# Total Syntheses of Four Metabolites of 15-$F_{2t}$-Isoprostane

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Total syntheses are described of the methyl esters of enantiomers of two major urinary metabolites of 15$F_{2t}$-isoprostane – 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane **1** and 2,3-dinor-15$F_{2t}$-isoprostane **2** – together with other, related, putative metabolites (15*R*)/(15*S*)-2,3-dinor-5,6,13,14-tetrahydro-15$F_{2t}$-isoprostane **3** and 2,3-dinor-5,6,13,14-tetrahydro-15-oxo-15$F_{2t}$-isoprostane **4**. The synthesis, starting from diacetone D-glucose, includes as its main steps a radical cyclization reaction of highly functionalized precursors, followed by Wittig and/or Horner–Wadsworth–Emmons elongation using phosphorus synthons. The compounds synthesized here have been used as reference compounds for studying the metabolism of 15$F_{2t}$-isoprostane and *ent*-15$F_{2t}$-isoprostane.

## Introduction

Since the discovery of isoprostanes by Roberts et al.,[1] there has been growing interest in the total synthesis[2] of these optically active prostaglandin-like compounds, which are formed in vivo by a free radical-catalyzed mechanism.[1,3] The most studied compound of this family is 15$F_{2t}$-isoprostane[4] (also known as 8-*epi*-$PGF_{2\alpha}$ or $iPGF_{2\alpha}$-III),[3] an isomer endowed with powerful biological activity,[5] and an extensively validated marker of oxidant stress in vivo.[5] Because of their close similarity, it seems likely that cyclooxygenase-derived $PGF_{2\alpha}$ and 15$F_{2t}$-isoprostane may undergo metabolism through similar degradation pathways. To date, two major metabolites have been identified in humans: 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane[6,7] and, more recently, 2,3-dinor-15$F_{2t}$-isoprostane.[7] We report here the first enantiospecific chemical synthesis leading to both compounds, and also to other putative related metabolites. The availability of enantiomerically pure metabolites is important from the viewpoint of the development of enantioselective assays for these products (e.g. by the use of immunoaffinity chromatography-GC-MS[7]). Such assays might be useful for assessment of in vivo formation and metabolism of 15$F_{2t}$-isoprostane versus *ent*-15$F_{2t}$-isoprostane. To date, it is not known to what proportion these enantiomers are formed in vivo and whether they can be similarly degraded. We have developed our strategy by using diacetone D-glucose to provide the enantiomeric counterparts of 15$F_{2t}$-isoprostane metabolites; the metabolites themselves should thus be accessible from L-glucose.

## Results and Discussion

In connection with our program directed towards the synthesis of isoprostanes, we have developed the first total syntheses of *ent*-2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane **1a**,[8] its 15 epimer **1b**, *ent*-2,3-dinor-15$F_{2t}$-isoprostane **2a**, its 15 epimer **2b**, *ent*-(15*R*)/(15*S*)-2,3-dinor-5,6,13,14-tetrahydro-15$F_{2t}$-isoprostane **3**, and *ent*-2,3-dinor-5,6,13,14-tetrahydro-15-oxo-15$F_{2t}$-isoprostane **4**, from the methyl ester **5**[9] (Scheme 1). Initially, **1a** allowed us to confirm the presence of endogenously produced 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane in human and rat urine and to identify its Δ5 unsaturated counterpart, 2,3-dinor-15$F_{2t}$-isoprostane, as another major endogenous metabolite.[7] Now, using direct comparison with synthetic **2a**, we have once again confirmed the identity of urinary and hepatocyte-derived 2,3-dinor-15$F_{2t}$-isoprostane.[7] The other putative metabolites synthesized are being used as reference compounds to study the in vitro metabolism of 15$F_{2t}$-isoprostane and *ent*-15$F_{2t}$-isoprostane by isolated rat hepatocytes (Chiabrando et al., in preparation).

The synthesis of (1*S*,2*S*,3*R*,4*R*)-di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-[(*E*)-3-oxo-1-octenyl)cyclopentane-1,4-diol **14** – precursor of **1**, **3**, and **4** – from commercially available diacetone-D-glucose, is shown in Scheme 2. The first 9 steps leading to methyl cyclopentylacetate **5** were accomplished in 27% overall yield by using the iodo pathway, according to our reported procedure.[9] The methyl ester **5** was converted into the aldehyde **6** by treatment with DIBAL-H (Scheme 2) in 93% yield.

The introduction of the α chain of the isoprostane was achieved by using a three-carbon homologating agent: (3,3-diisopropoxypropyl)triphenylphosphonium bromide.[10] The aldehyde **6** reacted with the ylide derived from this

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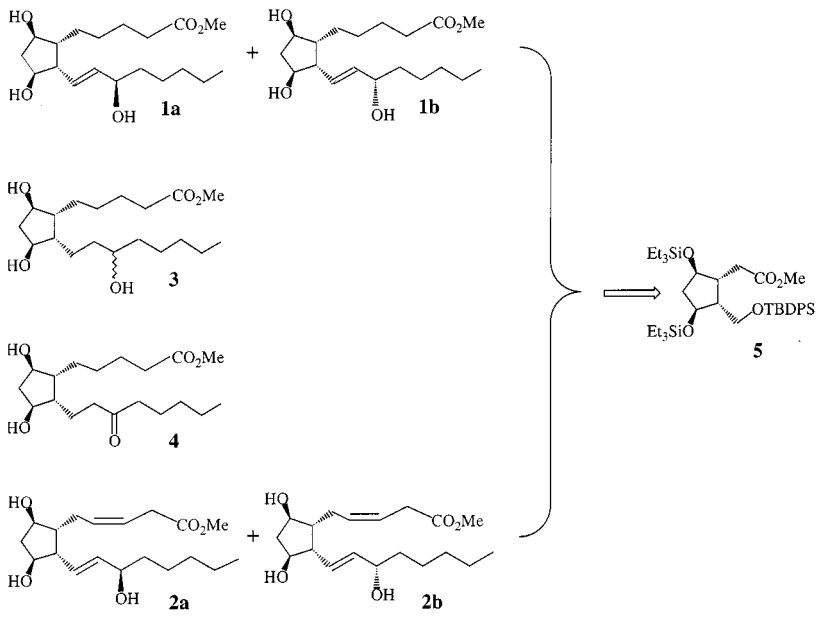
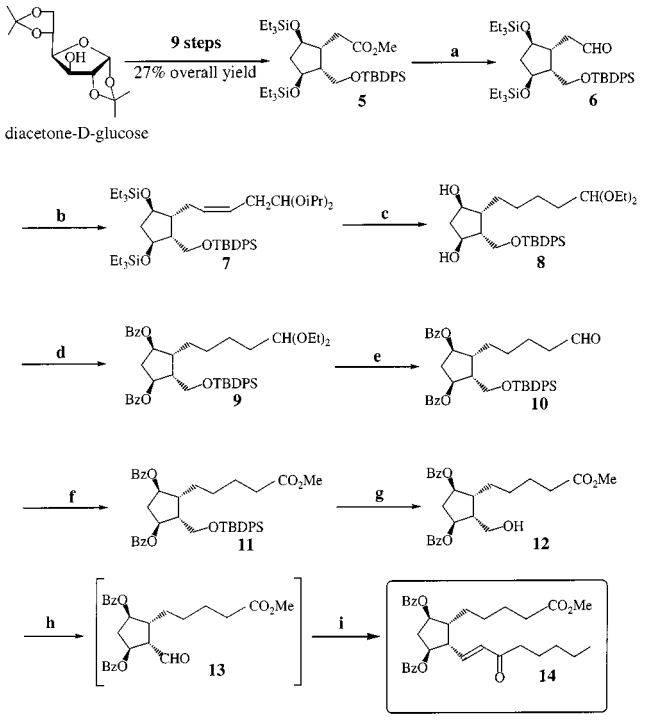



Scheme 1. Retrosynthesis of *ent*-15-$F_{2t}$-*iso*P **1**−**4**




Scheme 2. Synthesis of compound **14**; reagents and conditions: (a) DIBAL-H, toluene, reflux, 93%; (b) $Br^-$, $Ph_3P^+CH_2CH_2CH(OiPr)_2$, NaHMDS, THF, −80 °C, 83%; (c) $H_2$, Pd/C 10%, EtOH, 95%; (d) BzCl, pyridine, 91%; (e) $FeCl_3$, acetone, reflux, 87%; (f) *m*-CPBA, THF, followed by $CH_2N_2$, 89%; (g) HCl 3% methanolic solution, 83%; (h) $(ClCO)_2$, DMSO, $Et_3N$, $CH_2Cl_2$; (i) $(EtO)_2P(O)CH_2C(O)C_5H_{11}$, NaH, THF, room temp., 89% overall yield for Swern oxidation and HWE

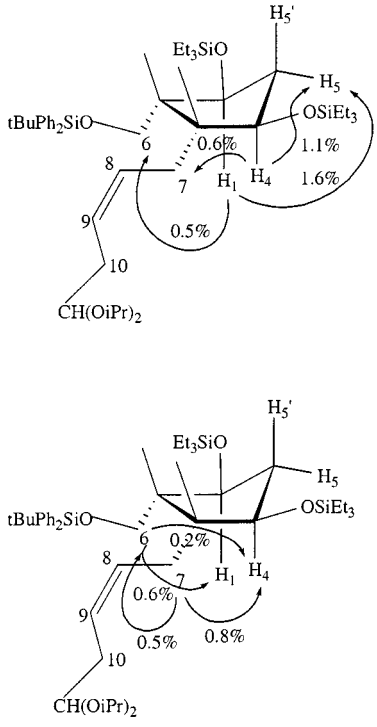



Figure 1. For compound **7**: observed NOEs resulting from irradiation of 1-H and 4-H (upper panel) and irradiation of 6-H and 7-H (lower panel) are indicated with solid lines; 0% = NOE not observed

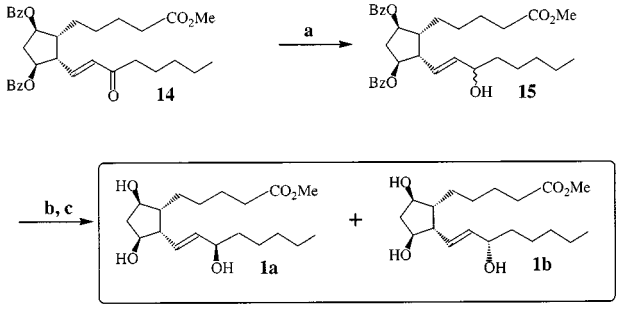
phosphonium salt and NaHMDS to afford the pure *cis*-β,γ-ethylenic diisopropyl acetal **7** in 83% yield. No trace of the *trans* compound could be detected by $^{13}C$ and $^1H$ NMR analysis. All the relative configurations were determined by homonuclear $^1H$ steady-state difference NOE spectroscopy (DNOES) experiments,[2f] as shown in Figure 1.

For compound **7**, irradiation of 1-H induces a NOE of 0.5% on 6-H and of 1.6% on 5-H, while irradiation of 4-H induces a NOE of 0.6% on 7-H and of 1.1% on 5-H. Similarly, irradiation of 7′-H induces a NOE of 0.5% on 6-H

and of 0.8% on 4-H, while irradiation of 6-H induces a NOE of 0.5% on 7′-H, of 0.6% on 1-H, and of 0.2% on 4-H. These observations verify the relative *cis* configuration of the protons 4-H, 1-H, 6-H, and 7′-H.

The *cis* double bond of **7** was reduced with $H_2$ on 10% Pd/C to give the diol diethyl acetal **8** in 95% yield. Interestingly, during this hydrogenation we could not avoid the deprotection of the triethylsilyl ethers and transacetalization with the solvent. Protection of the hydroxy functions of **8** with benzoyl chloride gave the colorless diesters **9** in 91% yield. Hydrolysis of the diethyl acetal **9** with aqueous $FeCl_3$ in acetone afforded the aldehyde **10** in 87% yield. Oxidation of **10** with *m*-CPBA and subsequent treatment with diazomethane gave the methyl ester **11** in 89% yield. The *tert*-butyldiphenylsilyl ether **11** was converted into the alcohol **12** with a solution of 3% hydrogen chloride.[11] Swern oxidation of **12** gave the unstable aldehyde **13**, which was immediately used, without purification, in the next step to avoid any epimerization of the aldehyde. The condensation of **13** with diethyl oxoheptylphosphonate, in the presence of NaH, afforded the *trans*-α,β-enone **14** in 89% overall yield from the alcohol **12**.

The synthesis of *ent*-2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane **1a** and its 15 epimer **1b** from **14** is shown in Scheme 3.




