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A practical asymmetric synthesis of *ent*-12-*epi*-PGF2α methyl ester

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Summary — The chiral cyclopentane formyllactone **1**, which is easily obtained from commercially available isopropylidene-D-glucose was converted into *ent*-12-*epi*-PGF2α methyl ester **3**. The key intermediate was all-*cis*-formyllactone **1** related to *ent*-Corey lactone **2**. The choice of a silyl protective group was found to be crucial in avoiding β-elimination observed with the benzoyl protective group during oxidation of primary alcohol and the following Horner–Wadworth–Emmons reaction.

isoprostaglandin / prostanoid / free radical / cyclization

Résumé — Synthèse asymétrique de l'ester méthylique de la *ent*-12-*épi*-PGF2α. *La formyllactone cyclopentanique **1**, qui est facilement obtenue à partir de l'isopropylidene-D-glucose commercial, a été transformée en l'ester méthylique de la* ent-*12-épi-PGF2α* ***3***. *L'intermédiaire clé est la formyllactone **1** corrélée avec la* ent-*lactone de Corey **2**. Le choix d'un éther silylé comme groupement protecteur s'est avéré déterminant pour empêcher la β-élimination observée avec un groupement benzoylé lors des réactions successives d'oxydation de l'alcool primaire et de Horner–Wadworth–Emmons.*

isoprostaglandine / prostanoïde / radical libre / cyclisation

Since the discovery of isoprostaglandins by Roberts et al [1], there has been a growing interest in the total synthesis of these optically active prostanoids [2, 3]. These new natural products are synthesized in vivo by a free-radical-catalyzed mechanism [1] and are indeed endowed with powerful biological activity [2]. Because regiomeric and diastereomeric mixtures are expected when 12-*epi*-PGF2α **4** is generated in vivo [1] (fig 1), we chose to perform the total synthesis of its enantiomer.

Over the last three years our interest has focused on the synthesis of chiral cyclopentane formyllactones [4–6], which are key synthons for the access to various isoprostane F2-like compounds. We now report a total synthesis of *ent*-12-*epi*-PGF2α methyl ester **3** (fig 2 and 3) from formyllactone **1**.

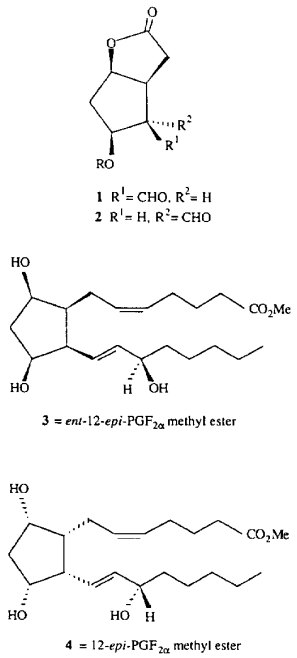

Fig 1

Results and discussion

The synthesis of (1*R*,5*S*,6*R*,7*S*)-6-[(benzoyloxy)methyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one **5** from 1,2-*O*-isopropylidene-D-glucose in eight steps, was previously reported by our group [4–6]. Treatment of **5** under basic conditions (MeONa in dry MeOH) afforded quantitatively alcohol **6** (fig 2). To avoid any β-elimination during the Swern oxidation of primary alcohol, and on the basis of several reports such as those of Vionnet

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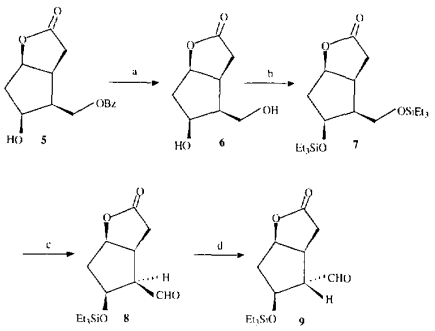

Fig 2. *Reagents and conditions*: a) MeONa, MeOH room temp, 4 h, 100%; b) Et_3SiCl, pyridine, 60 °C, 4 h, 99%; c) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, 65%; d) flash chromatography over silica gel (with 2% of Et_3N in eluent), 100%.

and Renaud [3b], we have chosen the triethylsilyl ether as a protective group for the hydroxyl functions [7] on derivative **6**. The completely protected compound **7** was prepared from **6** by reaction with Et_3SiCl in pyridine with quantitative yield. The Swern oxidation applied to the bis-triethylsilyl derivative **7** allowed the selective oxidation of primary alcohol and gave the rather unstable formyllactone **8** with 98% yield (determined by NMR).

