H 4.82, Cl 18.62.

(–)-6-Chloro-3-oxo-2-oxabicyclo[3.2.1]octane-8-carboxylic Acid (6): A solution of chlorocarboxylic acid (–)-**5** (4.00 g, 21.20 mmol) and anhydrous sodium acetate (1.74 g, 21.20 mmol) in glacial acetic acid (40 mL) was stirred at room temperature in a 100 mL three-necked flask fitted with a reflux condenser, a reaction thermometer, and a dropping funnel, and hydrogen peroxide (50 wt.-%, 8 mL) was added dropwise. The reaction mixture was then warmed to 60 °C for 6 h. Ethyl acetate (40 mL) was then added, and the mixture was washed with $NaHSO_3$ solution (10%, 20 mL) in order to remove peroxides. The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (5 × 100 mL). The organic phases were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dried by double addition and evaporation of toluene. The resultant crude product (4.80 g) was crystallized from ethyl acetate/petroleum ether to give pure (–)-**6** (3.80 g, 88%) as needles. R_f = 0.11 (petroleum ether/ethyl acetate/acetic acid, 65:35:0.5). M.p. 156–158 °C. $[\alpha]_D^{20}$ = –103.9 (*c* = 3.0, EtOH). ^{1}H NMR (300.13 MHz, [D_6]acetone): δ = 2.47 (dd, *J* = 5.2, *J* = 16.8 Hz, 1 H, 7-H_A), 2.62 (dt, *J* = 1.1, *J* = 19.2 Hz, 1 H, 4-H_A), 2.82–2.95 (m, 2 H, 5-H and 7-H_B), 3.18 (dd, *J* = 6.4, *J* = 19.2 Hz, 1 H, 4-H_B), 3.42–3.45 (m, 1 H, 8-H), 4.66 (dd, *J* = 2.3, *J* = 7.5 Hz, 1 H, 6-H), 5.05–5.08 (m, 1 H, 1-H) ppm. ^{13}C NMR (75.47 MHz, [D_6]acetone): δ = 36.23 (t, C-4), 46.31 (d, C-5), 46.88 (d, C-7), 47.92 (t, C-8), 62.97 (t, C-6), 80.94 (t, C-1), 168.80 (s, C-3), 171.82 (COOH) ppm. $C_8H_9ClO_4$ (204.61): calcd. C 46.96, H 4.43, Cl 17.33; found C 46.67, H 4.50, Cl 17.08.

(–)-5-Chloro-7-(hydroxymethyl)bicyclo[2.2.1]heptan-2-one (7): A cold (0 °C) solution of (–)-**5** (2.0 g, 10.6 mmol) in dry THF (43 mL) was treated dropwise with ethyl chloroformate (1.0 mL, 10.6 mmol) and subsequently with an ice-cold solution of dry triethylamine (1.5 mL, 10.6 mmol) in dry THF (21.5 mL). A white precipitate formed, and the mixture was stirred for another 30 min. The precipitate was filtered off and washed twice with a small amount of anhydrous THF. The filtrate was cooled to 0 °C and was treated dropwise with a solution of zinc borohydride (5.3 mL, 0.5 M in DME) and further stirred at 0 °C for 30 min. Dichloromethane was then added, together with saturated sodium bitartrate solution until evolution of hydrogen ceased, which caused precipitation of a white solid. This was filtered off and washed thoroughly with dichloromethane. Drying (Na_2SO_4) of the organic fraction and evaporation of the solvent afforded crude (–)-**7** as a colorless oil. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 8:2) yielded pure (–)-**7** (1.57 g, 85%) as a colorless oil. R_f = 0.31 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –21.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.77 (dd, *J* = 2.3, *J* = 18.8 Hz, 1 H, 3-H_A), 2.12–2.37 (m, 4 H, 3-H_B, 6-H, and OH), 2.55 (d, *J* = 4.0 Hz, 1 H, 1-H), 2.73–2.83 (m, 2 H, 4-H and 7-H), 3.63–3.69 (m_c, 2 H, 1′-H), 4.08 (dd, *J* = 3.4, *J* = 7.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 36.79 (t, C-6), 38.49 (t, C-3), 46.02 (d, C-4 or C-7), 47.88 (d, C-4 or C-7), 51.14 (d, C-1), 59.05 (d, C-5), 60.02 (t, C-1′), 214.94 (s, C-2) ppm. HRMS (EI+): $[M]^+$ ($C_8H_{11}O_2{}^{37}Cl$): calcd. 176.0418; found 176.0403; $[M]^+$ ($C_8H_{11}O_2{}^{35}Cl$): calcd. 174.0447; found 174.0446. $C_8H_{11}ClO_2$ (174.63): calcd. C 55.02, H 6.35, Cl 20.30; found C 54.95, H 6.32, Cl 19.65.

(–)-(4a*R*,5*R*,7*R*,7a*R*)-5-Chloro-7-hydroxy-hexahydrocyclopenta[*c*]-pyran-3(1*H*)-one (8): A cold (0 °C) solution of (–)-**6** (5.0 g, 24.4 mmol) in anhydrous THF (100 mL) was treated dropwise with ethyl chloroformate (2.3 mL, 24.4 mmol). At the same temperature, an ice-cold solution of anhydrous triethylamine (3.4 mL, 24.4 mmol) in anhydrous THF (40 mL) was added dropwise. A white precipitate formed, and the mixture was stirred for another 30 min. The precipitate was filtered off and washed twice with anhydrous THF. The red-brown filtrate was cooled to 0 °C, and a solution of zinc borohydride in DME (17.0 mL, 0.5 M) was added dropwise. The solution was further stirred at 0 °C for 3 h and was then diluted with dichloromethane. The mixture was treated with saturated sodium bitartrate solution until evolution of hydrogen ceased, which caused precipitation of a white solid. The residue was filtered off and washed thoroughly with dichloromethane. Drying of the filtrate (Na_2SO_4) and evaporation of the solvent afforded crude (–)-**8** as a brownish oil. Flash chromatography (dried silica gel, petroleum ether/ethyl acetate, 1:1) yielded pure alcohol (–)-**8** (3.06 g, 66%) as a yellowish oil. R_f = 0.19 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –55.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.67 (br. s, 1 H, OH), 2.13 (ddd, *J* = 5.0, *J* = 8.3, *J* = 13.3 Hz, 1 H, 6-H_A), 2.24 (ddd, *J* = 4.6, *J* = 5.0, *J* = 13.5 Hz, 1 H, 6-H_B), 2.52 (dd, *J* = 7.6, *J* = 14.9 Hz, 1 H, 4-H_A), 2.66–2.72 (m, 1 H, 4a-H), 2.74–2.81 (m, 1 H, 7a-H), 2.79 (dd, *J* = 6.6, *J* = 14.9 Hz, 1 H, 4-H_B), 4.10 (dt, *J* = 5.8, *J* = 7.9 Hz, 1 H, 5-H), 4.31 (dd, *J* = 5.5, *J* = 11.9 Hz, 1 H, 1-H_A), 4.47 (dd, *J* = 7.3, *J* = 11.9 Hz, 1 H, 1-H_B), 4.60 (dt, *J* = 4.6, *J* = 6.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 32.97 (t, C-4), 39.93 (d, C-7a), 44.79 (d, C-4a), 45.51 (t, C-6), 61.36 (d, C-5), 66.01 (t, C-1), 71.83 (d, C-7), 172.30 (s, C-3) ppm. $C_8H_{11}ClO_3$ (190.63): calcd. C 50.41, H 5.82, Cl 18.60; found C 50.60, H 5.90, Cl 18.40.