Scheme 3. Synthesis of *ent*-2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane methyl ester **1a** and its 15 epimer **1b**; reagents and conditions: (a) L-Selectride®, THF, −78 °C, 100%; (b) NaOH 1 N, 40 °C; (c) $CH_2N_2$ 83%

Reduction of the oxo function of **14** with L-Selectride® quantitatively afforded the epimeric allylic alcohols **15** as a 2:3 mixture that could not be separated by flash chromatography. Cleavage of the ester functions of **15** with 1 N NaOH at 40 °C, followed by treatment with diazomethane, gave a 3:2 mixture of methyl esters **1a** and **1b** in 83% yield. These two epimers were easily separated by flash chromatography on silica gel, using cyclohexane/ethyl acetate (30:70) as solvent. We confirmed the relative configurations of the chiral centers by homonuclear $^1H$ steady-state difference NOE spectroscopy (DNOES) experiments, as shown in Figure 2.

The two epimers (as their trimethylsilyl ether (TMS) pentafluorobenzyl ester (PFB) derivatives)[7] co-chromatographed on capillary GC-NICIMS ([M − PFB] at *m*/*z* = 543, $t_R$ = 10.16 min, 25 m NB54 column, 1 min at 160 °C, then to 300 °C at 10 °C/min).

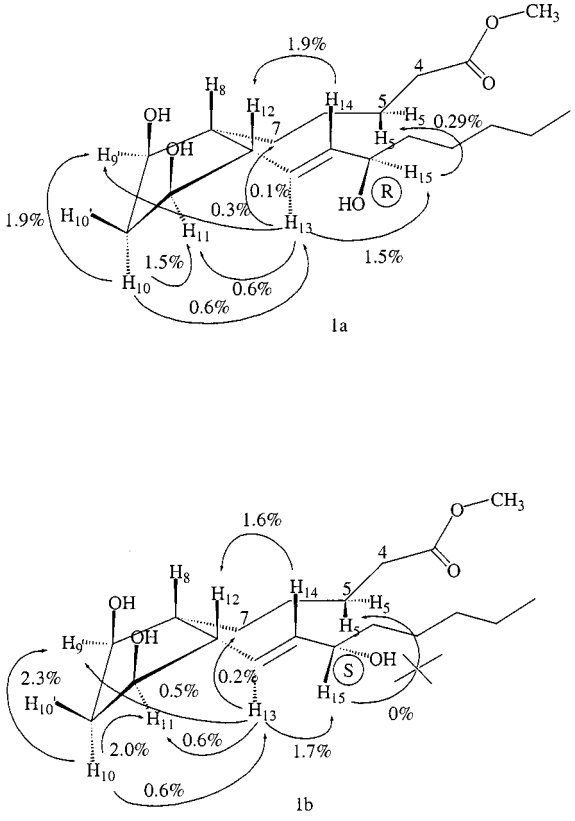



Figure 2. For compounds **1a** and **1b**: observed NOEs resulting from irradiation of 13-H are indicated with solid lines; 0% = NOE not observed

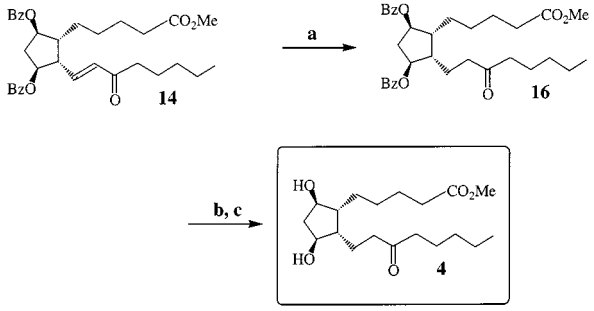
Synthetic **1a** showed GC-NICIMS characteristics identical to its enantiomeric counterpart 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane, recently commercially available from the Cayman Chemical Company (data not shown). Compound **1a** had the same GC-NICIMS behavior as 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane derived from in vitro metabolism of authentic 15$F_{2t}$-isoprostane[7] and of endogenous 2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane isolated from urine using an immobilized antibody stereo- and enantioselective towards the 15$F_{2t}$-isoprostane configuration.[7]

For compound **1b**, the relative *cis* configuration of the protons 13-H, 15-H, 7-H, 11-H, 9-H, and 10-H was determined by irradiation of 13-H, which induced NOEs of 1.7% on 15-H, of 0.6% on 11-H, of 0.5% on 9-H, and of 0.2% on 7-H. Also, irradiation of 10-H induced NOEs of 0.6% on 13-H, of 2.0% on 11-H, and of 2.3% on 9-H. Similar results were observed for compound **1a**.

The synthesis of *ent*-2,3-dinor-5,6,13,14-tetrahydro-15-oxo-15$F_{2t}$-isoprostane **4** from **14** is shown in Scheme 4.

The first step is the reduction of the *trans* double bond on the ω chain; this was achieved using $H_2$ on 10% Pd/C, giving the corresponding oxo derivative **16** in 100% yield. The last two steps were achieved using the same strategy that we had developed for **1**, and the 15-oxo metabolite **4** was obtained in 70% yield.

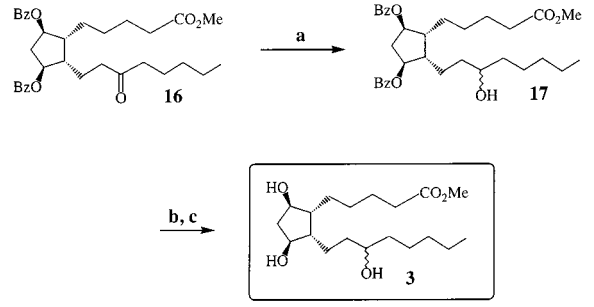
Derivatization of **4** as TMS-methyloxime-PFB resulted in equivalent amounts of *syn*/*anti* isomers, fully separable by



Scheme 4. Synthesis of *ent*-2,3-dinor-5,6,13,14-tetrahydro-15-oxo-$15F_{2t}$-isoprostane methyl ester **4**; reagents and conditions: (a) $H_2$, Pd/C 10%, EtOH, 100%; (b) NaOH 1 N, 40 °C; (c) $CH_2N_2$ 70%

GC-NICIMS ($[M - PFB]^-$ at $m/z = 500$, $t_R = 10.48$ and 10.57 min). The TMS-PFB derivative gave a single peak at $m/z = 471$ ($[M - PFB]^-$) and $t_R = 10.72$ min.

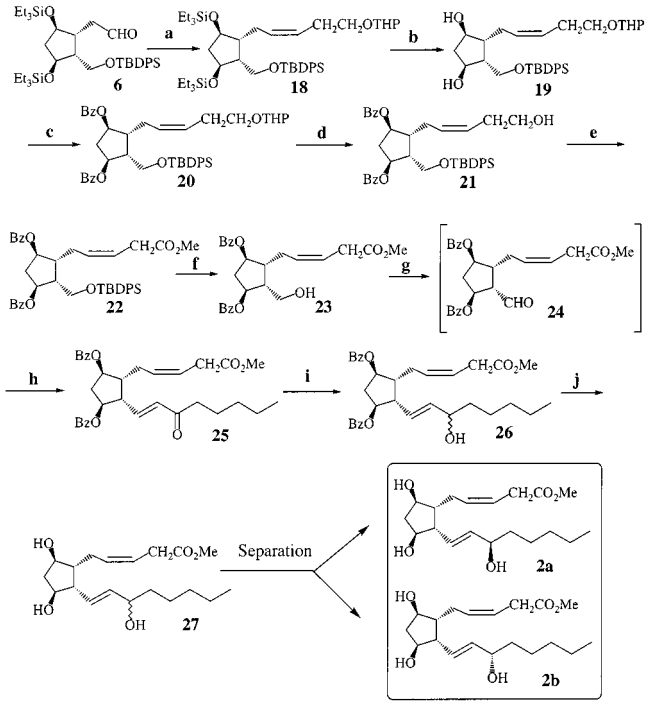
*ent*-(15*R*)/(15*S*)-2,3-Dinor-5,6,13,14-tetrahydro-$15F_{2t}$-isoprostane **3** was obtained in 50% overall yield from oxo derivative **16** (Scheme 5). The first step was the reduction of the carbonyl function by the action of $NaBH_4$, which afforded the racemic mixture of **17** in 71% yield. *ent*-(15*R*)/(15*S*)-2,3-Dinor-5,6,13,14-tetrahydro-$15F_{2t}$-isoprostane **3** was obtained using the same strategy that we have used for the other metabolites: i.e., saponification of the ester functions, followed by methylation of the carboxyl at C1. It is important to note that we were not able to separate the (15*R*)/(15*S*) epimers in this saturated series.



Scheme 5. Synthesis of *ent*-(15*RS*)-2,3-dinor-5,6,13,14-tetrahydro-$15F_{2t}$-isoprostane methyl ester **3**; reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 71%; (b) NaOH 1 N, 40 °C; (c) $CH_2N_2$ 83%

The (*R*) and (*S*) epimers of **3** cochromatographed when analyzed by GC-NICIMS as their TMS-PFB derivatives ($t_R = 10.36$ min, $[M - PFB]^-$ at $m/z = 545$).

The synthesis, using a similar strategy, of *ent*-2,3-dinor-$15F_{2t}$-isoprostane **2a** and its 15 epimer **2b** from aldehyde **6** is shown in Scheme 6. Our first attempts at the introduction of the upper chain, according to the first strategy, failed because of some silyloxyl migration during the hydrolysis of the diisopropyl acetal **7**. The introduction of the α chain to arrive at **2a** and **2b** was achieved by using a three-carbon homologating agent: 3-(tetrahydropyranyloxypropyl)triphenyl phosphonium bromide.[12] The aldehyde **6** reacted with the ylide derived from this phosphonium salt and



Scheme 6. Synthesis of *ent*-2,3-dinor-$15F_{2t}$-isoprostane methyl ester **2a** and its 15 epimer **2b**; reagents and conditions: (a) $Br^-$, $Ph_3P^+CH_2CH_2CH_2OTHP$, KHMDS, THF, −80 °C, 70%; (b) $NH_4F$, THF/MeOH, reflux, 88%; (c) BzCl, pyridine, 97%; (d) $Me_2AlCl$, $CH_2Cl_2$, −25 °C, 92%; (e) $CrO_3$, $H_2SO_4$, acetone, followed by $CH_2N_2$, 91%; (f) HCl 3% methanolic solution, 77%; (g) periodinane, $CH_2Cl_2$; (h) $(EtO)_2P(O)CH_2C(O)C_5H_{11}$, NaH, THF, room temp., 64% overall yield for Dess−Martin oxidation and HWE; (i) L-Selectride®, THF, −78 °C, 83%; (j) NaOH 1 N, 40 °C, then $CH_2N_2$ 75%

KHMDS to afford the pure *cis*-β,γ-ethylenic derivative **18** in 70% yield. No trace of *trans* compound could be detected by $^{13}C$ and $^1H$ NMR analysis. Deprotection of the triethylsilyl groups with $NH_4F$ gave the alcohol **19** in 88% yield. Protection using benzoyl chloride afforded the colorless diesters **20** in 97% yield. Selective deprotection of the THP group was carried out in the presence of dimethylaluminium chloride, affording the primary alcohol **21** in 92% yield. Oxidation of the primary alcohol in the presence of $CrO_3/H_2SO_4$ in dry acetone at −10 °C gave the corresponding acid, which in the presence of an excess of diazomethane was transformed in 91% yield into the methyl ester **22**.

The *tert*-butyldiphenylsilyl ether **22** was converted into the alcohol **23** in 77% yield, using a solution of 3% hydrogen chloride[11]. Dess−Martin oxidation[13] of **23** gave the unstable aldehyde **24**, which was used immediately, without purification, in the next step, to avoid any epimerization of the aldehyde. It is important to note that this Dess−Martin oxidation gave a higher yield, avoiding any epimerization, than our first attempts using Swern conditions. Condensation of **24** with diethyl oxoheptylphosphonate in the presence of NaH afforded the *trans*-α,β-enone **25** in 64% overall yield from the alcohol **23**. Reduction of the oxo function of **25** with L-Selectride® afforded the epimeric allylic alcohols **26**, in 83% yield, as a 2:3 mixture that we were unable to separate by flash chromatography. Cleavage of the ester

functions of **27** with 1 N NaOH, followed by treatment with diazomethane, gave a 3:2 mixture of methyl esters **2a** and **2b** in 75% yield. These two epimers were easily separated by flash chromatography on silica gel, using cyclohexane/ethyl acetate (30:70) as solvent.