As expected [8], the sensitiveness of the protected all-*cis*-formyllactone **8** (^1H NMR, CHO at δ 9.88) towards basic reagents was shown by the fully and quantitative epimerization to the more stable compound **9** (δ 9.71) during the purification step using silica gel with 2% Et_3N in eluent. The use of neutral silica gel avoids this epimerization. Because of the fragility and instability of compound **8**, it was used without further purification.

Introduction of the ω-chain on all-*syn*-formyllactone **8** in the presence of diethyl 2-(oxoheptyl)phosphonate/NaH afforded a mixture of enone **10** with 65% yield and epimerized derivative **10′** with 16% yield. Even in the mildest conditions and with the best control of the Horner–Wadworth–Emmons (HWE) reaction it was not possible to avoid C(12) epimerization (numbering of prostanoid structure) [3b]. Lastly, use of the triethylsilyl group instead of the benzoyl or *p*-phenylbenzoyl groups avoids not only a quantitative β-elimination during HWE on the C-11 position (PG numbering) as observed by Vionnet and Renaud [3b], but also allows the transformation [7] of the primary silyl ether **7** to the corresponding formyl compound **8** (fig 2).

The conversion of **10** into *ent*-12-*epi*-PGF2α methyl ester **3** was accomplished similarly to the original method reported by Vionnet and Renaud [3b]. Reduction of keto function on **10** was carried out with L-selectride [9] to afford quantitatively the epimeric hydroxy derivatives **11a** and **11b** as a 2:3 mixture easily separated by flash chromatography. The major isomer **11b** was reduced with DIBAL-H in toluene to the lactol **12b** with 75% yield. Pure lactol **12b** was also obtained directly from derivative **10**, using DIBAL-H in THF with 50% yield. The α-chain was introduced by a Wittig reaction in the presence of commercially available (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in

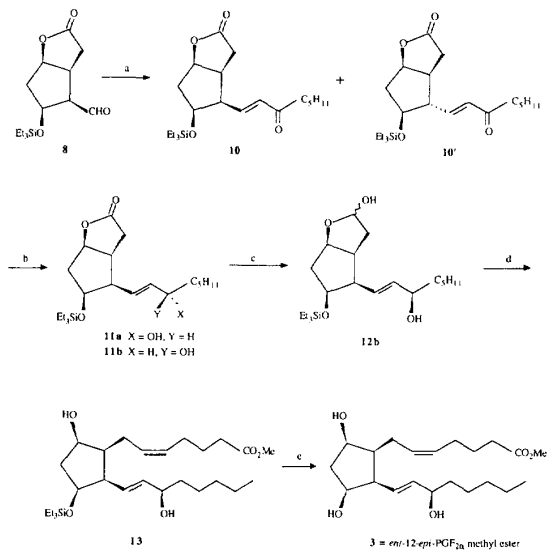

Fig 3. *Reagents and conditions*: a) diethyl 2-oxoheptylphosphonate, NaH, THF, −10 °C, 15 min, 65%; b) chromatography on silica gel followed by L-selectride, THF, −78 °C, 20 min, 100%; c) chromatography on silica gel, then DIBAL-H, THF, −78 °C, 20 min, 71%; d) 4-(carboxybutyl)triphenylphosphonium bromide, *t*-BuOK, THF, room temp, then CH_2N_2, 70%; e) *n*-Bu_4NF, THF, 98%.

dry THF to afford **13** with 70% yield after esterification by diazomethane. It is crucial that the Wittig reaction might be carried out with dry phosphonium salt (36 h at 100 °C under vacuum) for a good and reproductive generation of corresponding ylide. Moreover, it is important to add lactol **12b** immediately to the ylide red-orange solution in order to avoid the formation of by-products. Finally, deprotection of the silyl ether with *n*-Bu_4NF in THF yielded the desired *ent*-12-*epi*-PGF2α methyl ester **3** ($[\alpha]_D = -4.9$, $c = 14.2 \times 10^{-3}$ $CHCl_3$).

The IR, elemental analysis, ^1H and ^{13}C NMR spectra of compound **3** were fully in agreement with reported values [3].