Preparation of Alcohol (–)-8 from Ketone (–)-7: Ketone (–)-**7** (2.15 g, 12.30 mmol) was dissolved in a solution of anhydrous sodium acetate (1.00 g, 12.30 mmol) in glacial acetic acid (55 mL) in a 100 mL three-necked flask fitted with a reflux condenser and a reaction thermometer. The reaction mixture was stirred at room temperature, and hydrogen peroxide (50 wt.-%, 4.80 mL) was added dropwise. After complete addition, the mixture was warmed to 60 °C for 3 h and was then diluted with ethyl acetate and washed with $NaHSO_3$ solution (10%, 20 mL) in order to remove peroxides. The aqueous phase was reextracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dried by double addition and evaporation of toluene. The resultant crude (–)-**8** was subjected to flash chromatography (dried silica gel, petroleum ether/ethyl acetate, 1:1) to give pure alcohol (–)-**8** (1.49 g, 63%) as a colorless oil. For analytical data see previous procedure.

(–)-(4a*R*,5*R*,7*R*,7a*R*)-5-Chloro-7-[(4-methoxybenzyl)oxy]-hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (9): A solution of the alcohol (–)-**8** (0.60 g, 3.14 mmol) in dry THF (50 mL) was treated successively at room temperature with *p*-methoxybenzyl trichloroacetimid-

ate (2.60 g, 9.43 mmol) and triphenylcarbonium tetrafluoroborate (104 mg, 315 μmol). The pale yellow solution was stirred overnight at room temperature and then diluted with THF (20 mL), and the resultant mixture was treated with saturated $NaHCO_3$ solution. The organic solvent was evaporated under reduced pressure, and the remaining aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue (dried silica gel, petroleum ether/ethyl acetate, 75:25) yielded pure (–)-**9** (0.86 g, 87%) as a yellowish oil. R_f = 0.56 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –28.7 (*c* = 1.8, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.01 (ddd, *J* = 4.9, *J* = 7.8, *J* = 13.0 Hz, 1 H, 6-H_A), 2.34–2.45 (m, 2 H, 4-H_A and 6-H_B), 2.66 (m_c, 1 H, 4a-H), 2.76–2.86 (m, 2 H, 4-H_B and 7a-H), 3.79 (s, 3 H, OCH_3), 4.04 (dd, *J* = 5.7, *J* = 13.5 Hz, 1 H, 5-H), 4.21–4.27 (m, 2 H, 1-H_A and 7-H), 4.32 (d, *J* = 11.5 Hz, 1 H, 1′-H_A), 4.38 (dd, *J* = 9.4, *J* = 12.0 Hz, 1 H, 1-H_B), 4.50 (d, *J* = 11.5 Hz, 1 H, 1′-H_B), 6.87 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.19 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 32.89 (t, C-4), 39.48 (d, C-7a), 41.38 (t, C-6), 44.45 (d, C-4a), 55.28 (q, OCH_3), 61.39 (d, C-5), 65.89 (t, C-1), 71.54 (t, C-1′), 77.87 (d, C-7), 113.92 (d, Ar-CH), 129.09 (d, Ar-CH), 129.63 (s, Ar-C), 159.37 (s, Ar-C), 172.02 (s, C-3) ppm. HRMS (EI+): $[M]^+$ ($C_{16}H_{19}O_4{}^{37}Cl$): calcd. 312.0942; found 312.0964; $[M]^+$ ($C_{16}H_{19}O_4{}^{35}Cl$): calcd. 310.0972; found 310.0991.

(–)-(3a*R*,4*R*,5*R*,6a*S*)-4-(Hydroxymethyl)-5-[(4-methoxybenzyl)oxy]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (3a): A solution of (–)-**9** (1.00 g, 3.22 mmol) in THF (11 mL) was treated dropwise at room temperature with hydrogen peroxide (50 wt.-%; 3.70 mL) and with lithium hydroxide (1 N in water, 3.22 mL). After 24 h (TLC monitoring), peroxides were destroyed by addition of $NaHSO_3$ solution (10%), and the organic solvent was removed under reduced pressure. The remaining aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (5 × 30 mL), and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give crude (–)-**3a** as a yellowish oil. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 1:1, to ethyl acetate) yielded pure lactone (–)-**3a** (0.77 g, 82%) as a colorless oil. R_f = 0.06 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –52.0 (*c* = 1.1, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.71 (ddd, *J* = 3.8, *J* = 6.6, *J* = 15.6 Hz, 1 H, 6-H_A), 2.08–2.17 (m_c, 1 H, 4-H), 2.45–2.55 (m, 2 H, 3-H_A and 6-H_B), 2.83 (dd, *J* = 4.6, *J* = 18.5 Hz, 1 H, 3-H_B), 3.05–3.16 (m_c, 1 H, 3a-H), 3.77 (s, 3 H, OCH_3), 3.79–3.93 (m, 2 H, 1′′-H), 4.03 (t, *J* = 3.7 Hz, 1 H, 5-H), 4.15 (d, *J* = 11.5 Hz, 1 H, 1′-H_A), 4.56 (d, *J* = 11.5 Hz, 1 H, 1′-H_B), 5.10 (t, *J* = 7.2 Hz, 1 H, 6a-H), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.18 (d, *J* = 8.7 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 30.31 (t, C-3), 36.83 (t, C-6), 38.72 (d, C-3a), 48.94 (d, C-4), 55.25 (q, OCH_3), 59.82 (t, C-1′′), 70.13 (t, C-1′), 79.48 (d, C-5), 84.52 (d, C-6a), 113.83 (d, Ar-CH), 129.36 (d, Ar-CH), 129.85 (s, Ar-C), 159.24 (s, Ar-C), 177.75 (s, C-2) ppm. $C_{16}H_{20}O_5$ (292.33): calcd. C 65.74, H 6.90; found C 65.64, H 6.90.

(+)-*tert*-Butyl (6*E*)-7-{(3a*R*,4*S*,5*R*,6a*S*)-5-[(4-Methoxybenzyl)oxy]-2-oxo-hexahydro-2*H*-cyclopenta[*b*]furan-4-yl}-5-oxohept-6-enoate (12): A solution of lactone (–)-**3a** (1.36 g, 4.65 mmol) and Dess–Martin periodinane (2.37 g, 5.58 mmol) in dry dichloromethane (51 mL) was stirred at room temperature for 1.5 h. Diethyl ether (50 mL) was then added, and the resulting white suspension was poured into a solution of $Na_2S_2O_3$ (0.25 M) in a saturated $NaHCO_3$ solution (40 mL). The mixture was stirred until dissolution of the solid material, and then the layers were separated. The organic layer was extracted with saturated $NaHCO_3$ solution (40 mL) and water (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude aldehyde **10** as an oily residue.