Like **1a** and **1b**, the 15-epimers **2a** and **2b** co-chromatographed as their PFB-TMS derivatives ($t_R$ = 10.0 min, [M − PFB]$^-$ at *m/z* = 541) under the conditions shown above. Compound **2a** had the same GC-NICIMS behavior as 2,3-dinor-15$F_{2t}$-isoprostane derived from in vitro metabolism of authentic 15$F_{2t}$-isoprostane[7] and of the endogenous 2,3-dinor-15$F_{2t}$-isoprostane obtained from urine by immunoaffinity extraction using an antibody stereo- and enantioselective towards the 15$F_{2t}$-isoprostane configuration.[7]

## Conclusions

In conclusion, we describe here the first stereoselective syntheses of *ent*-2,3-dinor-5,6-dihydro-15$F_{2t}$-isoprostane **1a**, its 15 epimer **1b**, *ent*-2,3-dinor-15$F_{2t}$-isoprostane **2a**, its 15 epimer **2b**, *ent*-(15*R*)/(15*S*)-2,3-dinor-5,6,13,14-tetrahydro-15$F_{2t}$-isoprostane **3**, and *ent*-2,3-dinor-5,6,13,14-tetrahydro-15-oxo-15$F_{2t}$-isoprostane **4** from the methyl ester **5**. This route makes possible the enantiospecific synthesis of two recently identified major urinary metabolites of 15$F_{2t}$-isoprostane and of other putative metabolites. In addition to their proven use for such identification, these compounds should provide the basis for development of quantitative assays directed towards integrated and accurate determination of oxidative stress status in humans.

## Experimental Section

Melting points were determined on a Büchi Tottoli capillary apparatus and were not corrected. − $^1$H and $^{13}$C NMR spectra were recorded either on a Bruker AC100 spectrometer at 100 and 25 MHz respectively or on a Bruker AMX360 at 360 and 90 MHz respectively. 2D NMR spectra were recorded on a Bruker AMX360 spectrometer. Chemical shifts (δ) are quoted in ppm, coupling constants (*J*) are given in Hz. The residual hydrogenated solvent peak was used as internal reference (for $CHCl_3$: $\delta_H$ = 7.27, $\delta_C$ = 77.0). − Infrared spectra were obtained on a Beckman AccuLab2 spectrophotometer and absorption bands (ṽ) are given in cm$^{-1}$. − Elemental analysis were performed at the "Service de Microanalyses de l'ENSCN" at Montpellier (France), with the maximum error in the range of ±0.4% of calculated. − Analytical TLC was performed on Merck silica gel 60 $F_{254}$, aluminium sheets. Viewing methods included UV light, iodine vapors and anisaldehyde dipping. − Column chromatography was performed with Merck silica gel (Geduran 40 to 63 μm or 63 to 200 μm particle size). − All air-sensitive experiments were carried out under nitrogen, with freshly distilled, dried solvents. Methylene chloride ($CH_2Cl_2$) was distilled from $CaH_2$. THF was distilled from sodium-benzophenone. Triethylamine ($Et_3N$) was dried with KOH; benzene and diethyl ether were dried by standing with sodium wire. Methanol was distilled after treatment with sodium. Acetone was dried with anhydrous $CaSO_4$. DMSO was purchased anhydrous and kept over 4-Å molecular sieves.

For DNOES experiments, $^1$H NMR spectra were recorded on a Bruker AMX 360 spectrometer operating in the pulse mode. Compounds were dissolved in the indicated solvent (Table 1). The probe-head temperature was 32 °C. Solutions were degassed by argon bubbling. The NOE procedure was as follows: the standard Bruker library microprogram was used to perform steady-state NOE difference spectroscopy. The experiments were performed with interleaving. Thirty-two scans (preceded by two dummy scans to establish equilibrium: l1 = 2) were measured for each irradiation frequency, and the entire process was automatically repeated to provide the requisite signal-to-noise ratio. The irradiation time was typically 3 s. A 90° read pulse was employed in all cases. The decoupler power setting was chosen so as to minimize frequency spillover to neighboring multiplets. NOE values were calculated by comparing summed peak heights in the vertically expanded difference spectra with the control irradiation spectra. (3,3-Diisopropoxypropyl)-triphenylphosphonium bromide was prepared as previously reported by Viala et al.[10]

Table 1. NOE values for compounds **1a**, **1b**

| δb | 5.55 | 5.35 | 4.04 | 3.97 | 3.93 | 2.72 | 2.37 | 2.10 | 1.62 | 1.59 | 1.46 | 1.32 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| δa | 5.55 | 5.35 | 4.04 | 4.00 | 3.93 | 2.72 | 2.39 | 2.10 | 1.62 | 1.59 | 1.46 | 1.29 |
| | 14b | 13b | 15b | 11b | 9b | 12b | 10b | 8b | 10'b | 5b | 16b | 7b |
| | 14a | 13a | 15a | 11a | 9a | 12a | 10a | 8a | 10'a | 5a | 16a | 7a |
| 8b | - | - | - | - | 1,06 | 5,3 | - | Irr. | - | - | - | 0,5 |
| 8a | - | - | - | - | 0,96 | 3,8 | - | Irr. | - | - | - | 0,3 |
| 9b | - | 1,14 | - | - | Irr. | - | 2,2 | 0,68 | 0,17 | - | - | 0,43 |
| 9a | - | 0,95 | - | - | Irr. | - | 2,3 | 0,69 | 0,15 | - | - | 0,36 |
| 10b | - | 0,63 | - | 2,04 | 2,39 | - | Irr. | - | 1,64 | - | - | - |
| 10a | - | 0,66 | - | 1,53 | 1,94 | - | Irr. | - | 2,76 | - | - | - |
| 10'b | - | - | - | 0,82 | 0,5 | 0,67 | 0,53 | - | Irr. | - | - | - |
| 10'a | - | - | - | 1,39 | 1,07 | 0,77 | 4.9 | - | Irr. | - | - | - |
| 11b | 0,9 | 1,4 | - | Irr. | - | 1,3 | 2,4 | - | 0,23 | - | - | - |
| 11a | 0,8 | 1,6 | - | Irr. | - | 1,3 | 2,0 | - | 0,23 | - | - | - |
| 12b | 3,9 | 1,07 | - | 1,3 | - | Irr. | - | 3,7 | 0,10 | - | - | 0,12 |
| 12a | 3,5 | 1,02 | - | 1,18 | - | Irr. | - | 2,7 | 0,19 | - | - | 0,08 |
| 13b | 0 | Irr. | 1,7 | 0,6 | 0,5 | 0,89 | 0,5 | - | - | - | - | 0,2 |
| 13a | 0 | Irr. | 1,5 | 0,6 | 0,3 | 0,8 | 0,5 | - | - | - | - | 0,06 |
| 14b | Irr. | 0 | 0,7 | 0,2 | - | 1,6 | - | - | - | - | - | - |
| 14a | Irr. | 0 | 0,9 | 0,2 | - | 1,9 | - | - | - | - | - | - |
| 15b | 1,48 | 2,5 | Irr. | - | - | - | - | - | - | 0 | 0,8 | - |
| 15a | 1,5 | 2,9 | Irr. | - | - | - | - | - | - | 0,29 | 0,87 | - |

**(1*S*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-formylmethyl-1,4-di-*O*-(triethylsilyl)cyclopentane-1,4-diol (6):** To a solution of ester **5** (250 mg, 372 μmol, 1 equiv.) in dry toluene (3 mL) at −78 °C, under nitrogen atmosphere, was added dropwise DIBAL-H (1 M/toluene, 410 μL, 410 μmol, 1.1 equiv.). The resulting mixture was stirred for 30 min at −78 °C, then hydrolyzed with MeOH (500 μL). The reaction mixture was neutralized with a solution of HCl (2 M); then the aqueous layers were extracted three times with EtOAc. The organic layers were dried with $Na_2SO_4$ and evaporated under reduced pressure before being chromatographed on silica gel (cyclohexane/ethyl acetate, 97:3) to give the colorless oil **6** (221 mg, 93%): $R_f$ 0.58 (cyclohexane/ ethyl acetate, 90:10). − $^1$H NMR ($CDCl_3$): δ = 0.40−0.70 [m, 12 H, $(CH_3CH_2)_3Si$], 0.75−0.98 [m, 18 H, $(CH_3CH_2)_3Si$], 1.04 [s, 9 H, $C(CH_3)_3$], 2.12 (m, 2 H, 2-H, 5-H), 2.20−2.47 (m, 1 H, 3-H), 2.50−2.72 (m, 3 H, 5′-H, 7-H), 3.57 (m, 2 H, 6-H), 3.87 (q, *J* = 7.7 Hz, 1 H, 4-H), 4.05 (m, 1 H, 1-H), 7.31−7.50 (m, 6 H, Ar-H), 7.51−7.67 (m, 4 H, Ar-H), 9.7 (s, 1 H, 8-H). − $^{13}$C NMR ($CDCl_3$): δ = 4.5 [$(CH_3CH_2)_3Si$], 4.7 [$(CH_3CH_2)_3Si$], 6.5 [$(CH_3CH_2)_3Si$], 6.6 [$(CH_3CH_2)_3Si$], 18.9 [$C(CH_3)_3$], 26.7 [$C(CH_3)_3$], 42.7 (C-3), 43.1 (C-7), 44.7 (C-5), 50.1 (C-2), 62.7 (C-6), 72.7 (C-1), 75.9 (C-4), 127.5 (C-Ar), 129.6 (C-Ar), 132.8 (C-Ar), 135.5 (C-Ar), 202.4 (C-8).

**(1*S*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-[(*Z*)-5,5-bis(isopropyloxy)pent-2-enyl]-1,4-di-*O*-(triethylsilyl)cyclopentane-1,4-diol (7):** To a suspension of (3,3-diisopropoxypropyl)-triphenylphosphonium bromide[10] (345 mg, 686 μmol, 4 equiv.) in dry THF (2 mL) at −80 °C, was added $NaN(SiMe_3)_2$ (1 M/THF, 653 μL, 653 μmol, 3.8 equiv.). The orange solution of ylide was stirred for 2 h at −80 °C. A solution of aldehyde **6** (210 mg, 172 μmol, 1 equiv.) in dry THF (750 μL) was added to the ylide. After slow warming to room temperature over 2 h, the reaction mixture was hydrolyzed with saturated, aqueous $NH_4Cl$ solution (10 mL) and water (10 mL), diluted with diethyl ether (30 mL), and washed with brine (5 mL). The aqueous layers were extracted with diethyl ether (3× 10 mL), and the combined extracts were washed with brine (10 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving crude product. Flash chromatography over silica gel, cyclohexane/ethyl acetate, 98:2) gave pure diisopropyl acetal **7** (233 mg, 83%): $R_f$ 0.62 (cyclohexane/ethyl acetate, 90:10). − $^1$H NMR ($CDCl_3$): δ = 0.46 [t, *J* = 7.9 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.55 [t, *J* = 7.9 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.85 [q, *J* = 7.9 Hz, 9 H, $(CH_3CH_2)_3Si$], 0.93 [q, *J* = 7.9 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.04 [s, 9 H, $C(CH_3)_3$], 1.1−1.16 [m, 12 H, $OCH(CH_3)_2$], 1.5 (dt, *J* = 5.2 and 13.5 Hz, 1 H, 8-H), 1.97−2.02 (m, 1 H, 5-H), 2.07−2.15 (m, 1 H, 10-H), 2.17−2.26 (m, 3 H, 2-H, 5′-H, 6-H), 2.27−2.36 (m, 2 H, 2′-H, 8-H), 3.57−3.59 (m, 2 H, 11-H), 3.78−3.85 [m, 2 H, $OCH(CH_3)_2$], 3.91 (q, *J* = 6.8 Hz, 1 H, 7-H), 4.06 (dt, *J* = 4.4 and 7.7 Hz, 1 H, 9-H), 4.49 (t, *J* = 5.5 Hz, 1 H, 1-H), 5.37−5.42 (m, 2 H, 3-H, 4-H), 7.33−7.42 (m, 6 H, Ar-H), 7.6−7.63 (m, 4H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 4.7 [$(CH_3CH_2)_3Si$], 4.9 [$(CH_3CH_2)_3Si$], 6.8 [$(CH_3CH_2)_3Si$], 6.8 [$(CH_3CH_2)_3Si$], 19.2 [$C(CH_3)_3$], 22.6 [$OCH(CH_3)_2$], 23.3 [$OCH(CH_3)_2$], 25.9 (C-5), 26.9 [$C(CH_3)_3$], 33.8 (C-2), 45.1 (C-8), 48.2 (C-6), 50.7 (C-10), 62.6 (C-11), 67.8 [$OCH(CH_3)_2$], 73.2 (C-9), 76.4 (C-7), 100 (C-1), 124.9 (C-3), 127.6 (C-Ar), 129.6 (C-Ar), 130.7 (C-4), 133.5 (C-Ar), 135.7 (C-Ar). − $C_{45}H_{78}O_5Si_3$ (783.4): calcd. C 69.00, H 10.04; found C 69.04, H 10.08.