We have determined and confirmed the relative configurations of precursors **10′** and **11b** by steady-state NOE difference spectroscopy (DNOES) experiments, which have previously been employed by our group [6]. All the protons of compounds **10′** and **11b** were systematically irradiated and the most significant results are collected in table I. These values confirm an all-*cis* configuration for the compound **11b**. Indeed, the irradiation of the proton 8-H (to 5.80 ppm) induces an NOE of 2.4% on 2-H (to 2.77 ppm) and −1.1% on 2-H (to 2.42 ppm), and the irradiation of 3-H (to 3.01 ppm) induces an NOE of 10.8% on 4-H (to 5.04 ppm) and 6.6% on 7-H (to 2.48 ppm). The relative *cis* configuration of the protons 5′-H (to 1.86 ppm), 6-H (to 4.17 ppm) and 4-H (to 5.04 ppm) is determined in the same manner.

The relative *cis* configuration of compound **10′** of the protons 8-H (to 6.57 ppm), 3-H (to 2.71 ppm) and 6-H (to 4.02 ppm) compared to cyclopentane is characterized by the observation of NOEs of 1.6 and 1.9% on 3-H and 6-H after irradiation of 8-H.

Table I. Experimental steady-state values (NOE %) for compounds **10′** and **11b** ($CDCl_3$).

Compound	*Proton irradiated*	*2-H*	*2′-H*	*3-H*	*4-H*	*5-H*	*5′-H*	*6-H*	*7-H*	*8-H*
10′	8-H	–	–	1.6	–	–	–	1.9	1.1	Irr
	5′-H	–	–	–	–	9.9	Irr	–	2.1	–
	5-H	–	–	–	5.6	Irr	14.4	4.4	–	–
	3-H	–	7.2	Irr	6.6	–	–	–	–	2.9
	2′-H	5.4	Irr	2.6	–	–	–	–	–	–
11b	8-H	2.4	−1.1	–	–	–	–	0.9	2.9	Irr
	5′-H	–	–	–	8.2	15.6	Irr	5.8	3.8	–
	5-H	–	–	–	–	Irr	10.1	–	–	–
	3-H	–	5.7	Irr	10.8	–	–	–	6.6	–
	2-H	Irr	6.5	–	–	–	–	–	–	3.9

Irr: proton irradiated.

NOEs of the order of 5.6 and 4.4% measured for the protons 4-H (to 4.93 ppm) and 6-H from an irradiation on 5-H (to 2.34 ppm) are characteristic of a *cis* configuration for these protons. All measurement on other protons confirm these results. Figure 4 resumes the observed NOEs resulting from irradiation of 8-H and 3-H protons for compounds **10′** and **11b**. The experimental steady-state values for these compounds are collected in table I.

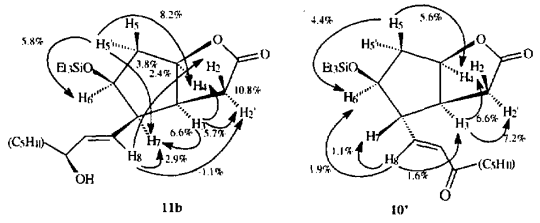

Fig 4. Observed NOEs resulting from irradiation of 3-H and 8-H, 3-protons only for compounds **10′** and **11b**, respectively.

Conclusion

We have demonstrated that (1*R*,5*S*,6*R*,7*S*)-6-[(benzoyloxy)methyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one **5** is a convenient precursor for convergent and stereoselective synthesis of *ent*-12-*epi*-PGF2α methyl ester **3**. This kind of compound will be an useful synthon to understand not only its biological activity but also the biomechanism of its formation. Using this strategy we can now perform a set of isoprostaglandins from our different prostanoid precursors prepared from isopropylidene-D- and L-glucose. Such studies are currently being investigated in our laboratory.

Experimental section

Materials

THF was freshly distilled from sodium benzophenone, methanol from sodium, triethylamine and cyclohexane from KOH, pyridine and dichloromethane from CaH_2 and ethyl acetate from $CaCl_2$. Reactions were monitored on TLC on Merck aluminium sheets with silica gel 60 F_{254} and visualized using UV light and heating with *p*-anisaldehyde solution. Crude products were purified by chromatography using SDS neutral silica gel (70–200 mesh) with the solvents described.