Freshly fused LiCl (237 mg, 5.58 mmol) was suspended in dry acetonitrile (51 mL) in a Schlenk tube, and phosphonate **11** (1.64 g, 5.58 mmol) and *i*Pr_2NEt (0.97 mL, 5.58 mmol) were then added at room temperature. After the mixture had been stirred for 15 min, a solution of aldehyde **10** in dry acetonitrile (20 mL) was added by syringe and the resulting solution was stirred for 1.5 h at room temperature. The reaction mixture was treated with saturated $NaHCO_3$ solution (25 mL) and with water (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were dried with $MgSO_4$. Evaporation of the solvent afforded an oily residue that was subjected to flash column chromatography (silica gel, petroleum ether/ethyl acetate, 1:1) to yield enone (+)-**12** (1.73 g, 81%) and 4′-*epi*-**12** (0.11 g, 5%) as colorless oils. R_f(**12**) = 0.21 (petroleum ether/ethyl acetate, 1:1), R_f(4′-*epi*-**12**) = 0.24 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +7.6 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, $OC(CH_3)_3$], 1.77 (ddd, *J* = 3.7, *J* = 6.7, *J* = 15.7 Hz, 1 H, 6′-H_A), 1.87 (quin, *J* = 7.4 Hz, 2 H, 3-H), 2.24 (t, *J* = 7.4 Hz, 2 H, 4-H), 2.47–2.53 (m, 2 H, 3′-H_A and 6′-H_B), 2.57 (t, *J* = 7.4 Hz, 2 H, 2-H), 2.69–2.77 (m, 2 H, 3′-H_B and 4′-H), 3.12–3.19 (m, 1 H, 3′a-H), 3.77 (s, 3 H, OCH_3), 3.99 (t, *J* = 3.4 Hz, 1 H, 5′-H), 4.19 (d, *J* = 11.4 Hz, 1 H, 1′′-H_A), 4.55 (d, *J* = 11.4 Hz, 1 H, 1′′-H_B), 5.11 (t, *J* = 6.7 Hz, 1 H, 6′a-H), 6.12 (d, *J* = 16.1 Hz, 1 H, 6-H), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.94 (dd, *J* = 7.7, *J* = 16.4 Hz, 1 H, 7-H), 7.17 (d, *J* = 8.7 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 19.37 (t, C-3), 28.10 [q, $OC(CH_3)_3$], 31.08 (t, C-3′), 34.56 (t, C-4), 37.25 (t, C-6′), 38.97 (t, C-2), 41.48 (d, C-3′a), 49.74 (d, C-4′), 55.23 (q, OCH_3), 70.38 (t, C-1′′), 80.30 [s, $OC(CH_3)_3$], 81.07 (d, C-5′), 84.11 (d, C-6′a), 113.82 (d, Ar-CH), 129.43 and 129.54 (d and s, Ar-CH and Ar-C), 132.87 (d, C-6), 142.14 (d, C-7), 159.28 (s, Ar-C), 172.49 (s, C-1), 176.97 (s, C-2′), 199.27 (s, C-5) ppm. $C_{26}H_{34}O_7$ (458.55): calcd. C 68.10, H 7.47; found C 68.07, H 7.54.

***tert*-Butyl (6*E*)-5-Hydroxy-7-{(3a*R*,4*S*,5*R*,6a*S*)-5-[(4-methoxybenzyl)oxy]-2-oxo-hexahydro-2*H*-cyclopenta[*b*]furan-4-yl}hept-6-enoate (13):** A solution of enone (+)-**12** (1.73 g, 3.77 mmol) in dry methanol (17 mL) in a Schlenk tube was treated with $CeCl_3 \cdot 7H_2O$ (1.41 g, 3.77 mmol), and the resulting slurry was stirred until all the solid was dissolved (approx. 15 min). After the solution had been cooled to 0 °C, $NaBH_4$ (143 mg, 3.77 mmol) was added in small portions. After 1.5 h the reaction mixture was treated with water and saturated with sodium chloride. The aqueous phase was extracted with ethyl acetate (5 × 20 mL) and the combined organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography (silica gel, petroleum ether/ethyl acetate, 1:1) to yield a mixture of diastereomeric alcohols **13a** and **13b** (1.53 g, 88%) as a colorless oil. Separation of the diastereomers was accomplished by preparative HPLC (column: LATEK 250 × 21 mm, 5 μ silica gel, solvent: petroleum ether/ethyl acetate, 1:1; flow: 20 mL min^{-1}, UV detection at 254 nm) to afford pure alcohol (–)-**13a** (878 mg, 50%) and pure alcohol (–)-**13b** (616 mg, 35%).

Analytical Data for (–)-13a: R_f = 0.13 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –10.7 (*c* = 1.07, $CHCl_3$). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.41 [s, 9 H, $OC(CH_3)_3$], 1.43–1.66 (m, 4 H, 3-H and 4-H), 1.72–1.77 (m, 2 H, 6′-H_A and OH), 2.21 (td, *J* = 2.7, *J* = 7.1 Hz, 2 H, 2-H), 2.41–2.47 (m, 2 H, 3′-H_A and 6′-H_B), 2.59 (td, *J* = 3.9, *J* = 8.3 Hz, 1 H, 4′-H), 2.74 (dd, *J* = 4.7, *J* = 18.3 Hz, 1 H, 3′-H_B), 2.99–3.06 (m_c, 1 H, 3′a-H), 3.76 (s, 3 H, OCH_3), 3.89 (t, *J* = 3.4 Hz, 1 H, 5′-H), 4.06 (q, *J* = 6.9 Hz, 1 H, 5-H), 4.17 (d, *J* = 11.3 Hz, 1 H, 1′′-H_A), 4.52 (d, *J* = 11.7 Hz, 1 H, 1′′-H_B), 5.05 (t, *J* = 6.9 Hz, 1 H, 6′a-H), 5.56 (dd, *J* = 6.9, *J* = 15.7 Hz, 1 H, 6-H), 5.84 (dd, *J* = 8.3, *J* = 15.7 Hz, 1 H, 7-H), 6.83 (d, *J* = 8.3 Hz,

2 H, Ar-H), 7.17 (d, J = 8.3 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 20.80 (t, C-3), 28.07 [q, OC(CH_3)$_3$], 30.95 (t, C-3′), 35.12 (t, C-2), 36.46 (t, C-4), 37.10 (t, C-6′), 41.68 (d, C-3′a), 49.51 (d, C-4′), 55.20 (q, OCH_3), 70.31 (t, C-1′′), 72.27 (d, C-5), 80.20 [s, OC(CH$_3$)$_3$], 81.60 (d, C-5′), 84.30 (d, C-6′a), 113.68 (d, Ar-CH), 126.92 (d, C-7), 129.35 (d, Ar-CH), 129.94 (s, Ar-C), 136.55 (d, C-6), 159.10 (s, Ar-C), 172.95 (s, C-1), 177.55 (s, C-2′) ppm. $C_{26}H_{36}O_7$ (460.56): calcd. C 67.80, H 7.88; found C 67.58, H 7.71.

Analytical Data for (–)-13b: R_f = 0.07 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –20.7 (c = 1.27, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, OC(CH$_3$)$_3$], 1.47–1.67 (m, 4 H, 3-H and 4-H), 1.71–1.79 (m, 2 H, 6′-H$_A$ and OH), 2.22 (t, J = 7.0 Hz, 2 H, 2-H), 2.41–2.51 (m, 2 H, 3′-H$_A$ and 6′-H$_B$), 2.59 (td, J = 3.7, J = 8.1 Hz, 1 H, 4′-H), 2.78 (dd, J = 4.0, J = 18.4 Hz, 1 H, 3′-H$_B$), 2.99–3.10 (m$_c$, 1 H, 3′a-H), 3.77 (s, 3 H, OCH_3), 3.89 (t, J = 3.3 Hz, 1 H, 5′-H), 4.07 (q, J = 7.0 Hz, 1 H, 5-H), 4.18 (d, J = 11.4 Hz, 1 H, 1′′-H$_A$), 4.51 (d, J = 11.4 Hz, 1 H, 1′′-H$_B$), 5.06 (t, J = 7.0 Hz, 1 H, 6′a-H), 5.57 (dd, J = 6.8, J = 15.6 Hz, 1 H, 6-H), 5.83 (dd, J = 7.9, J = 15.6 Hz, 1 H, 7-H), 6.83 (d, J = 8.8 Hz, 2 H, Ar-H), 7.17 (d, J = 8.5 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.81 (t, C-3), 28.11 [q, OC(CH_3)$_3$], 31.06 (t, C-3′), 35.15 (t, C-2), 36.53 (t, C-4), 37.14 (t, C-6′), 41.54 (d, C-3′a), 49.54 (d, C-4′), 55.22 (q, OCH_3), 70.39 (t, C-1′′), 72.32 (d, C-5), 80.22 [s, OC-(CH$_3$)$_3$], 81.79 (d, C-5′), 84.29 (d, C-6′a), 113.73 (d, Ar-CH), 126.88 (d, C-7), 129.33 (d, Ar-CH), 129.97 (s, Ar-C), 136.65 (d, C-6), 159.15 (s, Ar-C), 172.98 (s, C-1), 177.58 (s, C-2′) ppm. $C_{26}H_{36}O_7$ (460.56): calcd. C 67.80, H 7.88; found C 67.68, H 8.05.