**(1*S*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-[5,5-bis(isopropyloxy)pentyl]cyclopentane-1,4-diol (8):** A mixture of **7** (180 mg, 230 μmol, 1 equiv.) and 10% Pd/C (20 mg) in absolute ethanol (5 mL) was hydrogenated at 40 psi for 4 h. The mixture was filtered and the filtrate concentrated to provide **8** as a colorless oil (113 mg, 95%): $R_f$ 0.45 ($CH_2Cl_2$/MeOH 90:10). − IR: $\tilde{\nu}$ = 3360 $cm^{-1}$. − $^1$H NMR ($CDCl_3$): δ = 1.03 [s, 9 H, $C(CH_3)_3$], 1.10−1.24 (m, 12 H, 3-H, 4-H, 5-H, $OCH_2CH_3$), 1.51−1.62 (m, 3 H, 2-H, 8-H), 2.02−2.04 (m, 1 H, 6-H), 2.23−2.34 (m, 1 H, 10-H), 2.39 (dt, *J* = 4.5 and 6.9 Hz, 1 H, 8′-H), 3.42−3.45 (m, 2 H, $OCH_2CH_3$), 3.53−3.58 (m, 2 H, $OCH_2CH_3$), 3.73 (dd, *J* = 5.2 and 10 Hz, 1 H, 11′-H), 3.94 (dt, *J* = 4.5 and 6.6 Hz, 1 H, 7-H), 4.23 (dt, *J* = 4.5 and 6.7 Hz, 1 H, 9-H), 4.41 (t, *J* = 5.8 Hz, 1 H, 1-H), 7.37−7.41 (m, 6 H, Ar-H), 7.62−7.65 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 15.3 ($OCH_2CH_3$), 19.1 [$C(CH_3)_3$], 24.9 (C-4), 26.9 [$C(CH_3)_3$], 28.1 (C-3), 28.3 (C-5), 33.5 (C-2), 42.9 (C-8), 48.7 (C-6), 51.2 (C-10), 60.9 ($OCH_2CH_3$), 63.5 (C-11), 75.5 (C-9), 76.6 (C-7), 102.8 (C-1), 127.8 (C-Ar), 129.8 (C-Ar), 133.1 (C-Ar), 135.6 (C-Ar). − $C_{31}H_{48}O_5Si$ (528.8): calcd. C 70.41, H 9.15; found C 70.34, H 9.12

**(1*S*,2*R*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(5,5-diethoxypentyl)cyclopentane-1,4-diol (9):** To a solution of diol **8** (113 mg, 219 μmol, 1 equiv.) in dry pyridine (1 mL) under nitrogen atmosphere, was added benzoyl chloride (635 μL, 547 μmol, 2.5 equiv.). The reaction mixture was stirred for 2 h at room temperature. The pyridine was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) to provide **9** (151 mg, 91%): $R_f$ 0.51 (cyclohexane/ethyl acetate, 50:50). − IR: $\tilde{\nu}$ = 1710 $cm^{-1}$. − $^1$H NMR ($CDCl_3$): δ = 1.1 [s, 9 H, $C(CH_3)_3$], 1.14−1.23 (m, 6 H, $OCH_2CH_3$), 1.27−1.36 (m, 2 H, 3-H), 1.37−1.49 (m, 4 H, 4-H, 5-H), 1.51−1.59 (m, 2 H, 2-H), 1.91 (dt, *J* = 3.2 and 15.6 Hz, 1 H, 8-H), 2.54−2.63 (m, 2 H, 6-H, 10-H), 2.94 (dt, *J* = 7.4 and 15.6 Hz, 1 H, 8′-H), 3.44−3.5 (m, 2 H, $OCH_2CH_3$), 3.56−3.64 (m, 2 H, $OCH_2CH_3$), 3.68−3.72 (m, 1 H, 11-H), 3.84−3.88 (m, 1 H, 11′-H), 4.37−4.51 (m, 1 H, 1-H), 5.3−5.35 (m, 1 H, 7-H), 5.42−5.45 (m, 1 H, 9-H), 7.36−7.47 (m, 10 H, Ar-H), 7.54−7.59 (m, 2 H, Ar-H), 7.67−7.72 (m, 4 H, Ar-H), 8.01−8.07 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 15.3 ($OCH_2CH_3$), 19.1 [$C(CH_3)_3$], 23.3 (C-3), 26.9 [$C(CH_3)_3$], 27.8 (C-4), 28.2 (C-5), 33.5 (C-2), 38.8 (C-8), 45.5 (C-6), 48.8 (C-10), 60.9 ($OCH_2CH_3$), 61.8 (C-11), 77.2 (C-9), 79.5 (C-7), 102.9 (C-1), 127.7 (C-Ar), 128.3 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 130.5 (C-Ar), 132.8 (C-Ar), 133.1 (C-Ar), 135.7 (C-Ar), 166 [C(O)], 166.3 [C(O)]. − $C_{45}H_{56}O_7Si$ (737.0): calcd. C 73.33, H 7.66; found C, 73.45, H 7.59.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Di-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(formylbutyl)cyclopentane-1,4-diol (10):** An aqueous solution of $FeCl_3$ (0.02 M, 125 μL, 2.5 μmol, 0.025 equiv.) was added to a solution of acetal **9** (75 mg, 99.5 μmol, 1 equiv.) in 2 mL of dry acetone under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature, and then quenched with brine (5 mL). The aqueous layer was extracted with diethyl ether (3× 5 mL), and the combined extracts were washed with brine (5 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving crude aldehyde **10** (57 mg, 87%), which was used for the next steps without further purification. $R_f$ 0.34 (cyclohexane/ethyl acetate, 80:20). − IR: $\tilde{\nu}$ = 1710 $cm^{-1}$. − $^1$H NMR ($CDCl_3$): δ = 1.06 [s, 9 H, $C(CH_3)_3$], 1.46 (m, 6 H, 3-H, 4-H, 5-H), 1.86 (m, 1 H, 8-H), 2.34 (m, 2 H, 2-H), 2.58 (m, 2 H, 6-H, 10-H), 2.97 (dt, *J* = 7.5 and 14 Hz, 1 H, 8′-H), 3.79 (m, 2 H, 11-H), 5.39 (m, 2 H, 7-H, 9-H), 7.43 (m, 10 H, Ar-H), 7.66 (m, 6 H, Ar-H), 8.05 (m, 4 H, Ar-H), 9.72 (s, 1 H, 1-H).

**(1*S*,2*R*,3*R*,4*R*)-1,4-Bis-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(methoxycarbonylbutyl)cyclopentane-1,4-diol (11):** To a solution of aldehyde **10** (57 mg, 86 μmol, 1 equiv.) in THF (2 mL) at room temperature, was added *m*-CPBA (59 mg, 344 μmol, 4 equiv.). The resulting mixture was stirred for 12 h; then excess *m*-CPBA was destroyed using $Me_2S$ (25 μL, 344 μmol, 4 equiv.). Stir-

ring was continued for an additional 30 min. The solvent was removed under reduced pressure; then the crude material was diluted with diethyl ether and esterified by addition of diazomethane. After concentration, flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) gave **11** (53 mg, 89%): $R_f$ 0.73 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 1720, 1710 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 1.08 [s, 9 H, $C(CH_3)_3$], 1.35−1.46 (m, 4 H, 4-H, 5-H), 1.49−1.5 (m, 2 H, 3-H), 1.89 (dt, $J$ = 3.3 and 15.6 Hz, 1 H, 8-H), 2.22 (t, $J$ = 6.6 Hz, 2 H, 2-H), 2.47−2.57 (m, 2 H, 6-H, 10-H), 2.92 (dt, $J$ = 5.7 and 7.4 Hz, 1 H, 8′-H), 3.6 (s, 3 H, $OCH_3$), 3.66 (dd, $J$ = 4.9 and 10.7 Hz, 1 H, 11-H), 3.84 (dd, $J$ = 4.7 and 10.7 Hz, 1 H, 11′-H), 5.29 (m, 1 H, 7-H), 5.40 (m, 1 H, 9-H), 7.38 (m, 10 H, Ar-H), 7.54 (m, 2 H, Ar-H), 7.64−7.68 (m, 4 H, Ar-H), 8 (t, $J$ = 8.3 Hz, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 19.1 ($C(CH_3)_3$), 25 (C-3), 26.9 ($C(CH_3)_3$), 27.5 (C-5), 27.8 (C-4), 33.9 (C-2), 38.8 (C-8), 45.4 (C-6), 48.7 (C-10), 51.4 ($OCH_3$), 61.7 (C-11), 77.6 (C-9), 79.5 (C-7), 127.7 (C-Ar), 128.3 (C-Ar), 129.6 (C-Ar), 129.8 (C-Ar), 130.5 (C-Ar), 132.8 (C-Ar), 135.7 (C-Ar), 166.2 [C(O)], 166.8 [C(O)], 174 (C-1). − $C_{42}H_{48}O_7Si$ (692.9): calcd. C 72.8, H 6.98; found C, 72.65, H 7.06.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-(hydroxymethyl)cyclopentane-1,4-diol (12):** Acetyl chloride (770 μL) was added dropwise to methanol (18 mL), and the hydrogen chloride solution obtained was cooled to 20 °C. A solution of the silyl derivative **11** (400 mg, 577 μmol) in diethyl ether (18 mL) was added, and the mixture was stirred at room temperature overnight, and then neutralized with saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (3× 50 mL). The organic layers were dried with $Na_2SO_4$ and concentrated under reduced pressure, and the crude material was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 85:15) to provide alcohol **12** (261 mg, 83%): $R_f$ 0.21 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 3520, 1720, 1710 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 1.2−1.57 (m, 4 H, 4-H, 5-H), 1.65−1.73 (m, 2 H, 3-H), 2.05 (dt, $J$ = 3 and 15.6 Hz, 1 H, 8-H), 2.34 (t, $J$ = 7.5 Hz, 2 H, 2-H), 2.53−2.67 (m, 2 H, 6-H, 10-H), 2.91 (dt, $J$ = 7.5 and 15.1 Hz, 1 H, 8′-H), 3.66 (s, 3 H, $OCH_3$), 3.74 (dd, $J$ = 7.2 and 10.8 Hz, 1 H, 11-H), 3.88 (dd, $J$ = 5 and 10.8 Hz, 1 H, 11′-H), 5.23−5.27 (m, 1 H, 7-H), 5.40 (dt, $J$ = 3.4 and 7.4 Hz, 1 H, 9-H), 7.44 (q, $J$ = 7.4 Hz, 4 H, Ar-H), 7.56 (t, $J$ = 7.5 Hz, 2 H, Ar-H), 8.06 (t, $J$ = 8.5 Hz, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 25 (C-3), 27.3 (C-5), 27.7 (C-4), 33.8 (C-2), 38 (C-8), 45.7 (C-6), 49.2 (C-10), 51.5 ($OCH_3$), 60.7(C-11), 77.2 (C-9), 78.9 (C-7), 128.4 (C-Ar), 129.6 (C-Ar), 130.1 (C-Ar), 130.4 (C-Ar), 133 (C-Ar), 133.1 (C-Ar), 166.2 [C(O)], 166.8 [C(O)], 174 (C-1). − $C_{26}H_{30}O_7$ (454.5): calcd. C 68.71, H 6.65; found C, 68.79, H 6.57.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-[(*E*)-3-oxooct-1-enyl]cyclopentane-1,4-diol (14):** To a solution of oxalyl chloride (77 μL, 885 μmol, 2.5 equiv.) in dry $CH_2Cl_2$ (2.8 mL) at −60 °C was added dropwise under $N_2$ a solution of DMSO (125 μL, 1.17 mmol, 5 equiv.) in $CH_2Cl_2$ (400 μL). After 15 minutes, the solution of **12** (161 mg, 354 mmol, 1 equiv.) in $CH_2Cl_2$ (800 μL) was added dropwise and the reaction mixture was stirred for 40 minutes at −60 °C. Then triethylamine (197 μL, 1.41 μmol, 4 equiv.) was added and the reaction mixture was kept for 10 minutes at −60 °C before being allowed to cool to room temperature. The mixture was diluted with water (2 mL) and extracted three times with diethyl ether (15 mL). Organic layers were washed with brine, dried with $Na_2SO_4$, filtered, and evaporated under reduced pressure, and the crude product was used immediately for the next step. To a cooled (−10 °C) solution of aldehyde (previous crude product) in dry THF (2 mL) was added dropwise a solution of ylide prepared at room temperature from diethyl 2-oxoheptylphosphonate (316 μL, 885 μmol, 2.5 equiv.) and NaH (60% suspension in oil, 39 mg, 974 μmol) in THF (2 mL). The reaction was stirred for 10 minutes, neutralized with saturated NaCl, and extracted with diethyl ether (3× 10 mL). Organic phases were washed with brine, dried with $Na_2SO_4$, filtered, and evaporated under reduced pressure to give 173 mg of **14** (89%) after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10): $R_f$ 0.21 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 1720, 1710, 1670 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.88 (t, $J$ = 7.9 Hz, 3 H, 18-H), 1.26−1.31 (m, 4 H, 16-H, 17-H), 1.37−1.43 (m, 4 H, 4-H, 5-H), 1.55−1.62 (m, 4 H, 3-H, 15-H), 2.00 (dt, $J$ = 3.1 and 15.9 Hz, 1 H, 8-H), 2.27 (t, $J$ = 7.4 Hz, 2 H, 2-H), 2.53 (t, $J$ = 7.5 Hz, 2 H, 14-H), 2.56−2.62 (m, 1 H, 6-H), 2.95 (dt, $J$ = 7.5 and 15.9 Hz, 1 H, 8′-H), 3.23−3.29 (m, 1 H, 10-H), 3.62 (s, 3 H, $OCH_3$), 5.22−5.26 (m, 1 H, 7-H), 5.28−5.33 (m, 1 H, 9-H), 6.27 (dd, $J$ = 1 and 15.8 Hz, 1 H, 12-H), 6.71 (dd, $J$ = 9.1 and 15.8 Hz, 1 H, 11-H), 7.35 (t, $J$ = 7.7 Hz, 4 H, Ar-H), 7.54 (t, $J$ = 7.4 Hz, 2 H, Ar-H), 8.02 (t, $J$ = 7.8 Hz, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 13.9 (C-18), 22.5 (C-16), 23.8 (C-15), 24.9 (C-3), 27.5 (C-5), 28.3 (C-4), 31.4 (C-17), 33.8 (C-2), 38 (C-8), 40.9 (C-14), 47.7 (C-6), 50.2 (C-10), 51.5 ($OCH_3$), 77.4 (C-9), 78.4 (C-7), 128.4 (C-Ar), 129.6 (C-Ar), 132.4 (C-12), 133.2 (C-Ar), 141.5 (C-11), 165.9 [C(O)], 166.1 [C(O)], 173.8 (C-1), 199.8 (C-13). − $C_{33}H_{40}O_7$ (548.7): calcd. C 72.24, H 7.35; found C, 72.31, H 7.40.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-[(3*RS*,*E*)-3-hydroxyoct-1-enyl]cyclopentane-1,4-diol (15):** To a cooled (−78 °C) solution of **14** (20 mg, 36.4 μmol) in dry THF (400 μL) was added a solution of L-Selectride® (1 M in THF, 40 μL, 40 μmol). The mixture was stirred at −78 °C for 20 minutes, quenched with MeOH (10 μL), and diluted with diethyl ether (5 mL). The organic layer was washed with 1 M $NH_4Cl$ (5 mL), dried with $Na_2SO_4$, filtered, evaporated, and chromatographed (cyclohexane/ethyl acetate, 90:10) to give a mixture of isomers of **15** (20 mg, 100%) as a colorless oil. $R_f$ 0.37 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 3530, 1720, 1710 $cm^{-1}$.