Melting points were determined on a Büchi Tottoli apparatus. Mass spectra were recorded on a Jeol DX300 mass spectrometer with an ionization energy of 70 eV. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard on a Bruker AMX-360 spectrometer or a Bruker AC-100 spectrometer at room temperature. All *J* are given in Hz. Assignments were made with the aid of DEPT spectra and/or homonuclear and heteronuclear 2D spectra. DNOE experiments were used to confirm the stereochemistry of compounds. IR spectra were obtained with a Beckmann Acculab-8-spectrophotometer using NaCl cells or KBr disks.

(1R,5S,6R,7S)-7-Hydroxy-6-hydroxymethyl-2-oxabicyclo[3.3.0]octan-3-one **6**

To a suspension of lactone **5** (100 mg, 0.362 mmol) in dry methanol (2.3 mL) at 0 °C was added a solution of MeONa 1 M in methanol (0.058 mL). The reaction mixture was allowed to reach room temperature and stirred for 4 h. Evaporation under reduced pressure and purification by flash chromatography (dichloromethane/methanol, 90:10) gave white crystals of compound **6** (62 mg, 100%). R_f = 0.52 (CH_2Cl_2/MeOH 85:15). Mp 129–130 °C.

IR (KBr) ν cm^{-1}: 3 420 (OH), 1 750 (C=O).

^1H NMR (360 MHz, CD_3COCD_3): δ 1.95 (1H, ddd, H-8*exo*, J = 3.8, 6.5, 14.9 Hz), 2.14 (2H, m, H-8*endo*, H-6), 2.18 (2H, d, OH), 2.56 (1H, dd, H-4a, J = 11.6, 18.5 Hz), 2.86 (1H, dd, H-4b, J = 4.3 Hz), 3.10 (1H, m, H-5), 3.92 (1H, dd, H-1′a, J = 6.6, 10.6 Hz), 4.01 (1H, dd, H-1′b, J = 7.1 Hz), 4.45 (1H, t, H-7, J = 3.6 Hz), 5.11 (1H, t, H-1, J = 7.0 Hz).

^{13}C NMR (90 MHz, DMSO-d_6): δ 30.2 (C-4), 37.9 (C-5), 41.6 (C-8), 49.3 (C-6), 57.9 (C-1′), 71.5 (C-7), 84.7 (C-1), 177.7 (C-3).

Anal $C_8H_{12}O_4$ found: C 55.72, H 7.09, O 37.19; calc: C 55.81, H 7.02, O 37.17.

Mass spectrometry $[M + H]^+$: m/z 173.

(1R,5S,6R,7S)-7-[(Triethylsilyl)oxy]-6-{[(triethylsilyl)-oxy]methyl}-2-oxabicyclo[3.3.0]octan-3-one **7**

To a stirred solution of diol **6** (150 mg, 0.872 mmol) in freshly distilled pyridine (1.5 mL) was added Et_3SiCl (0.337 mL, 2 mmol) at room temperature. The reaction mixture was allowed to reach 60 °C and stirred for 4 h. Concentration under reduced pressure and flash chromatography (cyclohexane/ethyl acetate 100:0 to 80:20) gave **7** (345 mg, 99%) as a colorless oil. R_f = 0.64 (cyclohexane/ethyl acetate 70:30).

IR (NaCl) ν cm^{-1}: 1 760 (C=O).

^1H NMR (360 MHz, $CDCl_3$): δ 0.53–0.59 (12H, m, 6 CH_3CH_2SiO), 0.90–0.96 (18H, m, 6CH_3CH_2SiO), 1.83 (1H, ddd, H-8*exo*, J = 3.6, 6.8, 15.1 Hz), 1.98–2.05 (1H, m, H-6), 2.11 (1H, d, H-8*endo*, J = 3.6 Hz), 2.45 (1H, dd, H-4a, J = 11.8, 18.5 Hz), 2.71 (1H, dd, H-4b, J = 4.9 Hz, 3.03–3.10 (1H, m, H-5), 3.73 (1H, dd, H-1′a, J = 8.0, 10.0 Hz), 3.85 (1H, dd, H-1′b, J = 6.9 Hz), 4.25 (1H, t, H-7, J = 3.6 Hz), 5.05 (1H, t, H-1, J = 7.3 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.28 and 4.58 (CH_3CH_2SiO), 6.70 (CH_3CH_2SiO), 30.4 (C-4), 38.4 (C-5), 42.3 (C-8), 50.4 (C-6), 59.6 (C-1′), 73.5 (C-7), 84.6 (C-1), 178.0 (C-3).