(+)-*tert*-Butyl (5*R*,6*E*)-7-{(3a*R*,4*S*,5*R*,6a*S*)-5-[(4-Methoxybenzyl)-oxy]-2-oxo-hexahydro-2*H*-cyclopenta[*b*]furan-4-yl}-5-{[(2*S*)-2-methoxy-2-phenylacetyl]oxy}hept-6-enoate (15a): DCC (9.0 mg, 43.0 μmol) was added to a cold (0 °C) solution of alcohol (–)-**13a** (16.6 mg, 36.0 μmol), (*S*)-*O*-methylmandelic acid ((+)-**14**, 18.0 mg, 108.0 μmol), and DMAP (1.0 mg, 8.2 μmol) in dry dichloromethane (1 mL). The solution was allowed to warm to room temperature and was stirred overnight. Dichloromethane was then added, and the mixture was filtered through a short pad of Celite in order to remove the solids. The filtrate was washed with aqueous HCl (0.5 N) and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, petroleum ether/ethyl acetate, 6:4) to yield (+)-**15a** (19.1 mg, 86%) as a colorless oil that contained traces of *N*,*N*-dicyclohexylurea. The compound was purified by preparative HPLC (solvent: petroleum ether/ethyl acetate, 1:1; flow: 20 mL min^{-1}, UV detection at 254 nm). R_f = 0.22 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +19.7 (c = 1.06, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.24–1.36 (m, 2 H, 3-H), 1.39 [s, 9 H, OC(CH$_3$)$_3$], 1.46–1.60 (m, 2 H, 4-H), 1.70 (ddd, J = 3.7, J = 6.7, J = 15.5 Hz, 1 H, 6′′-H$_A$), 2.02 (t, J = 7.4 Hz, 2 H, 2-H), 2.32–2.46 (m, 2 H, 3′′-H$_A$ and 6′′-H$_B$), 2.54 (td, J = 3.5, J = 8.0 Hz, 1 H, 4′′-H), 2.64 (dd, J = 4.6, J = 18.6 Hz, 1 H, 3′′-H$_B$), 2.95–3.06 (m$_c$, 1 H, 3a′′-H), 3.36 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.87 (t, J = 3.5 Hz, 1 H, 5′′-H), 4.16 (d, J = 11.5 Hz, 1 H, 1′′′-H$_A$), 4.50 (d, J = 11.5 Hz, 1 H, 1′′′-H$_B$), 4.70 (s, 1 H, 2′-H), 5.05 (t, J = 7.0 Hz, 1 H, 6a′′-H), 5.22 (q, J = 6.5 Hz, 1 H, 5-H), 5.50 (dd, J = 6.5, J = 15.6 Hz, 1 H, 6-H), 5.85 (dd, J = 7.9, J = 15.6 Hz, 1 H, 7-H), 6.84 (d, J = 8.7 Hz, 2 H, Ar-H), 7.17 (d, J = 8.7 Hz, 2 H, Ar-H), 7.27–7.32 (m, 3 H, Ar-H), 7.37–7.41 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.30 (t, C-3), 28.06 [q, OC(CH_3)$_3$], 30.87 (t, C-3′′), 33.41 (t, C-4), 34.79 (t, C-2), 37.20 (t, C-6′′), 41.59 (d, C-3′′a), 49.55 (d, C-4′′), 55.21 (q, OCH_3), 57.30 (q, OCH_3), 70.31 (t, C-1′′′), 74.66 (d, C-5), 80.14 [s, OC(CH$_3$)$_3$], 81.33 (d, C-5′′), 82.68 (d, C-2′), 84.19 (d, C-6′′a), 113.73 (d, Ar-CH), 127.11 (d, Ar-CH), 128.59 (d, Ar-CH), 128.74 (d, C-7), 129.21 (d, Ar-CH), 129.37 (d, Ar-CH), 129.88 (s, Ar-C), 131.24 (d, C-6), 136.29 (s, Ar-C), 159.13 (s, Ar-C), 169.93 (s, C-1′), 172.37 (s, C-1), 177.41 (s, C-2′′) ppm. HRMS (FAB+): [M + K]$^+$ ($C_{35}H_{44}O_9K$): calcd. 647.2622; found 647.2573; [M – H]$^+$ ($C_{35}H_{43}O_9$): calcd. 607.2907; found 607.2870.

(–)-*tert*-Butyl (5*R*,6*E*)-7-{(3a*R*,4*S*,5*R*,6a*S*)-5-[(4-Methoxybenzyl)-oxy]-2-oxo-hexahydro-2*H*-cyclopenta[*b*]furan-4-yl}-5-{[(2*R*)-2-methoxy-2-phenylacetyl]oxy}hept-6-enoate (15b): Compound **15b** was prepared from alcohol (–)-**13a** (12.5 mg, 27.0 μmol) as described above for ester **15a**. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 6:4) and preparative HPLC (solvent: petroleum ether/ethyl acetate, 1:1; flow: 20 mL min^{-1}, UV detection at 254 nm) afforded ester (–)-**15b** (14.4 mg, 88%) as a colorless oil. R_f = 0.20 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –46.1 (c = 1.70, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.41 [s, 9 H, OC(CH$_3$)$_3$], 1.49–1.70 (m, 5 H, 3-H, 4-H and 6′′-H$_A$), 2.15–2.25 (m, 3 H, 2-H and 3′′-H$_A$), 2.36–2.45 (m, 3 H, 3′′-H$_B$, 4′′-H and 6′′-H$_B$), 2.82–2.93 (m$_c$, 1 H, 3a′′-H), 3.36 (s, 3 H, OCH_3), 3.74–3.78 (m, 1 H, 5′′-H), 3.77 (s, 3 H, OCH_3), 4.12 (d, J = 11.5 Hz, 1 H, 1′′′-H$_A$), 4.44 (d, J = 11.5 Hz, 1 H, 1′′′-H$_B$), 4.73 (s, 1 H, 2′-H), 4.99 (t, J = 7.0 Hz, 1 H, 6a′′-H), 5.24–5.29 (m$_c$, 1 H, 5-H), 5.36 (dd, J = 5.8, J = 15.5 Hz, 1 H, 6-H), 5.57 (dd, J = 7.7, J = 15.5 Hz, 1 H, 7-H), 6.85 (d, J = 8.7 Hz, 2 H, Ar-H), 7.13 (d, J = 8.7 Hz, 2 H, Ar-H), 7.25–7.29 (m, 3 H, Ar-H), 7.35–7.38 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.53 (t, C-3), 28.08 [q, OC(CH_3)$_3$], 30.69 (t, C-3′′), 33.60 (t, C-4), 34.89 (t, C-2), 37.15 (t, C-6′′), 41.45 (d, C-3′′a), 49.61 (d, C-4′′), 55.21 (q, OCH_3), 57.21 (q, OCH_3), 70.19 (t, C-1′′′), 74.21 (d, C-5), 80.24 [s, OC(CH$_3$)$_3$], 81.28 (d, C-5′′), 82.54 (d, C-2′), 84.08 (d, C-6′′a), 113.68 (d, Ar-CH), 127.09 (d, Ar-CH), 128.30 (d, C-7), 128.65 (d, Ar-CH), 128.84 (d, Ar-CH), 129.37 (d, Ar-CH), 129.90 (s, Ar-C), 130.84 (d, C-6), 136.13 (s, Ar-C), 159.10 (s, Ar-C), 169.81 (s, C-1′), 172.95 (s, C-1), 177.55 (s, C-2′′) ppm. HRMS (FAB+): [M + K]$^+$ ($C_{35}H_{44}O_9K$): calcd. 647.2622; found 647.2591; [M – H]$^+$ ($C_{35}H_{43}O_9$): calcd. 607.2907; found 607.2848.