**Minor Isomer:** $^1H$ NMR ($CDCl_3$): δ = 0.85−0.92 (m, 3 H, 18-H), 1.23−1.28 (m, 4 H, 16-H, 17-H), 1.41−1.46 (m, 8 H, 4-H, 5-H, 14-H, 15-H), 1.57−1.65 (m, 2 H, 3-H), 1.92−1.97 (m, 1 H, 8-H), 2.27 (t, $J$ = 7.3 Hz, 2 H, 2-H), 2.47−2.52 (m, 1 H, 6-H), 2.84−2.93 (m, 1 H, 8′-H), 3.06−3.11 (m, 1 H, 10-H), 3.62 (s, 3 H, $OCH_3$), 4.63 (q, $J$ = 6.1 Hz, 1 H, 13-H), 5.14−5.23 (m, 2 H, 7-H, 9-H), 5.42−5.5 (m, 1 H, 11-H), 5.61−5.65 (m, 1 H, 12-H), 7.39 (t, $J$ = 7.6 Hz, 4 H, Ar-H), 7.54 (t, $J$ = 7.6 Hz, 2 H, Ar-H), 8.02 (d, $J$ = 8.3 Hz, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.6 (C-16), 25 (C-3), 26.9 (C-15), 27.3 (C-5), 28.3 (C-4), 31.7 (C-17), 33.7 (C-2), 37.2 (C-14), 38 (C-8), 47.1 (C-6), 50.2 (C-10), 51.4 ($OCH_3$), 72.6 (C-13), 78.7 (C-7), 78.8 (C-9), 126.3 (C-11), 128.3 (C-Ar), 129.6 (C-Ar), 130.3 (C-Ar), 133 (C-Ar), 137.3 (C-12), 166 [C(O)], 166.3 [C(O)], 174.2 (C-1). − $C_{33}H_{42}O_7$ (550.7): calcd. C 71.97, H 7.69; found C, 72.21, H 7.80.

**Major Isomer:** $^1H$ NMR ($CDCl_3$): δ = 0.85−0.92 (m, 3 H, 18-H), 1.23−1.28 (m, 4 H, 16-H, 17-H), 1.41−1.46 (m, 8 H, 4-H, 5-H, 14-H, 15-H), 1.57−1.65 (m, 2 H, 3-H), 1.92−1.97 (m, 1 H, 8-H), 2.27 (t, $J$ = 7.3 Hz, 2 H, 2-H), 2.47−2.52 (m, 1 H, 6-H), 2.84−2.93 (m, 1 H, 8′-H), 3.06−3.11 (m, 1 H, 10-H), 3.62 (s, 3 H, $OCH_3$), 4.09 (q, $J$ = 6.5 Hz, 1 H, 13-H), 5.14−5.23 (m, 2 H, 7-H, 9-H), 5.46 (dd, $J$ = 8.6 and 15.4 Hz, 1 H, 11-H), 5.63 (m, 1 H, 12-H), 7.39 (t, $J$ = 7.6 Hz, 4 H, Ar-H), 7.54 (t, $J$ = 7.6 Hz, 2 H, Ar-H), 8.02 (d, $J$ = 8.3 Hz, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.6 (C-16), 25 (C-3), 26.9 (C-15), 27.4 (C-5), 28.3 (C-4), 31.7 (C-17), 33.8 (C-2), 376 (C-14), 37.9 (C-8), 47.1 (C-6), 50.2 (C-10), 51.4 ($OCH_3$), 72.6 (C-13), 78.7 (C-7), 78.8 (C-9), 126.3 (C-11), 128.3 (C-

Ar), 129.6 (C-Ar), 130.3 (C-Ar), 133 (C-Ar), 137.5 (C-12), 166 [C(O)], 166.3 [C(O)], 174.2 (C-1). − $C_{33}H_{42}O_7$ (550.7): calcd. C 71.97, H 7.69; found C 72.21, H 7.80.

***ent*-15(*RS*)-2,3-Dinor-5,6-dihydro-15-$F_{2t}$-isoprostane Methyl Ester (1a and 1b):** To a solution of **15** (24 mg, 53.2 μmol) in methanol (350 μL) and THF (230 μL) was added NaOH (1 N solution, 400 μL). The mixture was stirred for two hours at 40 °C. $NaHSO_4$ (1 N solution, 710 μL) was then added for neutralization. The reaction was diluted in water (1 mL) and extracted with ethyl acetate (3× 5 mL). The organic layers were dried with $Na_2SO_4$ and evaporated. The residue was esterified with diazomethane. After neutralization of excess with acetic acid and evaporation of solvents, the crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 30:70) to give 15 mg of **1a** and **1b** in a ratio of 3:2.

***ent*-(15*R*)-2,3-Dinor-5,6-dihydro-15-$F_{2t}$-isoprostane Methyl Ester (1a):** $R_f$ 0.51 (ethyl acetate/acetic acid, 95:5). − IR: $\tilde{\nu}$ = 3520, 1720 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.5 Hz, 3 H, 18-H), 1.24−1.41 (m, 10 H, 4-H, 5-H, 15-H, 16-H, 17-H), 1.56−1.65 (m, 5 H, 3-H, 8-H, 14-H), 1.97 (brs, 1 H, OH), 2.10 (t, *J* = 4.5 Hz, 1 H, 6-H), 2.29 (t, *J* = 7.3 Hz, 2 H, 2-H), 2.38 (dt, *J* = 6.9 and 14 Hz, 1 H, 8′-H), 2.70−2.76 (m, 1 H, 10-H), 3.64 (s, 3 H, $OCH_3$), 3.93−3.96 (m, 1 H, 7-H), 3.98−4 (m, 1 H, 9-H), 4.01−4.07 (m, 1 H, 13-H), 5.35 (dd, *J* = 9.7 and 15.3 Hz, 1 H, 11-H), 5.55 (dd, *J* = 6.7 and 15.3 Hz, 1 H, 12-H). − $[\alpha]_D^{20}$ = −5.9 (*c* = 0.76·$10^{-3}$, MeOH). − NICI-MS of PFB-TMS derivative: carboxylate anion [M − PFB]$^-$ at *m*/*z* = 543.

***ent*-(15*S*)-2,3-Dinor-5,6-dihydro-15-$F_{2t}$-isoprostane Methyl Ester (1b):** $R_f$ 0.6 (ethyl acetate/acetic acid, 95:5). − IR: $\tilde{\nu}$ = 3520, 1720 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.7 Hz, 3 H, 18-H), 1.24−1.37 (m, 10 H, 4-H, 5-H, 15-H, 16-H, 17-H), 1.56−1.62 (m, 5 H, 3-H, 8-H, 14-H), 1.88 (brs, 1 H, OH), 2.08 (m, 1 H, 6-H), 2.27−2.39 (m, 3 H, 2-H, 8′-H), 2.71−2.75 (m, 1 H, 10-H), 3.65 (s, 3 H, $OCH_3$), 3.91−4 (m, 2 H, 7-H, 9-H), 4.04 (q, *J* = 6.7 Hz, 1 H, 13-H), 5.36 (dd, *J* = 9.8 and 15.3 Hz, 1 H, 11-H), 5.55 (dd, *J* = 6.7 and 15.3 Hz, 1 H, 12-H). − $[\alpha]_D^{20}$ = −16 (*c* = $10^{-3}$, MeOH). − NICI-MS of PFB-TMS derivative: carboxylate anion [M − PFB]$^-$ at *m*/*z* = 543.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-(3-oxooctanyl)cyclopentane-1,4-diol (16):** A solution of **14** (45.3 mg, 0.1 mmol) was hydrogenated with Pd/C (4.5 mg) in ethanol (2 mL) for 4 hours at atmospheric pressure. The mixture was filtered through Celite and evaporated under reduced pressure to give 45.4 mg of **16** (100%): $R_f$ 0.37 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 1720, 1710 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3 H, 18-H), 1.22−1.58 (m, 6 H, 4-H, 16-H, 17-H), 1.60−1.72 (m, 7 H, 3-H, 5-H, 15-H, 11-H), 1.76−1.85 (m, 1 H, 11′-H), 1.86−1.94 (m, 1 H, 8-H), 2.30 (t, *J* = 7.4 Hz, 2 H, 2-H), 2.39 (m, 4 H, 6-H, 10-H, 14-H), 2.57 (t, *J* = 7 Hz, 2 H, 12-H), 2.86 (dt, *J* = 7.3 and 16 Hz, 1 H, 8′-H), 3.62 (s, 3 H, $OCH_3$), 5.11−5.18 (m, 2 H, 7-H, 9-H), 7.38−7.44 (m, 4 H, Ar-H), 7.5−7.58 (m, 2 H, Ar-H), 7.99−8.04 (m, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 13.9 (C-18), 20.7 (C-11), 22.4 (C-16), 23.5 (C-15), 25.1 (C-3), 27.1 (C-4), 27.5 (C-5), 31.4 (C-17), 33.9 (C-2), 37.7 (C-8), 40.6 (C-14), 43 (C-12), 45.9 (C-6), 46.3 (C-10), 51.4 ($OCH_3$), 78.4 (C-9), 78.7 (C-7), 128.3 (C-Ar), 129.5 (C-Ar), 130.3 (C-Ar), 133 (C-Ar), 166.3 [C(O)], 174 (C-1), 210.9 (C-13). − $C_{33}H_{42}O_7$ (550.7): calcd. C 71.97, H 7.69; found C 72.18, H 7.75.