Anal $C_{20}H_{40}O_4Si_2$ found: C 59.82, H 10.11, O 15.85; calc: C 59.95, H 10.06, O 15.97.

(1R,5S,6R,7S)-6-Formyl-7-[(triethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one **8**

To a solution of oxalyl chloride (0.028 mL, 0.325 mmol) in dry CH_2Cl_2 (0.9 mL) at −60 °C was added dropwise under N_2 a solution of DMSO (0.044 mL, 0.625 mmol) in CH_2Cl_2 (0.1 mL). After 15 min, the solution of **7** (100 mg, 0.250 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise and stirred for 40 min at −60 °C. Triethylamine was then added and the reaction mixture was kept 10 min at −60 °C before it was allowed to reach room temperature. The mixture was diluted with water, extracted three times with CH_2Cl_2. The organic layers were washed with brine, dried on Na_2SO_4, filtered, evaporated under reduced pressure and the crude product was used immediately for the next step after filtration over neutral silica gel. R_f = 0.35 (cyclohexane/ethyl acetate 50:50).

^1H NMR (100 MHz, $CDCl_3$): δ 9.88 (1H, s, CHO), 5.24 (1H, t, H-1), 4.84 (1H, t, H-7), 3.26 (1H, m, H-6), 1.70–3.50 (5H, m, H-5, H-4, H-8), 0.75–1.05 (9H, m, CH_3CH_2SiO), 0.40–0.75 (6H, m, CH_3CH_2SiO).

(1R,5S,6R,7S)-6-[(E)-3′-Oxooct-1′-enyl]-7-[(triethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one **10**

To a cooled (−10 °C) solution of **8** (above crude product) in dry THF (0.5 mL) was added dropwise a solution of ylide prepared at room temperature from the diethyl 2-oxoheptylphosphonate (115 mg, 0.259 mmol) and NaH (60% suspension in oil, 10 mg, 0.250 mmol) in THF (0.5 mL). The reaction was stirred 10 min, neutralized with 70% aqueous AcOH and extracted with CH_2Cl_2. Organic phases were washed with brine, dried on Na_2SO_4, filtered and evaporated under reduced pressure to give after purification by flash chromatography on neutral silica gel (cyclohexane/ethyl acetate 95:5 to 80:20) 57 mg of a mixture **10/10′** 80:20 (determined by NMR) and 26 mg of **8** which had not reacted during Swern oxidation. The compound **10** (65% yield on the two steps) is a colorless oil. R_f = 0.55 (cyclohexane/ethyl acetate 50:50).

IR (NaCl) ν cm^{-1}: 1 760 (C=O lactone), 1 680 (C=O conjugated), 1 655 (C=C), 1 615 (C=C).

^1H NMR (360 MHz, $CDCl_3$): δ 0.54–0.61 (6H, m, 3CH_3CH_2SiO), 0.85–0.95 (12H, m, 3CH_3CH_2SiO and H-8′); 1.22–1.33 (4H, m, H-6′, H-7′), 1.56–1.63 (2H, m, H-5′), 1.92 (1H, ddd, H-8*exo*, J = 15.2, 3.7, 6.8 Hz), 2.20 (1H, d, H-8*endo*, J = 15.2 Hz), 2.46–2.55 (2H, m, H-4a, H-4′), 2.62 (1H, td, H-6, J = 8.2, 3.4 Hz), 2.77 (1H, dd, H-4b, J = 4.7, 18.4 Hz), 3.08–3.18 (1H, m, H-5), 4.27 (1H, t, H-7, J = 3.4 Hz), 5.10 (1H, t, H-1, J = 7.2 Hz), 6.14 (1H, d, H-2′, J = 16.2 Hz), 6.93 (1H, dd, H-1′, J = 16.2, 8.2 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.5 (CH_3CH_2SiO), 6.6 (CH_3CH_2SiO), 13.8 (C-8′), 22.4 (C-7′), 23.9 (C-5′), 31.1 (C-6′), 31.4 (C-4), 39.7, 41.6 (C-8, C-4′), 42.5 (C-5), 50.5 (C-6), 76.3 (C-7), 84.5 (C-1), 132.9 (C-2′), 142.7 (C-1′), 176.9 (C-3), 200.2 (C-3′).

Anal $C_{21}H_{36}O_4Si$ found: C 66.31, H 9.49, O 16.85; calc: C 66.27, H 9.53, O 16.90.