(–)-*tert*-Butyl (5*R*,6*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-{(3a*R*,4*S*,5*R*,6a*S*)-5-[(4-methoxybenzyl)oxy]-2-oxo-hexahydro-2*H*-cyclopenta[*b*]furan-4-yl}hept-6-enoate (16a): A solution of alcohol (–)-**13a** (93.9 mg, 0.2 mmol), imidazole (27.3 mg, 0.4 mmol), and TBSCl (46.1 mg, 0.3 mmol) in dry dichloromethane (1 mL) was stirred at room temperature overnight. Saturated $NaHCO_3$ solution (2 mL) was then added, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 78:22) afforded pure (–)-**16a** (108.0 mg, 91%) as a colorless oil. R_f = 0.64 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –18.2 (c = 1.03, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = –0.05 (s, 3 H, $SiCH_3$), 0.00 (s, 3 H, $SiCH_3$), 0.83 [s, 9 H, SiC(CH$_3$)$_3$], 1.41 [s, 9 H, OC(CH$_3$)$_3$], 1.43–1.63 (m, 4 H, 3-H and 4-H), 1.71 (ddd, J = 3.5, J = 6.6, J = 15.5 Hz, 1 H, 6′-H$_A$), 2.17 (t, J = 7.3 Hz, 2 H, 2-H), 2.38–2.48 (m, 2 H, 3′-H$_A$ and 6′-H$_B$), 2.56 (td, J = 3.7, J = 8.2 Hz, 1 H, 4′-H), 2.79 (dd, J = 4.6, J = 18.4 Hz, 1 H, 3′-H$_B$), 2.98–3.09 (m$_c$, 1 H, 3′a-H), 3.76 (s, 3 H, OCH_3), 3.86 (t, J = 3.8 Hz, 1 H, 5′-H), 4.06 (q, J = 6.1 Hz, 1 H, 5-H), 4.16 (d, J = 11.3 Hz, 1 H, 1′′-H$_A$), 4.51 (d, J = 11.3 Hz, 1 H, 1′′-H$_B$), 5.06 (t, J = 7.1 Hz, 1 H, 6′a-H), 5.50 (dd, J = 6.3, J = 15.7 Hz, 1 H, 6-H), 5.76 (dd, J = 7.7, J = 15.5 Hz, 1 H, 7-H), 6.82 (d, J = 8.7 Hz, 2 H, Ar-H), 7.16 (d, J = 8.7 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = –4.77 (q, $SiCH_3$), –4.30 (q, $SiCH_3$), 18.15 [s, SiC-(CH$_3$)$_3$], 20.95 (t, C-3), 25.82 [q, SiC(CH_3)$_3$], 28.09 [q, OC(CH_3)$_3$], 30.90 (t, C-3′), 35.45 (t, C-2), 37.13 (t, C-6′), 37.52 (t, C-4), 41.70 (d, C-3′a), 49.72 (d, C-4′), 55.19 (q, OCH_3), 70.34 (t, C-1′′), 73.02

(d, C-5), 79.95 [s, O*C*(CH_3)$_3$], 81.89 (d, C-5′), 84.35 (d, C-6′a), 113.67 (d, Ar-CH), 125.42 (d, C-7), 129.31 (d, Ar-CH), 129.98 (s, Ar-C), 137.14 (d, C-6), 159.08 (s, Ar-C), 172.92 (s, C-1), 177.68 (s, C-2′) ppm. $C_{32}H_{50}O_7Si$ (574.83): calcd. C 66.86, H 8.77; found C 67.13, H 8.69.

(+)-*tert*-Butyl (5*R*,6*E*,8β,9β,11β,14*Z*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-[(4-methoxybenzyl)oxy]-11-hydroxyprosta-6,14-dien-1-oate (18a): A solution of DIBAL-H (1 M in hexane, 704 μL) was added slowly by syringe to a cooled (–78 °C) solution of (–)-**16a** (332 mg, 578 μmol) in dry THF (13 mL). After the mixture had been stirred for 15 min at –78 °C, another portion of DIBAL-H (500 μL) was added. Stirring was continued for 15 min and a last portion of DIBAL-H (300 μL) was added. After TLC analysis showed complete consumption of the starting material, methanol (5 mL) and water (1.3 mL) were added to the cold (–78 °C) mixture, and it was then allowed to warm to room temperature. The mixture was poured onto a mixture of $MgSO_4$ (120 g) in diethyl ether (600 mL) and the resultant slurry was stirred for 1 h at room temperature. The solids were filtered off and the volatiles were evaporated under reduced pressure to yield crude lactol.

n-Hexyltriphenylphosphonium bromide (**17**, 1.05 g, 2.34 mmol) in dry THF (4 mL) was cooled to –78 °C, and KHMDS (0.5 M in toluene, 4.46 mL) was added by syringe. The resultant orange solution was allowed to warm to –45 °C over a period of 1 h and was then added slowly by syringe to a precooled (–45 °C) solution of the lactol in dry THF (4 mL). The temperature was raised to –20 °C and the yellow reaction mixture was stirred overnight at this temperature. Saturated aqueous NH_4Cl was added, and the aqueous phase was extracted with diethyl ether (4 × 50 mL). Drying over Na_2SO_4 and evaporation of the solvent afforded crude (+)-**18a**, which was purified by flash chromatography (silica gel, petroleum ether/diethyl ether, 8:2) to yield pure diene (+)-**18a** (259 mg, 69%) as a colorless oil. R_f = 0.46 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = +9.0 (*c* = 0.55, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.84–0.88 (m, 3 H, 20-H), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.24–1.34 (m, 6 H, 17-H, 18-H and 19-H), 1.41 [s, 9 H, $OC(CH_3)_3$], 1.46–1.69 (m, 4 H, 3-H and 4-H), 1.81–2.12 (m, 6 H, 10-H_A, 12-H, 13-H_A, 16-H and OH), 2.14–2.26 (m, 4 H, 2-H, 10-H_B and 13-H_B), 2.72–2.81 (m_c, 1 H, 8-H), 3.78 (s, 3 H, OCH_3), 3.89 (q, *J* = 5.9 Hz, 1 H, 9-H), 4.10–4.16 (m, 2 H, 5-H and 11-H), 4.35 (d, *J* = 11.5 Hz, 1 H, 1′-H_A), 4.45 (d, *J* = 11.3 Hz, 1 H, 1′-H_B), 5.33–5.40 (m, 2 H, 14-H and 15-H), 5.45 (dd, *J* = 6.3, *J* = 15.4 Hz, 1 H, 6-H), 5.82 (dd, *J* = 10.4, *J* = 15.4 Hz, 1 H, 7-H), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.81 (q, $SiCH_3$), –4.23 (q, $SiCH_3$), 14.05 (q, C-20), 18.20 [s, Si*C*(CH_3)$_3$], 21.11 (t, C-3), 22.57 (t, C-18 or C-19), 24.33 (t, C-13), 25.92 [q, SiC(*C*H_3)$_3$], 27.37 (t, C-16), 28.10 [q, $CO_2C(CH_3)_3$], 29.35 (t, C-17), 31.55 (t, C-18 or C-19), 35.57 (t, C-2), 37.97 (t, C-4), 39.96 (t, C-10), 47.47 (d, C-12), 48.41 (d, C-8), 55.25 (q, OCH_3), 70.93 (t, C-1′), 72.74 (d, C-5 or C-11), 73.11 (d, C-5 or C-11), 79.89 [s, $CO_2C(CH_3)_3$], 81.44 (d, C-9), 113.69 (d, Ar-CH), 127.67 (d, C-7), 128.38 (d, C-14 or C-15), 129.13 (d, Ar-CH), 130.50 (d, C-14 or C-15), 130.83 (s, Ar-C), 136.07 (d, C-6), 159.07 (s, Ar-C), 173.00 (s, C-1) ppm. $C_{38}H_{64}O_6Si$ (645.01): calcd. C 70.76, H 10.00; found C 70.80, H 9.93.