***ent*-2,3-Dinor-5,6,13,14-tetrahydro-15-oxo-15-$F_{2t}$-isoprostane Methyl Ester (4):** To a solution of **16** (15.1 mg, 33.5 μmol) in methanol (300 μL) and THF (195 μL) was added NaOH (1 N solution, 270 μL). The same procedure as for **1** was used to give **4** (8 mg, 70%): $R_f$ 0.66 (ethyl acetate/acetic acid, 95:5). − IR: $\tilde{\nu}$ = 3510, 1720, 1710 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.1 Hz, 3 H, 18-H), 1.23−1.39 (m, 7 H, 4-H, 11-H, 16-H, 17-H), 1.53−1.65 (m, 8 H, 3-H, 5-H, 8-H, 11′-H, 15-H), 1.93−2.03 (m, 2 H, 6-H, 10-H), 2.30 (t, *J* = 7.3 Hz, 2 H, 2-H), 2.31−2.39 (m, 1 H, 8′-H), 2.38 (t, *J* = 7.5 Hz, 2 H, 14-H), 2.47 (q, *J* = 8.2 Hz, 2 H, 12-H), 3.64 (s, 3 H, $OCH_3$), 3.89 (dt, *J* = 3.7 and 7.1 Hz, 1 H, 7-H), 3.95 (dt, *J* = 3.2 and 6.7 Hz, 1 H, 9-H). − $^{13}C$ NMR ($CDCl_3$): δ = 13.9 (C-18), 21.8 (C-11), 22.4 (C-16), 23.5 (C-15), 24.9 (C-3), 27.4 (C-5), 27.7 (C-4), 31.4 (C-17), 33.9 (C-2), 41.3 (C-14), 42.9 (C-8, C-12), 49 (C-6), 49.5 (C-10), 51.5 ($OCH_3$), 76.3 (C-9), 76.5 (C-7), 174.1 (C-1), 211.3 (C-13). − $[\alpha]_D^{20}$ = −10 (*c* = $10^{-3}$, MeOH). − NICI-MS of PFB-TMS derivative, carboxylate anion [M − PFB]$^-$ at *m*/*z* = 471; NICI of PFB-MO-TMS derivatives (*syn*/*anti* isomers), carboxylate anion at *m*/*z* = 500.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-(methoxycarbonylbutyl)-2-[(3*RS*)-octanol]cyclopentane-1,4-diol (17):** To a cooled (0 °C) solution of **16** (30 mg, 66.5 μmol, 1 equiv.) in distilled ethanol (140 μL) was added $NaBH_4$ (1 mg, 26.4 μmol, 0.4 equiv.), diluted in the same solvent (140 μL). The reaction was stirred for 4 hours at room temperature. The mixture was hydrolyzed with 1 mL of brine and extracted with 3× 2 mL of ether. The organic layers were dried and evaporated with $Na_2SO_4$ and evaporated under reduced pressure to give 21.4 mg of **17** (71%), after purification by flash chromatography on silica gel (cyclohexane/ethyl acetate, 90:10): $R_f$ 0.47 (cyclohexane/ethyl acetate, 70:30). − IR: $\tilde{\nu}$ = 3520, 1720 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3 H, 18-H), 1.22−1.29 (m, 8 H, 4-H, 11-H, 16-H, 17-H), 1.4−1.66 (m, 9 H, 3-H, 5-H, 12-H, 14-H, 15-H), 1.89 (d, *J* = 16 Hz, 1 H, 8-H), 2.3 (q, *J* = 6.9 Hz, 2 H, 2-H), 2.39−2.47 (m, 3 H, 6-H, 10-H, 12′-H), 2.85 (dt, *J* = 8.1 and 16 Hz, 1 H, 8′-H), 3.58−3.63 (m, 1 H, 13-H), 3.63 (s, 3 H, $OCH_3$), 5.15−5.22 (m, 2 H, 7-H, 9-H), 7.39−7.43 (m, 4 H, Ar-H), 7.52−7.56 (m, 2 H, Ar-H), 8.01−8.03 (m, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.6 (C-16), 22.9 (C-11), 25.1 (C-3), 25.3 (C-4), 26.9 (C-15), 27.5 (C-5), 31.8 (C-17), 33.8 (C-2), 34.1 (C-12), 35.5 (C-14), 35.9 (C-14′), 39.9 (C-8), 46.3 (C-6), 46.5 (C-10), 51.5 ($OCH_3$), 71.6 (C-13), 72.1 (C-7), 78.8 (C-9), 128.3 (C-Ar), 129.6 (C-Ar), 130.4 (C-Ar), 132.9 (C-Ar), 166.3 [C(O)], 174 (C-1). − $C_{33}H_{44}O_7$ (552.7): calcd. C 71.71, H 8.02; found C 71.61, H 7.97.

***ent*-(15*RS*)-2,3-Dinor-5,6,13,14-tetrahydro-15-$F_{2t}$-isoprostane Methyl Ester (3):** To **17** (19.9 mg, 43.9 μmol) in methanol (395 μL) and THF (295 μL) was added NaOH solution (1 N, 350 μL). The same procedure as for **1** was used to give a mixture of (15*R*)/(15*S*) isomers of **3** (13.5 mg, 83%): $R_f$ 0.55 (ethyl acetate/acetic acid, 95:5). − IR: $\tilde{\nu}$ = 3520, 1720 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, 18-H), 1.24−1.47 (m, 10 H, 4-H, 5-H, 11-H, 16-H, 17-H), 1.54−1.67 (m, 8 H, 3-H, 8-H, 12-H, 14-H, 15-H), 1.99−2.07 (m, 3 H, 6-H, 8′-H, 10-H), 2.30 (t, *J* = 7.4 Hz, 2 H, 2-H), 2.34−2.40 (m, 1 H, 12′-H), 3.56−3.61 (m, 1 H, 13-H), 3.65 (s, 3 H, $OCH_3$), 3.93−3.96 (m, 2 H, 7-H, 9-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.6 (C-16), 24.1 (C-11), 25 (C-3), 25.3 (C-4), 27.2 (C-15), 27.7 (C-5), 29.7 (C-12), 31.8 (C-17), 33.9 (C-2), 35.9 (C-14), 37.5 (C-8), 42.8 (C-6), 49.5 (C-10), 51.5 ($OCH_3$), 72 (C-13), 72.2 (C-7), 76.2 (C-9), 173.6 (C-1). − NICI-MS of PFB-TMS derivative, carboxylate anion at *m*/*z* = 545.

**(1*S*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-[(*Z*)-5-tetrahydropyranyloxypent-2-enyl]-1,4-bis(triethylsilyl)cyclopentane-1,4-diol (18):** To a suspension of 3-(tetrahydropyranyloxypropyl)triphenylphosphonium bromide[12] (1.4 g, 2.9 mmol, 3 equiv.), in dry THF (10 mL) at −80 °C, was added $KN(SiMe_3)_2$ (5.4 mL, 2.85 equiv, 0.5 M in toluene). The orange solution of ylide was stirred

for 10 min. A solution of aldehyde **6** (611 mg, 9.5 mmol, 1 equiv.) in dry THF (8 mL) was added to the ylide. After slow warming to room temperature over 1 h, the reaction mixture was hydrolyzed with water (10 mL). The aqueous layer was extracted with diethyl ether (3× 10 mL), and the combined extracts were washed with brine (10 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/diethyl ether 96:4) gave pure **18** (511 mg, 70%): $R_f$ 0.65 (cyclohexane/ethyl acetate, 90:10). − $^1$H NMR ($CDCl_3$): δ = 0.45 [q, *J* = 7.9 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.55 [q, *J* = 7.9 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.85 [t, *J* = 7.9 Hz, 9 H, $(CH_3CH_2)_3Si$], 0.93 [t, *J* = 7.9 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.05 [s, 9 H, $C(CH_3)_3$], 1.42−1.59 (m, 5 H, 8-H, THP-H), 1.62−1.72 (m, 1 H, THP-H), 1.75−1.85 (m, 1 H, THP-H), 1.98−2.14 (m, 2 H, 5-H, 10-H), 2.15−2.37 (m, 5 H, 2-H, 5′-H, 6-H, 8′-H), 3.33 (td, *J* = 6.9 and 9.6 Hz, 1 H, 1-H), 3.41−3.51 (m, 1 H, THP-H) 3.58 (d, *J* = 5.1 Hz, 2 H, 11-H), 3.61−3.72 (m, 1 H, 1′-H), 3.81−3.85 (m, 1 H, THP-H), 3.91 (q, *J* = 7.4 Hz, 1 H, 7-H), 4.07 (m, 1 H, 9-H), 4.53−4.56 (m, 1 H, THP-H), 5.29−5.47 (m, 2 H, 3-H, 4-H), 7.30−7.44 (m, 6 H, Ar-H), 7.58−7.67 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 4.7 [$(CH_3CH_2)_3Si$], 4.9 [$(CH_3CH_2)_3Si$], 6.7 [$(CH_3CH_2)_3Si$], 6.8 [$(CH_3CH_2)_3Si$], 19.1 [$C(CH_3)_3$], 19.5 (C-THP), 25.5 (C-THP), 25.7 (C-5), 26.9 [$C(CH_3)_3$], 28.1 (C-2), 30.7 (C-THP), 45.2 (C-8), 48.2 (C-6), 50.7 (C-10), 62.1 (C-THP), 62.6 (C-11), 66.9 (C-1), 73.2 (C-9), 76.4 (C-7), 98.7 (C-THP), 126.1 (C-3), 127.6 (C-Ar), 129.6 (C-Ar), 130.6 (C-4), 133.5 (C-Ar), 135.7 (C-Ar). − $C_{44}H_{74}O_5Si_3$ (767.3): calcd. C 68.87, H 9.72; found C, 68.89, H 9.80.