(1R,5S,6R,7S,3′RS)-6-[(E)-3′-Hydroxyoct-1′-enyl]-7-[(triethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one **11a/11b**

To a cooled (−78 °C) solution of **10** (80 mg, 0.210 mmol) in dry THF (1.5 mL) was added a solution of L-selectride 1 M in THF (0.232 mL, 0.232 mmol). The mixture was stirred at −78 °C for 20 min, quenched with MeOH (0.040 mL) and diluted with Et_2O (2.5 mL). The organic layer was washed with 1 M NH_4Cl (2 × 0.8 mL), dried (Na_2SO_4), filtered, evaporated and chromatographed (cyclohexane/ethyl acetate 90:10 to 80:20) to give separately **11b** (48 mg) and **11a** (32 mg) as colorless oil, ie, **11b/11a** (60:40, 80 mg, 100%).

11b: R_f = 0.52 (cyclohexane/ethyl acetate 50:50).

IR (NaCl) ν cm^{-1}: 3 420 (OH), 1 750 (C=O).

^1H NMR (360 MHz, $CDCl_3$): δ 0.52 (6H, m, 3CH_3CH_2SiO), 0.84–0.94 (12H, m, 3CH_3CH_2SiO and H-8′), 1.20–1.31 (4H, m, H-7′, H-6′), 1.46–1.52 (4H, m, H-5′, H-4′), 1.86 (1H, ddd, H-8*exo*, J = 15.1, 3.8, 6.9 Hz), 2.12 (1H, d, H-8*endo*, J = 15.1 Hz), 2.42 (1H, dd, H-4a, J = 18.4, 11.7 Hz), 2.50 (1H, m, H-6), 2.77 (1H, dd, H-4b, J = 18.4, 4.8 Hz), 2.98–3.06 (1H, m, H-5), 4.06–4.09 (1H, m, H-3′), 4.17 (1H, t, H-7, J = 3.8 Hz), 5.04 (1H, t, H-1, J = 6.9 Hz), 5.57 (1H, dd, H-2′, J = 15.5, 6.7 Hz), 5.81 (1H, dd, H-1′, J = 15.5, 8.3 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.6 (CH_3CH_2SiO), 6.7 (CH_3CH_2SiO), 14.0 (C-8′), 22.5 (C-7′), 25.1 (C-5′), 31.1, 31.7 (C-6′, C-4), 37.1 (C-4′), 41.5 (C-8), 42.4 (C-5), 50.4 (C-6), 72.9 (C-3′), 76.3 (C-7), 84.7 (C-1), 127.3 (C-2′), 136.6 (C-1′), 177.6 (C-3).

Anal $C_{21}H_{38}O_4Si$ found: C 65.74, H 10.03, O 16.71; calc: C 65.80, H 9.93, O 16.69.

11a: R_f = 0.35 (cyclohexane/ethyl acetate 50:50).

IR (NaCl) ν cm^{-1}: 3 420 (OH), 1 750 (C=O).

^1H NMR (360 MHz, $CDCl_3$): δ 0.51–0.58 (6H, m, CH_3CH_2SiO), 0.86–0.93 (12H, m, 3CH_3CH_2SiO and H-8′), 1.22–1.39 (4H, m, H-6′, H-7′), 1.42–1.58 (4H, m, H-5′, H-4′), 1.62–1.80 (OH), 1.86 (1H, ddd, H-8*exo*, J = 3.7, 6.8, 15.0 Hz), 2.12 (1H, d, H-8*endo*, J = 15.0 Hz), 2.44 (1H, dd, H-4a, J = 11.7, 18.5 Hz), 2.43–2.50 (1H, m, H-6), 2.79 (1H, dd, H-4b, J = 4.7, 18.5 Hz), 2.96–3.06 (1H, m, H-5), 4.06 (1H, q, H-3′, J = 6.2 Hz), 4.15 (1H, t, H-7, J = 3.7 Hz), 5.04 (1H, t, H-1, J = 6.8 Hz), 5.58 (1H, dd, H-2′, J = 15.6, 6.2 Hz), 5.79 (1H, dd, H-1′, J = 15.6, 8.5 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.6 (CH_3CH_2SiO), 6.7 (CH_3CH_2SiO), 14.0 (C-8′), 22.5 (C-7′), 25.1 (C-5′), 31.1, 31.7 (C-4, C-6′), 37.1 (C-4′), 41.6 (C-8), 42.3 (C-5), 50.5 (C-6), 73.0 (C-3′), 76.5 (C-7), 84.7 (C-1), 127.5 (C-2′), 136.7 (C-1′), 177.8 (C-3).