(+)-*tert*-Butyl (5*R*,6*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(3a*R*,4*S*,5*R*,6a*S*)-5-hydroxy-2-oxo-hexahydro-2*H*-cyclopenta[*b*]-furan-4-yl]hept-6-enoate (19a): A solution of lactone (–)-**16a** (82 mg, 142 μmol) in dichloromethane (2 mL) was treated at room temperature with a KH_2PO_4/Na_2HPO_4 buffer solution (pH 7.2, 0.7 mL) and DDQ (49 mg, 213 μmol). The resultant green suspension was stirred for 4 h at room temperature (TLC monitoring). Dichloromethane was then added, and the mixture was filtered through a short pad of Celite. Evaporation of the solvent under reduced pressure afforded crude alcohol **19a**, which was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) to yield pure (+)-**19a** (60 mg, 93%) as a colorless oil. R_f = 0.39 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +9.9 (*c* = 1.75, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.41 [s, 9 H, $OC(CH_3)_3$], 1.45–1.69 (m, 5 H, 3-H, 4-H and OH), 1.96 (ddd, *J* = 3.8, *J* = 6.7, *J* = 15.2 Hz, 1 H, 6′-H_A), 2.17–2.22 (m, 3 H, 2-H and 6′-H_B), 2.44–2.60 (m, 2 H, 3′-H_A and 4′-H), 2.77 (dd, *J* = 4.6, *J* = 18.6 Hz, 1 H, 3′-H_B), 2.99–3.10 (m_c, 1 H, 3′a-H), 4.12 (q, *J* = 6.1 Hz, 1 H, 5-H), 4.26 (t, *J* = 3.2 Hz, 1 H, 5′-H), 5.07 (t, *J* = 7.2 Hz, 1 H, 6′a-H), 5.59 (dd, *J* = 6.1, *J* = 15.6 Hz, 1 H, 6-H), 5.77 (dd, *J* = 7.7, *J* = 15.6 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.77 (q, $SiCH_3$), –4.29 (q, $SiCH_3$), 18.20 [s, Si*C*(CH_3)$_3$], 20.91 (t, C-3), 25.85 [q, SiC(*C*H_3)$_3$], 28.10 [q, OC(*C*H_3)$_3$], 31.34 (t, C-3′), 35.41 (t, C-2), 37.41 (t, C-4), 41.27 (d, C-3′a), 42.00 (t, C-6′), 50.07 (d, C-4′), 72.86 (d, C-5), 75.62 (d, C-5′), 80.09 [s, O*C*(CH_3)$_3$], 84.67 (d, C-6′a), 124.99 (d, C-7), 137.93 (d, C-6), 172.99 (s, C-1), 177.67 (s, C-2′) ppm. $C_{24}H_{42}O_6Si$ (454.68): calcd. C 63.40, H 9.31; found C 63.20, H 9.26.

(+)-*tert*-Butyl (5*S*,6*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(3a*R*,4*S*,5*R*,6a*S*)-5-hydroxy-2-oxo-hexahydro-2*H*-cyclopenta[*b*]-furan-4-yl]hept-6-enoate (19b): Compound **19b** was prepared from alcohol (–)-**16b** (78 mg, 135 μmol) as described above for **19a**. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) afforded alcohol (+)-**19b** (58 mg, 94%) as a colorless oil. R_f = 0.43 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +3.8 (*c* = 1.16, $CHCl_3$). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = –0.01 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.40 [s, 9 H, $OC(CH_3)_3$], 1.44–1.69 (m, 4 H, 3-H, 4-H), 1.94 (ddd, *J* = 3.8, *J* = 6.7, *J* = 15.3 Hz, 1 H, 6′-H_A), 1.99 (br. s, 1 H, OH), 2.16–2.22 (m, 3 H, 2-H and 6′-H_B), 2.44–2.58 (m, 2 H, 3′-H_A and 4′-H), 2.78 (dd, *J* = 4.4, *J* = 18.6 Hz, 1 H, 3′-H_B), 3.00–3.11 (m_c, 1 H, 3′a-H), 4.10 (q, *J* = 6.0 Hz, 1 H, 5-H), 4.23 (t, *J* = 3.4 Hz, 1 H, 5′-H), 5.08 (t, *J* = 7.1 Hz, 1 H, 6′a-H), 5.57 (dd, *J* = 6.6, *J* = 15.6 Hz, 1 H, 6-H), 5.74 (dd, *J* = 8.1, *J* = 15.6 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.76 (q, $SiCH_3$), –4.28 (q, $SiCH_3$), 18.18 [s, Si*C*-(CH_3)$_3$], 20.86 (t, C-3), 25.83 [q, SiC(*C*H_3)$_3$], 28.07 [q, OC(*C*H_3)$_3$], 31.30 (t, C-3′), 35.31 (t, C-2), 37.38 (t, C-4), 41.24 (d, C-3′a), 42.00 (t, C-6′), 50.03 (d, C-4′), 73.05 (d, C-5), 75.54 (d, C-5′), 80.12 [s, O*C*(CH_3)$_3$], 84.77 (d, C-6′a), 125.22 (d, C-7), 137.82 (d, C-6), 173.09 (s, C-1), 177.86 (s, C-2′) ppm. $C_{24}H_{42}O_6Si$ (454.68): calcd. C 63.40, H 9.31; found C 63.12, H 9.19.

(–)-*tert*-Butyl (5*R*,6*E*,8β,9β,11β,14*Z*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-9,11-dihydroxyprosta-6,14-dien-1-oate (20a): A solution of DIBAL-H in hexane (1 M, 300 μL) was added slowly by syringe to a cold (–78 °C) solution of (+)-**19a** (114 mg, 251 μmol) in dry THF (14 mL). After the mixture had been stirred at –78 °C for 15 min, another portion of DIBAL-H (300 μL) was added. Stirring was continued for 15 min and a last portion of DIBAL-H (60 μL) was added (TLC monitoring). Methanol (2.3 mL) and water (0.5 mL) were added at –78 °C, and the reaction mixture was allowed to warm to room temperature. The mixture was poured onto a mixture of $MgSO_4$ (51 g) and diethyl ether (255 mL) and was then stirred for 1 h at room temperature. The solids were filtered off, and the volatiles were evaporated under reduced pressure to yield crude lactol.

A solution of hexyltriphenylphosphonium bromide (**17**, 677 mg, 1.50 mmol) in dry THF (6 mL) was cooled to –78 °C, and

KHMDS (0.5 M in toluene, 2.90 mL) was added by syringe. The resulting orange solution was allowed to warm to –45 °C over a period of 1 h and was then added slowly by syringe to a precooled (–45 °C) solution of the lactol in dry THF (6 mL). The temperature was raised to –25 °C and the yellow reaction mixture was stirred overnight at this temperature. Saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate (4 × 40 mL). Drying over Na_2SO_4 and evaporation of the solvent afforded crude diol (–)-**20a**, which was purified by flash chromatography (silica gel, petroleum ether/diethyl ether, 7:3) to yield the pure compound (61.8 mg, 47%) as a colorless oil. R_f = 0.63 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = –2.8 (*c* = 0.90, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.84–0.88 (m, 3 H, 20-H), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.20–1.34 (m, 6 H, 17-H, 18-H, and 19-H), 1.41 [s, 9 H, $OC(CH_3)_3$], 1.46–1.53 (m, 2 H, 4-H), 1.56–1.68 (m, 2 H, 3-H), 1.80 (ddd, *J* = 2.1, *J* = 4.8, *J* = 14.4 Hz, 1 H, 10-H_A), 1.89–2.06 (m, 6 H, 12-H, 13-H_A, 16-H, and 2 × OH), 2.11–2.33 (m, 4 H, 2-H, 10-H_B, and 13-H_B), 2.65–2.74 (m, 1 H, 8-H), 4.12–4.18 (m, 2 H, 5-H and 9-H), 4.12–4.23 (m, 1 H, 11-H), 5.36–5.39 (m, 2 H, 14-H and 15-H), 5.52 (dd, *J* = 6.0, *J* = 15.4 Hz, 1 H, 6-H), 5.79 (dd, *J* = 10.4, *J* = 15.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.78 (q, $SiCH_3$), –4.30 (q, $SiCH_3$), 14.04 (q, C-20), 18.20 [s, $SiC(CH_3)_3$], 21.00 (t, C-3), 22.56 (t, C-18 or C-19), 24.47 (t, C-13), 25.87 [q, $SiC(CH_3)_3$], 27.40 (t, C-16), 28.10 [q, $OC(CH_3)_3$], 29.34 (t, C-17), 31.54 (t, C-18 or C-19), 35.50 (t, C-2), 37.66 (t, C-4), 42.59 (t, C-10), 47.05 (d, C-12), 50.38 (d, C-8), 72.79 (d, C-5 or C-9), 73.58 (d, C-11), 75.45 (d, C-5 or C-9), 80.00 [s, $OC(CH_3)_3$], 126.81 (d, C-7), 128.25 (d, C-14 or C-15), 131.14 (d, C-14 or C-15), 138.33 (d, C-6), 173.00 (s, C-1) ppm. $C_{30}H_{56}O_5Si$ (524.86): calcd. C 68.65, H 10.75; found C 68.93, H 10.73.