**(1*S*,2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-[(*Z*)-5-tetrahydropyranyloxypent-2-enyl]cyclopentane-1,4-diol (19):** A mixture of **18** (952 mg, 1.2 mmol, 1 equiv.) and $NH_4F$ (9.9 mL, 4 equiv, 0.5 M in MeOH) in 14 mL of MeOH/THF (7:3) was stirred for 2 h at reflux. The reaction mixture was diluted with brine (5 mL) and ethyl acetate (10 mL). The aqueous layers were extracted with ethyl acetate (3× 10 mL), and the combined extracts were washed with brine (10 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 60:40) gave pure **19** (589 mg, 88%): $R_f$ 0.4 (cyclohexane/ethyl acetate, 50:50). − IR: $\tilde{\nu}$ = 3360 $cm^{-1}$. − $^1$H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $C(CH_3)_3$], 1.45−1.70 (m, 6 H, 8-H, THP-H), 1.73−1.81 (m, 1 H, THP-H), 1.92−2.03 (m, 4 H, 5-H, OH), 2.11−2.23 (m, 3 H, 2-H, 6-H), 2.25−2.43 (m, 2 H, 8′-H, 10-H), 3.30−3.35 (m, 1 H, 1-H), 3.43−3.49 (m, 1 H, THP-H), 3.54−3.84 (m, 4 H, 1′-H, 11-H, THP-H), 3.92−4.02 (m, 1 H, 7-H), 4.19−4.23 (m, 1 H, 9-H), 4.51−4.57 (m, 1 H, THP-H), 5.34−5.44 (m, 2 H, 4-H, 3-H), 7.37−7.40 (m, 6 H, Ar-H), 7.62−7.65 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 19.1 [$C(CH_3)_3$], 19.6 (C-THP), 25.4 (C-THP), 26.4 (C-5), 26.9 [$C(CH_3)_3$], 28 (C-2), 30.6 (C-THP), 42.5 (C-8), 48.6 (C-6), 51.3 (C-10), 62.4 (C-THP), 63.7 (C-11), 66.9 (C-1), 75.2, (C-9), 76.6 (C-7), 98.8 (C-THP), 127.4 (C-4), 127.7 (C-Ar), 129.8 (C-Ar), 130 (C-3), 133.1 (C-Ar), 133.2 (C-Ar), 135.6 (C-Ar). − $C_{32}H_{46}O_5Si$ (538.8): calcd. C 71.33, H 8.61; found C 71.40, H 8.70.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Bis-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-[(*Z*)-5-tetrahydropyranyloxypent-2-enyl]cyclopentane-1,4-diol (20):** To a stirred solution of diol **19** (546 mg, 1 mmol, 1 equiv.) in dry pyridine (7 mL) under nitrogen atmosphere, was added benzoyl chloride (411 μL, 3.5 mmol, 3.5 equiv.). The reaction mixture was stirred for 20 min at room temperature. MeOH (1 mL) was added to the reaction mixture; then the pyridine was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5) to provide **20** (735 mg, 97%): $R_f$ 0.62 (cyclohexane/ethyl acetate, 80:20). IR: $\tilde{\nu}$ = 1715 $cm^{-1}$. − $^1$H NMR ($CDCl_3$): δ = 1.07 [s, 9 H, $C(CH_3)_3$], 1.41−1.55 (m, 4 H, THP-H), 1.62−1.69 (m, 1 H, THP-H), 1.72−1.81 (m, 1 H, THP-H), 1.91 (d, *J* = 15.6 Hz, 1 H, 8-H), 2.19−2.25 (m, 4 H, 2-H, 5-H), 2.60−2.64 (m, 2 H, 6-H, 10-H), 2.91 (dt, *J* = 7.4 and 15.6 Hz, 1 H, 8′-H), 3.31−3.34 (m, 1 H, 1-H), 3.42−3.48 (m, 1 H, THP-H), 3.66−3.89 (m, 4 H, 1′-H, 11-H, THP-H), 4.53−4.54 (m, 1 H, THP-H), 5.30−5.32 (m, 1 H, 4-H), 5.36−5.44 (m, 3 H, 3-H, 7-H, 9-H), 7.34−7.41 (m, 10 H, Ar-H), 7.50−7.57 (m, 2 H, Ar-H), 7.63−7.68 (m, 4 H, Ar-H), 7.93−8.03 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 19.1 [$C(CH_3)_3$], 19.5 (C-THP), 25.5 (C-THP), 25.7 (C-2), 26.9 [$C(CH_3)_3$], 28.1 (C-5), 30.6 (C-THP), 38.6 (C-8), 45.9 (C-6), 48.7 (C-10), 61.9 (C-11), 62.1 (C-THP), 66.8 (C-1), 77.2 (C-9), 79.2 (C-7), 98.7 (C-THP), 127.5 (C-4), 127.7 (C-Ar), 128.3 (C-Ar), 129.1 (C-3), 129.6 (C-Ar), 129.7 (C-Ar), 132.8 (C-Ar), 135.7 (C-Ar), 166.1 [C(O)]. − $C_{46}H_{54}O_7Si$ (747.0): calcd. C 73.96, H 7.29; found C 74.12, H 7.36.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Bis-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-[(*Z*)-5-hydroxypent-2-enyl]cyclopentane-1,4-diol (21):** To a stirred solution of **20** (735 mg, 1 mmol, 1equiv.) in dry $CH_2Cl_2$ (8.4 mL) at −25 °C under nitrogen atmosphere was added $(CH_3)_2AlCl$ (3.9 mL, 3.9 mmol, 4 equiv, 1 M in hexane). After slow warming to room temperature over 2 h, the reaction mixture was hydrolyzed with a solution of $Na_2CO_3$ in water (5 mL) and washed with brine (5 mL). The aqueous layers were extracted with ethyl acetate (3× 5 mL) and the combined extracts were washed with brine (5 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 80:20) gave pure **21** (602 mg, 92%): $R_f$ 0.29 (cyclohexane/ethyl acetate, 80:20). − IR: $\tilde{\nu}$ = 3426 $cm^{-1}$, 1717 $cm^{-1}$ − $^1$H NMR ($CDCl_3$): δ = 1.07 [s, 9 H, $C(CH_3)_3$], 1.87−1.95 (m, 1 H, 8-H), 2.09−2.26 (m, 4 H, 2-H, 5-H), 2.56−2.69 (m, 2 H, 6-H, 10-H), 2.92 (dt, *J* = 7.8 and 15.7 Hz, 1 H, 8′-H), 3.56 (t, *J* = 6.4 Hz, 2 H, 1-H), 3.73 (dd, *J* = 5.3 and 10.8 Hz, 1 H, 11-H), 3.87 (dd, *J* = 5.3 and 10.8 Hz, 1 H, 11′-H), 5.33−5.42 (m, 3 H, 3-H, 7-H, 9-H), 5.48−5.56 (m, 1 H, 4-H), 7.31−7.43 (m, 10 H, Ar-H), 7.51−7.56 (m, 2 H, Ar-H), 7.63−7.68 (m, 4 H, Ar-H), 7.97−8.01 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 19.1 [$C(CH_3)_3$], 25.8 (C-5), 26.9 [$C(CH_3)_3$], 31 (C-2), 38.6 (C-8), 46 (C-6), 48.8 (C-10), 61.9 (C-11), 62.1 (C-1), 77.2 (C-9), 79.1 (C-7), 127 (C-3), 127.7 (C-Ar), 128.3 (C-Ar), 129.6 (C-Ar), 129.8 (C-Ar), 130.5 (C-Ar), 132.9 (C-4), 133.2 (C-Ar), 135.7 (C-Ar), 166.1 [C(O)], 166.2 [C(O)]. − $C_{41}H_{46}O_6Si$ (662.9): calcd. C 74.29, H 6.99; found C 74.22, H 6.96.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Bis-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-[(*Z*)-methoxycarbonylbut-2-enyl]cyclopentane-1,4-diol (22):** To a stirred solution of **21** (602 mg, 0.91 mmol, 1 equiv.) in freshly distilled acetone (15 mL) at −10 °C was added Jones′ reagent (627 μL, 1.36 mmol, 1.5 equiv, 2.17 M). After slow warming to room temperature over 2 h, the reaction was terminated using 2-propanol. The crude material was filtered on Celite; then a solution of $CH_2N_2$ in diethyl ether was added. After concentration, flash chromatography over silica gel (cyclohexane/ethyl acetate, 90:10) gave pure **22** (570 mg, 91%): $R_f$ 0.64 (cyclohexane/ethyl acetate, 50:50). − IR: $\tilde{\nu}$ = 1718 $cm^{-1}$ − $^1$H NMR ($CDCl_3$): δ = 1.08 [s, 9H $C(CH_3)_3$], 1.87−1.95 (m, 1 H, 8-H), 2.19−2.24 (m, 2 H, 5-H), 2.56−2.67 (m, 2 H, 6-H, 10-H), 2.88−3.01 (m, 3 H, 2-H, 8′-H), 3.63 (s, 3 H, $OCH_3$), 3.71 (dd, *J* = 5.3 and 10.8 Hz, 1 H, 11-H), 3.86 (dd, *J* = 5.3 and 10.8 Hz, 1 H, 11′-H), 5.29−5.33 (m, 1 H, 7-H), 5.38−5.40 (m, 1 H, 9-H), 5.54−5.57 (m, 2 H, 3-H, 4-H), 7.35−7.42 (m, 10 H, Ar-H), 7.5−7.55 (m, 2 H, Ar-H), 7.63−7.66 (m, 4 H, Ar-H), 7.97−8.03 (m, 4 H, Ar-H). − $^{13}$C NMR ($CDCl_3$): δ = 19.1 [$C(CH_3)_3$], 25.8 (C-5), 26.9 [$C(CH_3)_3$], 32.8 (C-2), 38.6 (C-8), 45.7 (C-6), 48.7 (C-10), 51.8 ($OCH_3$), 61.9 (C-11), 77.1 (C-9), 79.1 (C-7), 122.3 (C-3), 127.8 (C-Ar), 128.3 (C-Ar), 129.6 (C-Ar),

129.8 (C-Ar), 130.4 (C-Ar), 130.9 (C-4), 132.9 (C-Ar), 133.1 (C-Ar), 135.7 (C-Ar), 166.1 [C(O)], 166.2 [C(O)], 171.9 (C-1). − $C_{42}H_{46}O_7Si$ (690.9): calcd. C 73.01, H 6.71; found C 73.15, H 6.86.

**(1*S*,2*R*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-[(*Z*)-methoxycarbonylbut-2-enyl]-2-(hydroxymethyl)cyclopentane-1,4-diol (23):** Acetyl chloride (1.07 mL) was added dropwise to methanol (18 mL), and the hydrogen chloride solution obtained was cooled to 20 °C. A solution of **22** (560 mg, 0.8 mmol, 1 equiv.) in freshly distilled diethyl ether (18 mL) was added, and the mixture was stirred at room temperature for 20 h, then neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3×10 mL), and the combined extracts were washed with brine (10 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 80:20) gave pure **23** (282 mg, 77%): $R_f$ 0.54 (cyclohexane/ethyl acetate, 50:50). − IR: $\tilde{\nu}$ = 3520 $cm^{-1}$, 1711 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 1.75 (s, 1 H, OH), 2.05 (dt, *J* = 3.7 and 5.2 Hz, 1 H, 8-H), 2.16−2.22 (m, 1 H, 5-H), 2.28−2.33 (m, 1 H, 5′-H), 2.64 (m, 2 H, 6-H, 10-H), 2.87 (dt, *J* = 7.4 and 15.2 Hz, 1 H, 8′-H), 3.1 (d, *J* = 5.4 Hz, 2 H, 2-H), 3.66 (s, 3 H, $OCH_3$), 3.77 (dd, *J* = 6 and 11 Hz, 1 H, 11-H), 3.85 (dt, *J* = 5.1 and 11 Hz, 1 H, 11′-H), 5.21−5.24 (m, 1 H, 7-H), 5.37−5.41 (m, 1 H, 9-H), 5.62−5.68 (m, 2 H, 3-H, 4-H), 7.37−7.44 (m, 4 H, Ar-H), 7.53−7.55 (m, 2 H, Ar-H), 7.99−8.04 (m, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 25.7 (C-5), 33 (C-2), 37.8 (C-8), 46 (C-6), 49.1 (C-10), 60.8 (C-11), 77 (C-9), 78.7 (C-7), 122.6 (C-3), 128.4 (C-Ar), 129.6 (C-Ar), 131 (C-4), 133 (C-Ar), 133.2 (C-Ar), 165.9 (C(O)), 166 (C(O)), 173.2 (C-1). − $C_{26}H_{28}O_7$: calcd. C 69.01, H 6.24; found C 69.12, H 6.34.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Dis-*O*-benzoyl-3-[(*Z*)-methoxycarbonylbut-2-enyl]-2-[(*E*)-3-oxooct-1-enyl]cyclopentane-1,4-diol (25):** To a stirred solution of **23** (47 mg, 0.1 mmol, 1 equiv.) in freshly distilled $CH_2Cl_2$ (2.5 mL) and water (2.5 μL) at room temperature was added Dess−Martin periodinane (53 mg, 1.2 equiv.). The reaction mixture was stirred for 2 h, diluted with diethyl ether (3 mL), and washed with 1:1 $NaHCO_3$ (10%)/$Na_2S_2O_3$ (10%) (3× 2 mL). The aqueous layers were extracted with diethyl ether (3× 3 mL), and the combined extracts were washed with brine (6 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material **24**. This was used immediately for the next step: $R_f$ 0.6 (cyclohexane/ethyl acetate, 50:50).

To a solution of **24** (previous crude product, 0.31 mmol, 1 equiv.) in dry THF (0.8 mL) was added dropwise a solution of ylide prepared at room temperature from diethyl 2-oxoheptylphosphonate (178 μL, 0.9 mmol, 2.75 equiv.) and NaH (10 mg, 2.5 equiv, 60% suspension in oil) in THF (0.8 mL). The reaction was stirred for 10 min, neutralized with saturated $NH_4Cl$ (2 mL), extracted with diethyl ether (3× 2 mL), and the combined extracts washed with brine (2 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 80:20) gave pure **25** (31 mg, 54%): $R_f$ 0.34 (cyclohexane/ethyl acetate, 80:20). − IR: $\tilde{\nu}$ = 1715 $cm^{-1}$. − $^1H$ NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H, 18-H), 1.23−1.31 (m, 4 H, 16-H, 17-H), 1.56−1.64 (m, 2 H, 15-H), 2.03 (dt, *J* = 3.3 and 16 Hz, 1 H, 8-H), 2.18 (t, *J* = 6.7 Hz, 2 H, 5-H), 2.52 (t, *J* = 7.4 Hz, 2 H, 14-H), 2.66−2.71 (m, 1 H, 6-H), 2.97 (m, 1 H, 8′-H), 3.04−3.06 (m, 2 H, 2-H), 3.27−3.33 (m, 1 H, 10-H), 3.65 (s, 3 H, $OCH_3$), 5.21−5.26 (m, 1 H, 7-H), 5.33−5.37 (m, 1 H, 9-H), 5.56−5.69 (m, 2 H, 3-H, 4-H), 6.27 (dd, *J* = 1 and 15.7 Hz, 1 H, 12-H), 6.74 (dd, *J* = 9 and 15.7 Hz, 1 H, 11-H), 7.39−7.44 (m, 4 H, Ar-H), 7.53−7.58 (m, 2 H, Ar-H), 8−8.04 (m, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 13.9 (C-18), 22.4 (C-17), 23.7 (C-15), 26.5 (C-5), 31.4 (C-16), 32.9 (C-2), 37.9 (C-8), 40.9 (C-14), 48 (C-6), 50 (C-10), 51.9 ($OCH_3$), 77.2 (C-9), 78.1 (C-7), 123.1 (C-3), 128.4 (C-Ar), 129.6 (C-Ar), 130.1 (C-4), 132.5 (C-12), 133.2 (C-Ar), 141.3 (C-11), 165.9 [C(O)], 166 [C(O)], 172 (C-1), 199.8 (C-13). − $C_{33}H_{38}O_7$ (546.7): calcd. C 72.51, H 7.01; found C 72.65, H 7.16.