(1R,3RS,5S,6R,7S,3′R)-6-[(E)-3′-Hydroxyoct-1′-enyl]-7-[(triethylsilyl)oxy]-2-oxabicyclo[3.3.0]-octan-3-ol **12b**

- *Method A*

To a cooled (−78 °C) solution of **11b** (21 mg, 0.055 mmol) in dry THF (0.360 mL) was added dropwise a solution of DIBAL-H (1 M in hexane, 0.220 mL, 0.220 mmol). The

mixture was stirred at −78 °C for 20 min, quenched by addition of MeOH (0.5 mL) and diluted with AcOEt. The organic layer was washed with H_2O and HCl (1 M), then the aqueous layers were extracted three times with AcOEt. The organic layers were dried on Na_2SO_4 and evaporated under reduced pressure before being chromatographed on silica gel (cyclohexane/ethyl acetate 70:30) to give the colorless oil **12b** (15 mg, 71%).

• *Method B*

To a cooled (−78 °C) solution of **10** (50 mg, 0.132 mmol) in dry THF (1 mL) was added dropwise in three goes a solution of DIBAL-H (1 M in hexane, 0.792 mL, 0.792 mmol). The evolution of the reaction was monitored on TLC and formation of **11b/11a** was observed. Ten minutes after the last addition of DIBAL-H, the reaction was quenched with MeOH (1 mL), treated in the same conditions of *Method A* and chromatographed on silica gel (cyclohexane/ethyl acetate 85:15 to 80:20) to give separately **12b** (25 mg) and **12a** (19 mg) as colorless oils, ie, **12b/12a** (57:43, 44 mg, 87%).

12b: R_f = 0.45 (cyclohexane/ethyl acetate 50:50).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.4, 4.8 (CH_3CH_2SiO), 6.7, 6.8 (CH_3CH_2SiO), 14.0 (C-8′), 22.6 (C-7′), 25.1 (C-5′), 31.7 (C-4′, C-6′), 36.8, 37.2 (C-4), 42.3, 44.3 (C-8), 45.4, 46.3 (C-5), 49.9, 50.5 (C-6), 73.1, 73.3 (C-3′), 77.0 (C-7), 83.6, 85.3 (C-1), 100.2, 101.7 (C-3), 128.6, 129.5 (C-2′), 135.1, 136.0 (C-1′).

Anal $C_{21}H_{40}O_4Si$ found: C 66.55, H 10.51, O 16.61; calc: C 65.59, H 10.48, O 16.64.

12a: R_f = 0.28 (cyclohexane/ethyl acetate 50:50).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.4, 4.7 (CH_3CH_2SiO), 6.7 (CH_3CH_2SiO), 14.0 (C-8′), 22.6, 22.9 (C-7′), 23.7, 25.1 (C-5′), 28.9, 29.6, 30.3, 31.8 (C-4′, C-6′), 36.1, 38.6 (C-4), 41.6, 42.3 (C-8), 45.3, 46.2 (C-5), 50.1, 50.6 (C-6), 73.1 (C-3′), 77.5 (C-7), 83.5, 85.3 (C-1), 100.1, 101.7 (C-3), 128.7, 130.8 (C-2′), 135.2, 136.7 (C-1′).

ent-*12*-epi-*11-[(Triethylsilyl)oxy]PGF2α methyl ester* **13**

To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (58 mg, 0.130 mmol) (dried for 36 h at 100 °C under vacuum) in dry THF (0.5 mL) was added *t*-BuOK (29 mg, 0.260 mmol) under N_2 at room temperature. The red-orange ylide was stirred for 5 min and added dropwise to a solution of lactol **12b** (25 mg, 0.065 mmol) in dry THF (0.2 mL). The mixture was stirred for 10 min (it turned brown) and quenched with excess H_2O. The aqueous layer was extracted with AcOEt, acidified with HCl 2 M and extracted with CH_2Cl_2. The organic layers were dried on Na_2SO_4, evaporated under reduced pressure. The crude product was treated with a solution of CH_2N_2 1 M in ether. Evaporation under reduced pressure and chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) gave **13** as a colorless oil (22 mg, 70%). R_f = 0.65 (cyclohexane/ethyl acetate 50:50).