(–)-*tert*-Butyl (5*S*,6*E*,8β,9β,11β,14*Z*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-9,11-dihydroxyprosta-6,14-dien-1-oate (20b): Compound **20b** was prepared from alcohol (+)-**19b** (53.6 mg, 118 μmol) as described above for **20a**. Flash chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) afforded diol (–)-**20b** (37.0 mg, 60%) as a colorless oil. R_f = 0.14 (petroleum ether/diethyl ether, 7:3). $[\alpha]_D^{20}$ = –15.9 (*c* = 0.91, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.84–0.88 (m, 3 H, 20-H), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.21–1.35 (m, 6 H, 17-H, 18-H, and 19-H), 1.41 [s, 9 H, $OC(CH_3)_3$], 1.45–1.67 (m, 4 H, 3-H and 4-H), 1.79 (ddd, *J* = 2.1, *J* = 4.9, *J* = 14.4 Hz, 1 H, 10-H_A), 1.90–2.09 (m, 5 H, 12-H, 13-H_A, 16-H, and OH), 2.11–2.21 (m, 4 H, 2-H, 10-H_B, and OH), 2.27–2.38 (m, 1 H, 13-H_B), 2.66–2.74 (m_c, 1 H, 8-H), 4.09–4.16 (m, 2 H, 5-H and 9-H), 4.19–4.25 (m_c, 1 H, 11-H), 5.38–5.41 (m, 2 H, 14-H and 15-H), 5.49 (dd, *J* = 6.9, *J* = 15.1 Hz, 1 H, 6-H), 5.76 (dd, *J* = 10.3, *J* = 15.2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.77 (q, $SiCH_3$), –4.22 (q, $SiCH_3$), 14.04 (q, C-20), 18.20 [s, $SiC(CH_3)_3$], 21.01 (t, C-3), 22.57 (t, C-18 or C-19), 24.45 (t, C-13), 25.87 [q, $SiC(CH_3)_3$], 27.39 (t, C-16), 28.11 [q, $OC(CH_3)_3$], 29.35 (t, C-17), 31.55 (t, C-18 or C-19), 35.37 (t, C-2), 37.75 (t, C-4), 42.56 (t, C-10), 47.06 (d, C-12), 50.45 (d, C-8), 73.16 (d, C-5 or C-9), 73.52 (d, C-11), 75.42 (d, C-5 or C-9), 80.12 [s, $OC(CH_3)_3$], 127.39 (d, C-7), 128.24 (d, C-14 or C-15), 131.18 (d, C-14 or C-15), 138.24 (d, C-6), 173.16 (s, C-1) ppm. $C_{30}H_{56}O_5Si$ (524.86): calcd. C 68.65, H 10.75; found C 68.56, H 10.75.

(–)-*tert*-Butyl (5*R*,6*E*,8β,9β,11β,14*Z*)-5,9,11-Trihydroxyprosta-6,14-dien-1-oate (21a): A solution of diol (–)-**20a** (18 mg, 34 μmol) in dry THF (2 mL) was treated at room temperature with TBAF·3 H_2O (32 mg, 102 μmol) and stirred for 24 h. The solvent was removed in vacuo and the residue was subjected to flash chromatography (silica gel, ethyl acetate) to yield pure triol (–)-**21a** (10 mg, 71%) as a colorless oil. R_f = 0.16 (ethyl acetate). $[\alpha]_D^{20}$ = –9.4 (*c* = 0.73, MeOH). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3 H, 20-H), 1.22–1.35 (m, 6 H, 17-H, 18-H, and 19-H), 1.42 [s, 9 H, $OC(CH_3)_3$], 1.48–1.68 (m, 4 H, 3-H and 4-H), 1.72 (br. s, 1 H, OH), 1.84 (ddd, *J* = 2.0, *J* = 4.4, *J* = 14.2 Hz, 1 H, 10-H_A), 1.88–1.94 (m_c, 1 H, 12-H), 1.99–2.04 (m, 3 H, 13-H_A and 16-H), 2.14 (dt, *J* = 6.2, *J* = 14.6 Hz, 1 H, 10-H_B), 2.21–2.27 (m, 3 H, 2-H and 13-H_B), 2.69–2.74 (m_c, 1 H, 8-H), 2.91 (br. s, 1 H, OH), 2.96 (br. s, 1 H, OH), 4.08–4.12 (m, 1 H, 5-H), 4.16–4.22 (m, 2 H, 9-H and 11-H), 5.33–5.40 (m, 2 H, 14-H and 15-H), 5.51 (dd, *J* = 7.1, *J* = 15.4 Hz, 1 H, 6-H), 5.83 (dd, *J* = 10.5, *J* = 15.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 14.04 (q, C-20), 20.94 (t, C-3), 22.56 (t, C-18 or C-19), 24.26 (t, C-13), 27.36 (t, C-16), 28.10 [q, $OC(CH_3)_3$], 29.33 (t, C-17), 31.51 (t, C-18 or C-19), 35.22 (t, C-2), 36.38 (t, C-4), 42.54 (t, C-10), 47.17 (d, C-12), 50.04 (d, C-8), 72.40 (d, C-5), 73.81 (d, C-9 or C-11), 75.57 (d, C-9 or C-11), 80.18 [s, $OC(CH_3)_3$], 128.10 (d, C-14 or C-15), 129.41 (d, C-7), 131.13 (d, C-14 or C-15), 136.98 (d, C-6), 173.12 (s, C-1) ppm. HRMS (FAB+): $[M + Na]^+$ ($C_{24}H_{42}O_5Na$): calcd. 433.2930; found 433.2955; $[M – H]^+$ ($C_{24}H_{41}O_5$): calcd. 409.2954; found 409.2955.