**(1*S*,2*S*,3*R*,4*R*)-1,4-Di-*O*-benzoyl-3-[(*Z*)-methoxycarbonylbut-2-enyl]-2-[(3*RS*,*E*)--hydroxyoct-1-enyl]cyclopentane-1,4-diol (26):** To a cooled (−78 °C) solution of **25** (83 mg, 0.2 mmol, 1 equiv.) in dry THF (1.6 mL) was added dropwise a solution of L-Selectride® (200 μL, 0.2 mmol, 1 eq, 1 M in THF). The reaction was stirred at −78 °C for 20 min, quenched with methanol (40 μL), then diluted with diethyl ether (5 mL), washed with brine (5 mL) and extracted with diethyl ether (3× 5 mL). The combined extracts were washed with brine (5 mL). All organic solutions were dried with $Na_2SO_4$ and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 92:8) gave pure **26** (69 mg, 83%): $R_f$ 0.52 (cyclohexane/ethyl acetate, 50:50). − $^1H$ NMR ($CDCl_3$): δ = 0.85−0.88 (m, 3 H, 18-H), 1.22−1.26 (m, 6 H, 15-H, 16-H, 17-H), 1.43−1.54 (m, 2 H, 14-H), 1.75 (s, 1 H, OH), 1.96 (d, *J* = 15.9 Hz, 1 H, 8-H), 2.18−2.20 (m, 2 H, 5-H), 2.55−2.63 (m, 1 H, 6-H), 2.91 (dt, *J* = 8.2 and 15.9 Hz, 1 H, 8′-H), 3.07 (d, *J* = 5.3 Hz, 2 H, 2-H), 3.11−3.16 (m, 1 H, 10-H), 3.65 (s, 3 H, $OCH_3$), 4.07−4.11 (m, 1 H, 13-H), 5.19−5.27 (m, 2 H, 7-H, 9-H), 5.51−5.62 (m, 3 H, 3-H, 4-H, 11-H), 5.66−5.73 (m, 1 H, 12-H), 7.39−7.44 (m, 4 H, Ar-H), 7.52−7.57 (m, 2 H, Ar-H), 8−8.03 (m, 4 H, Ar-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.5 (C-17), 25 (C-15), 26.5 (C-5), 31.7 (C-16), 33.1 (C-2), 37.2 (C-14), 38.9 (C-8), 47.6 (C-6), 50 (C-10), 51.9 ($OCH_3$), 72.4 (C-13), 78.4 (C-7, C-9), 122.4 (C-3), 126.2 (C-11), 128.4 (C-Ar), 129.6 (C-Ar), 130.2 (C-Ar), 130.8 (C-4), 133 (C-Ar), 137.5 (C-12), 166 [C(O)], 166.1 [C(O)], 171.9 (C-1). − $C_{33}H_{40}O_7$ (548.7): calcd. C 72.24, H 7.35; found C 72.32, H 7.39.

***ent*-(15*RS*)-2,3-Dinor-15-$F_{2t}$-isoprostane Methyl Ester (2a and 2b):** To a stirred solution of **26** (30 mg, 65 μmol) in THF (285 μL) and MeOH (435 μL) at 40 °C was added NaOH (520 mL, 1 M solution). The same procedure as for **1** was used, to give a mixture of **2a** and **2b** [16.5 mg, 75%; 9.9 mg/6.6 mg (*R*)/(*S*)].

***ent*-(15*R*)-2,3-Dinor-15-$F_{2t}$-isoprostane Methyl Ester (2a):** $R_f$ 0.46 (ethyl acetate/acetic acid, 95:5). − IR (15*S*): $\tilde{\nu}$ = 3363 $cm^{-1}$, 1737 $cm^{-1}$. − UV ($CH_3CN$): 197 nm. − $^1H$ NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.7 Hz, 3 H, 18-H), 1.23−1.27 (m, 6 H, 15-H, 16-H, 17-H), 1.45−1.5 (m, 2 H, 14-H), 1.63 (dt, *J* = 4.0 and 14.5 Hz, 1 H, 8-H), 1.98−2.03 (m, 2 H, 5-H), 2.14−2.17 (m, 1 H, 6-H), 2.25−2.46 (m, 4 H, 8′-H, OH), 2.71−2.77 (m, 1 H, 10-H), 3.06 (t, *J* = 5.7 Hz, 2 H, 2-H), 3.67 (s, 3 H, $OCH_3$), 3.92−4.05 (m, 3 H, 7-H, 9-H, 13-H), 5.43 (dd, *J* = 9.4 and 15.3 Hz, 1 H, 11-H), 5.52−5.62 (m, 3 H, 3-H, 4-H, 12-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18), 22.6 (C-17), 25.1 (C-16), 27.2 (C-5), 29.7 (C-15), 31.7 (C-14), 33 (C-2), 42.5 (C-8), 50.3 (C-6), 52 ($OCH_3$), 53.5 (C-10), 72.5 (C-13), 76.2 (C-7, C-9), 121.8 (C-11), 129 (C-12), 132.1 (C-3), 136.4 (C-4), 172.4 (C-1). − $[\alpha]_D^{20}$ = −11.8 (*c* = 2·10$^{-3}$, MeOH). − NICI-MS of PFB-TMS derivative, carboxylate anion at *m*/*z* = 541.

***ent*-(15*S*)-2,3-Dinor-15-$F_{2t}$-isoprostane Methyl Ester (2b):** $R_f$ 0.35 (ethyl acetate/acetic acid, 95:5). − IR (15*R*): $\tilde{\nu}$ = 3351 $cm^{-1}$, 1739 $cm^{-1}$. − UV ($CH_3CN$): 199 nm. − $^1H$ NMR ($CDCl_3$): δ = 0.84−0.89 (m, 3 H, 18-H), 1.23−1.27 (m, 6 H, 17-H, 16-H, 15-H), 1.43−1.51 (m, 2 H, 14-H), 1.62 (dt, *J* = 3.9 and 14.4 Hz, 1 H, 8-H), 2−2.07 (m, 5 H, 5-H, OH), 2.13−2.18 (m, 1 H, 6-H), 2.39−2.45 (m, 1 H, 8′-H), 2.71−2.77 (m, 1 H, 10-H), 3.06 (d, *J* = 6.1 Hz, 2 H, 2-H), 3.67 (s, 3 H, $OCH_3$), 3.93−4.05 (m, 3 H, 7-H, 9-H, 13-H), 5.40 (dd, *J* = 9.4 and 15.9 Hz, 1 H, 11-H), 5.54−5.64 (m, 3 H, 12-H, 3-H, 4-H). − $^{13}C$ NMR ($CDCl_3$): δ = 14 (C-18),

22.6 (C-17), 25.1 (C-16), 27.2 (C-5), 29.7 (C-15), 31.7 (C-14), 33 (C-2), 42.5 (C-8), 50.3 (C-6), 52 ($OCH_3$), 53.5 (C-10), 72.7 (C-13), 76.4 (C-7, C-9), 121.8 (C-11), 128.3 (C-12), 132.2 (C-3), 136.4 (C-4), 172.5 [C(O)]. – $[\alpha]_D^{20} = -2.3$ ($c = 10^{-3}$, MeOH). – NICI-MS of PFB-TMS derivative, carboxylate anion at $m/z = 541$.

**Supporting Information Available:** $^1H$ and $^{13}C$ NMR of the major compounds (47 pages). Ordering information is given on the first page of this article.

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[1] J. D. Morrow, K. E. Hill, R. F. Burk, T. M. Nammour, K. F. Badr, L. J. Roberts II, *Proc. Natl. Acad. Sci. U. S. A.* **1990**, *87*, 9383−9387.

[2] [2a] E. J. Corey, C. Shih, N-Y. Shih, K. Shimoji, *Tetrahedron Lett.* **1984**, *25*, 5013−5016. – [2b] E. J. Corey, K. Shimoji, C. Shih, *J. Am. Chem. Soc.* **1984**, *106*, 6425−6427. – [2c] R. C. Larock, N. H. Lee, *J. Am. Chem. Soc.* **1991**, *113*, 7815−7816. – [2d] B. Rondot, T. Durand, J-P. Girard, J-C. Rossi, L. Schio, S. P. Khanapure, J. Rokach, *Tetrahedron Lett.* **1993**, *34*, 8245−8248. – [2e] J-P. Vionnet, P. Renaud, *Hely. Chim. Acta.* **1994**, *77*, 1781−1790 and references therein. – [2f] J. Mulzer, A. K. Kermanchahi, J. Buschmann, P. Luger, *Liebigs. Ann. Chem.* **1994**, 531−539. – [2g] B. Rondot, T. Durand, J-P. Vidal, J-P. Girard, J-C. Rossi, *J. Chem. Soc., Perkin Trans.* **1995**, *2*, 1589−1593. – [2h] A. Roland, T. Durand, B. Rondot, J-P. Vidal, J-C. Rossi, *Bull. Soc. Chim. Fr.* **1996**, *133*, 1149−1154. – [2I] A. Guy, T. Durand, J-P. Vidal, J-C. Rossi, *Tetrahedron Lett.* **1997**, *38*, 1543−1546. – [2j] D. F. Taber, R. J. Herr, D. M. Gleave, *J. Org. Chem.* **1992**, *62*, 194−198. – [2k] D. F. Taber, K. Kanai, *Tetrahedron* **1998**, *54*, 11767−11782. – [2l] J. Rokach, S. P. Khanapure, S. W. Hwang, M. Adiyaman, L. Schio, G. A. FitzGerald, *Synthesis* **1998**, 569−580.

[3] [3a] J. D. Morrow, Y. Chen, C. J. Brame, J. Yang, S. C. Sanchez, J. Xu, W. E. Zackert, J. A. Awad, L. J. Roberts II, *Drug Metab. Rev.* **1999**, *31*, 117−139. – [3b] J. A. Lawson, J. Rokach, G. A. FitzGerald, *J. Biol. Chem.* **1999**, *274*, 2441−2444.

[4] D. F. Taber, J. D. Morrow, L. J. Roberts II, *Prostaglandins* **1997**, *53*, 63−67.

[5] [5a] K. Takahashi, T. M. Nammour, M. Fukunaga, J. Ebert, J. D. Morrow, L. J. Roberts II, R. L. Hoover, K. D. Badr, *J. Clin. Invest.* **1992**, *90*, 136−141. – [5b] K. H. Kang, J. D. Morrow, L. J. Roberts II, J. H Newman, M. J. Banerjee, *J. Appl. Physiol.* **1993**, *74*, 460−465. – [5c] M. Fukunaga, N. Makita, L. J. Roberts II, J. D. Morrow, K. Takahashi, K. F. Badr, *Am. J. Physiol.* **1993**, *264*, C1619−1624. – [5d] M. Fukunaga, K. Takahashi, K. F. Badr, *Biochem. Biophys. Res. Commun.* **1993**, *195*, 507−515. – [5e] J. D. Morrow, T. A. Minton, C. R. Mukundan, M. D. Cambell, W. E. Zakert, V. C. Daniel, K. F. Badr, I. A. Blair, L. J. Roberts II, *J. Biol. Chem.* **1994**, *269*, 4317−4326. – [5f] J. D. Morrow, L. J. Roberts II, *Biochem. Pharmacol.* **1996**, *51*, 1−9 and references therein.

[6] L. J. Roberts II, K. P. Moore, W. E. Zackert, J. A. Oates, J. D. Morrow, *J. Biol. Chem.* **1996**, *271*, 20617−20620.

[7] C. Chiabrando, A. Valagussa, C. Rivalta, T. Durand, A. Guy, E. Zuccato, P. Villa, J-C. Rossi, R. Fanelli, *J. Biol. Chem.* **1999**, *274*, 1313−1319.

[8] [8a] A. Guy, T. Durand, A. Roland, E. Cormenier, J-C. Rossi, *Tetrahedron Lett.* **1998**, *39*, 6181−6184. – [8b] During the preparation of this manuscript, Taber et al. reported the synthesis of the $15F_{2t}$-isoprostane **1a**: D. F. Taber, K. Kanai, *J. Org. Chem.* **1999**, *64*, 7983−7987.

[9] [9a] D. Egron, T. Durand, A. Roland, J-P. Vidal, J-C. Rossi, *Synlett.* **1999**, *4*, 435−437. – [9b] A. Roland, T. Durand, D. Egron, J-P. Vidal, J-C. Rossi, *J. Chem. Soc., Perkin Trans 1* **2000**, *2*, 245−252.

[10] J. Viala, M. Santelli, *Synthesis* **1988**, 395.

[11] E. Nashed, G. Glaudemans, *J. Org. Chem.* **1987**, *52*, 5255−5260.

[12] R. B. Bennett III, J. K. Cha, *Tetradron Lett.* **1990**, *31*, 5437−5440.

[13] [13a] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155−4156. – [13b] R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.

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