^{1}H NMR (360 MHz, $CDCl_3$): δ 0.54–0.60 (6H, m, $3CH_3CH_2SiO$), 0.85–0.88 (1H, m, H-20), 0.91–0.96 (9H, m, $3CH_3CH_2SiO$), 1.23–1.32 (6H, m, H-19, H-18, H-17), 1.41–1.70 (6H, m, H-3, H-16, H-8), 1.70–2.25 (5H, m, H-4, H-7, H-10), 2.29 (2H, t, H-2, J = 7.5 Hz), 2.58–2.67 (1H, m, H-12), 3.63 (3H, s, OMe), 4.05–4.12 (2H, m, H-11, H-15), 4.22–4.26 (1H, m, H-9), 5.29–5.34 (1H, m, CH=CH), 5.41–5.48 (2H, m and t, CH=CH and H-14, J = 6.9, 15.2 Hz), 5.75–5.82 (1H, dd, H-13, J = 9.8, 15.3 Hz).

^{13}C NMR (25 MHz, $CDCl_3$): δ 4.7 (CH_3CH_2SiO), 6.8 (CH_3CH_2SiO), 14.0 (C-20), 22.6 (C-19), 24.5, 25.2, 26.6 (C-18, C-17, C-3), 29.6, 31.9, 33.4, 37.0 (C-4, C-7, C-10, C-16), 43.2, 47.5 (C-2, C-8), 50.3 (C-12), 51.5 (OMe), 73.2 (C-15), 74.0 (C-9), 76.8 (C-11), 128.9 (C-14), 130.0 (C-5, C-6), 135.7 (C-13), 174.0 (C-1).

ent-*12*-epi-*PGF2α methyl ester* **3**

To a stirred solution of compound **13** (19 mg, 0.039 mmol) in dry THF (0.7 mL) was added a solution of tetrabutylammonium fluoride 1 M in THF (0.059 mL) at room temperature. The reaction was finished in few minutes, concentrated and directly purified by chromatography on silica gel (cyclohexane/ethyl acetate 30:70 to 0:100) to give **3** as a white solid (14 mg, 98%). $[\alpha]_D$ = −4.9 (c = 14.2 × 10^{-3} in $CHCl_3$). R_f = 0.18 (ethyl acetate).

IR (NaCl) ν cm^{-1}: 3 420 (OH), 1 750 (C=O).

^{1}H NMR (360 MHz, $CDCl_3$): δ 0.85–0.91 (3H, m, H-20), 1.25–1.40 (6H, m, H-19, H-18, H-17), 1.43–1.69 (6H, m, H-3, H-16, H-8), 1.83 (1H, ddd, H-10*exo*, J = 2.1, 4.4, 14.5 Hz), 1.89–2.17 (4H, m, H-10*endo*, H-4, H-7), 2.28 (2H, t, H-2, J = 7.4 Hz), 2.69–2.76 (1H, m, H-12), 3.65 (3H, s, OMe), 4.07–4.13 (1H, q, H-15, J = 6.2, 12.8 Hz), 4.17–4.21 (2H, m, H-9, H-11), 5.31–5.46 (2H, m, H-5, H-6), 5.53 (1H, dd, H-14, J = 6.9, 15.4 Hz), 5.83 (1H, dd, H-13, J = 10.2, 15.5 Hz).

^{13}C NMR (90 MHz, $CDCl_3$): δ 13.9 (C-20), 22.6 (C-19), 24.4, 24.9, 25.2 (C-3, C-18, C-17), 26.8, 31.8, 33.5, 37.3 (C-16, C-4, C-7, C-10), 43.0, 47.4 (C-2, C-8), 50.3 (C-12), 51.4 (OMe), 72.9 (C-15), 73.8 (C-9), 75.5 (C-11), 128.7 (C-14), 129.5, 129.6 (C-5, C-6), 137.8 (C-13), 174.1 (C-1).

Anal $C_{21}H_{36}O_5$ found: C 68.42, H 9.87, O 21.68; calc: C 68.44, H 9.85, O 21.71.

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Supplementary material available

^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and DEPT spectral data for the main compounds described in this paper (24 pages). Supplementary material data have been deposited with the British Library, Document Supply Centre at Boston Spa, West Yorkshire, LS23 7BQ, UK, as supplementary publication N° = SUP 90439 and are available on request from the Document Supply Centre.

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