(–)-*tert*-Butyl (5*S*,6*E*,8β,9β,11β,14*Z*)-5,9,11-Trihydroxyprosta-6,14-dien-1-oate (21b): A solution of diol (–)-**20b** (24.9 mg, 47 μmol) in dry THF (2 mL) was treated at room temperature with TBAF·3 H_2O (45.0 mg, 141 μmol) and stirred for 48 h. Water (1 mL) and brine (1 mL) were added, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (silica gel, dichloromethane/methanol, 10:1) yielded pure triol (–)-**21b** (15.3 mg, 79%) as a colorless oil. R_f = 0.49 (dichloromethane/methanol, 5:1). $[\alpha]_D^{20}$ = –2.1 (*c* = 1.05, EtOH). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H, 20-H), 1.23–1.34 (m, 6 H, 17-H, 18-H, and 19-H), 1.42 [s, 9 H, $OC(CH_3)_3$], 1.50–1.70 (m, 4 H, 3-H and 4-H), 1.84 (ddd, *J* = 2.0, *J* = 4.6, *J* = 14.4 Hz, 1 H, 10-H_A), 1.91–2.18 (m, 5 H, 10-H_B, 12-H, 13-H_A, and 16-H), 2.23 (t, *J* = 7.0 Hz, 2 H, 2-H), 2.24–2.32 (m, 1 H, 13-H_B), 2.67–2.76 (m_c, 1 H, 8-H), 4.11–4.23 (m, 3 H, 5-H, 9-H, and 11-H), 5.32–5.42 (m, 2 H, 14-H and 15-H), 5.57 (dd, *J* = 6.1, *J* = 15.5 Hz, 1 H, 6-H), 5.87 (dd, *J* = 10.2, *J* = 15.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.03 (q, C-20), 20.91 (t, C-3), 22.55 (t, C-18 or C-19), 24.35 (t, C-13), 27.39 (t, C-16), 28.10 [q, $OC(CH_3)_3$], 29.34 (t, C-17), 31.51 (t, C-18 or C-19), 35.15 (t, C-2), 36.48 (t, C-4), 42.58 (t, C-10), 47.15 (d, C-12), 50.22 (d, C-8), 71.83 (d, C-5), 73.84 (d, C-9 or C-11), 75.62 (d, C-9 or C-11), 80.26 [s, $OC(CH_3)_3$], 128.24 (d, C-7 or C-14 or C-15), 128.29 (d, C-7 or C-14 or C-15), 131.06 (d, C-14 or C-15), 137.04 (d, C-6), 173.23 (s, C-1) ppm. HRMS (FAB+): $[M + Na]^+$ ($C_{24}H_{42}O_5Na$): calcd. 433.2930; found 433.2919; $[M – H]^+$ ($C_{24}H_{41}O_5$): calcd. 409.2954; found 409.2930.

(–)-(5*R*,6*E*,8β,9β,11β,14*Z*)-5,9,11-Trihydroxyprosta-6,14-dien-1-oic Acid (*ent*-1): A solution of *tert*-butyl ester (–)-**21a** (12.5 mg, 30.4 μmol) in dry methanol (1 mL) was treated at room temp. with powdered potassium hydroxide (53.2 mg, 900 μmol). After stirring for 48 h, the reaction mixture was acidified (ca. pH 3) with hydrochloric acid (0.2 N) and was then extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried with $MgSO_4$, and volatiles were removed in vacuo. The residue was subjected to flash chromatography (silica gel, dichloromethane/methanol, 5:1 to 2:1) to yield pure isoprostane (–)-*ent*-**1** (9.8 mg, 92%) as a colorless oil. R_f = 0.20 (CH_2Cl_2/methanol, 5:1). $[\alpha]_D^{20}$ = –10.7 (*c* = 0.83, MeOH). ^{1}H NMR (500.13 MHz, [D$_6$]DMSO): δ = 0.84 (t, *J* = 6.9 Hz, 3 H, 20-H), 1.20–1.43 (m, 8 H, 4-H, 17-H, 18-H, and 19-H), 1.44–1.56 (m, 3 H, 3-H and 10-H_A), 1.58–1.64 (m, 1 H, 12-H), 1.93–1.99 (m, 3 H, 13-H_A and 16-H), 2.03–2.16 (m, 3 H, 2-H and

13-H_B), 2.22–2.27 (m_c, 1 H, 10-H_B), 2.37–2.42 (m_c, 1 H, 8-H), 3.84–3.91 (m, 2 H, 5-H and 9-H), 3.93–3.96 (m, 1 H, 11-H), 5.23–5.29 (m, 2 H, 6-H and 15-H), 5.33–5.38 (m, 1 H, 14-H), 5.68 (dd, J = 10.5, J = 15.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.76 MHz, [D_6]-DMSO): δ = 13.91 (q, C-20), 20.99 (t, C-3), 21.97 (t, C-17 or C-18 or C-19), 23.79 (t, C-13), 26.74 (t, C-16), 28.79 (t, C-17 or C-18 or C-19), 30.90 (t, C-17 or C-18 or C-19), 34.31 (t, C-2), 37.16 (t, C-4), 43.07 (t, C-10), 46.85 (d, C-12), 50.38 (d, C-8), 70.19 (d, C-11), 71.26 (d, C-5 or C-9), 72.60 (d, C-5 or C-9), 128.33 (d, C-7), 129.04 (d, C-15), 129.48 (d, C-14), 136.25 (d, C-6), 175.22 (s, C-1) ppm. HRMS (FAB+): $[M - H + Na + K]^+$ ($C_{20}H_{33}O_5NaK$): calcd. 415.1862; found 415.1866; $[M + K]^+$ ($C_{20}H_{34}O_5K$): calcd. 393.2043; found 393.2079; $[M + Na]^+$ ($C_{20}H_{34}O_5Na$): calcd. 377.2304; found 377.2281.

(–)-(5*S*,6*E*,8β,9β,11β,14*Z*)-5,9,11-Trihydroxyprosta-6,14-dien-1-oic Acid (*ent*-2): Isoprostane ***ent*-2** was prepared analogously to isoprostane ***ent*-1** from *tert*-butyl ester (–)-**21b** (10.5 mg, 25.6 μmol). Flash chromatography (silica gel, dichloromethane/methanol, 5:1 to 2:1) afforded isoprostane (–)-*ent*-**2** (8.9 mg, 98%) as a colorless oil. R_f = 0.19 (dichloromethane/methanol, 5:1). $[a]_D^{20}$ = –7.4 (c = 0.86, MeOH). ^{1}H NMR (500.13 MHz, [D_6]DMSO): δ = 0.84 (t, J = 6.7 Hz, 3 H, 20-H), 1.22–1.29 (m, 6 H, 17-H, 18-H and 19-H), 1.34–1.38 (m, 2 H, 4-H), 1.45–1.63 (m, 4 H, 3-H, 10-H_A, and 12-H), 1.95–2.02 (m, 3 H, 13-H_A and 16-H), 2.06–2.12 (m, 3 H, 2-H and 13-H_B), 2.20–2.26 (m_c, 1 H, 10-H_B), 2.37–2.42 (m_c, 1 H, 8-H), 3.84–3.90 (m, 2 H, 5-H and 9-H), 3.93–3.96 (m_c, 1 H, 11-H), 5.23–5.31 (m, 2 H, 6-H and 15-H), 5.36–5.41 (m, 1 H, 14-H), 5.69 (dd, J = 10.7, J = 15.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125.76 MHz, [D_6]DMSO): δ = 13.93 (q, C-20), 21.17 (t, C-3), 21.98 (t, C-17 or C-18 or C-19), 23.81 (t, C-13), 26.71 (t, C-16), 28.85 (C-17 or C-18 or C-19), 30.91 (C-17 or C-18 or C-19), 34.88 (t, C-2), 37.24 (t, C-4), 42.98 (t, C-10), 46.91 (d, C-12), 50.53 (d, C-8), 70.19 (d, C-11), 70.58 (d, C-5 or C-9), 72.56 (d, C-5 or C-9), 127.48 (d, C-7), 129.00 (d, C-15), 129.59 (d, C-14), 136.10 (d, C-6), 175.14 (s, C-1) ppm. HRMS (FAB+): $[M - H + 2Na]^+$ ($C_{20}H_{33}O_5Na_2$): calcd. 399.2123; found 399.2152; $[M + Na]^+$ ($C_{20}H_{34}O_5Na$): calcd. 377.2304; found 377.2272.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR chemical shifts of 5-F_{2c}-IsoP (Rokach et al.) and 5-*epi*-*ent*-F_{2c}-IsoP (this work) recorded in [D_6]acetone. GC data and chromatograms for compound **5**. HPLC data and chromatograms for compounds **16a** and **16b**. ^{13}C NMR spectra of compounds **7**, **9**, **15a**, **15b**, **21a**, **21b**, *ent*-**1**, and *ent*-**2**.

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