Synthesis of a Corey Lactone Analogue from Iridoid Glucoside Aucubin and Its Utilization in the Synthesis of a New 12-*epi*-$PGF_{2\alpha}$ Modified at C-11

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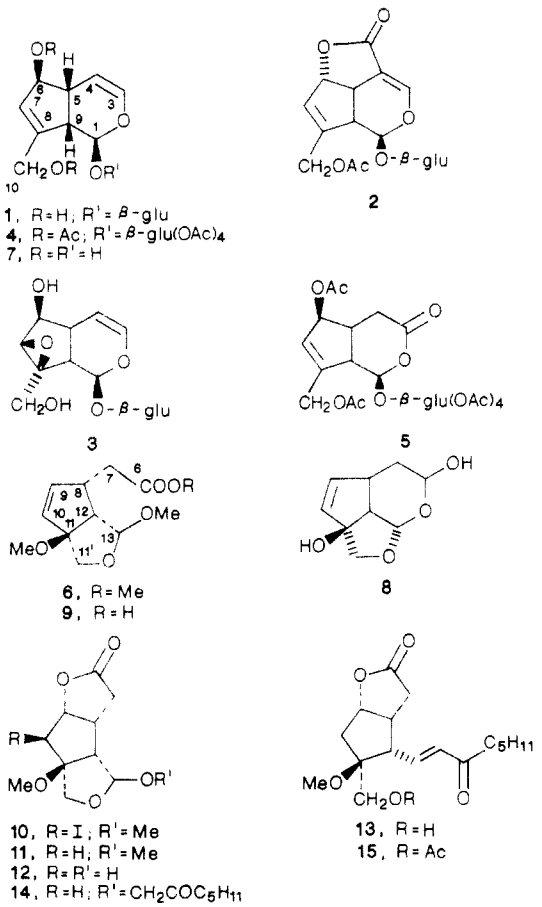
The titled intermediate **12** was prepared in nine steps from aucubin (**1**). The enol-ether system of this iridoid glucoside was oxidized to lactone **5**, which, with acid methanolysis, afforded good yields of the rearrangement product **6** easily transformed into Corey's lactone analogue **12** with a new substitution pattern at C-11. From **12**, by established methodology, the new 11-deoxy-11β-methoxy-11α-(hydroxymethyl)-12-*epi*-$PGF_{2\alpha}$ methyl ester (**18**) was obtained.

In the last few years there has been a growing interest in the synthesis of optically active intermediates of bioactive compounds from appropriate, readily available natural products utilized as chiral starting material.[1]

This was the background to our research program on the utilization of iridoid glucosides for synthesis of biologically active cyclopentanoid compounds or their intermediates.[2] The starting material we decided on was aucubin (**1**), the most abundant, widespread iridoid, which we isolated, in a yield of about 2%, from a common ornamental shrub (*Aucuba japonica*).



The important role that iridoids can play in synthetic strategies has been attested by the publication, to date, of 18 papers[4] and 4 patents,[5] all concerning prostanoid synthons or prostaglandins, obtained mainly from aucubin (**1**)[4a-f,l-n,q,r,5a,c] but also from asperuloside (**2**)[4h,i,5d] and catalpol (**3**).[4g,o,p,s,t,5b]

We noticed that these synthetic approaches to PG's from **1** were all carried out starting either from its 3,4,7,8-tetrahydro derivative or 7,8-dihydro derivative of lactone **5**, easily accessible from hexaacetylaucubin **4** following Dalton's procedure.[6] The aim of these procedures, above all the reduction of the Δ^7 double bond, was that of ensuring the highest possible stability for the transformation products.

The main feature of syntheses beginning with **1** was, however, the initial preservation of the Δ^7 double bond so that it could be functionalized at C-8 (corresponding for instance to C-11 of PG's) prior to the final transformation into appropriate compounds.

Our purpose here is to propose an alternative route for the transformation of the iridoid skeleton of **1** into chiral PG intermediate **12**, which could be conveniently employed in the synthesis of 11-deoxy-11-disubstituted $PGF_{2\alpha}$ derivatives. As an example, we carried out the transformation of **12** into the 11-deoxy-11β-methoxy-11α-(hydroxymethyl)-12-*epi*-$PGF_{2\alpha}$ methyl ester (**18**).

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Results and Discussion

Employing Dalton's procedure (NBS, Me_2SO),[6] we obtained from hexaacetylaucubin **4**, the known lactone **5** (y = 85%) whose 7,8-dihydro derivative was previously used in a PG synthesis.[4e]

Attempts to open the lactone ring under basic conditions to transform **5** into the corresponding γ-formyl acid or ester were unsuccessful. Hydrolysis (aqueous K_2CO_3 or $Ba(OH)_2$) and methanolysis ($MeOH/MeO^-$ or anhydrous K_2CO_3/MeOH) invariably produced complex reaction mixtures, even at low reaction temperatures. A clean reaction was, however, obtained by acid-catalyzed methanolysis of **5**,[7] which afforded a good yield (>85%) of bicyclic methyl acetal **6**[8] as single product.

Besides the expected formation of the Me ester function and the splitting of the glucose moiety from the hemiacetal function, the **5** → **6** transformation also implied an acid-catalyzed rearrangement of the cyclopentene moiety induced by the allylic 1,4 diol system. The pathway is probably analogous to that proposed[10] for the acid-catalyzed rearrangement of aucubigenin (**7**) (the aglycon of **1**) into the tricyclic hemiacetal **8**.

The structure and stereochemistry of **6** were clearly indicated by the ^1H and ^{13}C NMR data,[11] which were in good agreement with the corresponding values found for the closely related hemiacetal **8**.[10] The double doublets of olefinic protons at δ 5.89 (H-10, $J_{9,10}$ = 6.3, $J_{8,10}$ = 1.8) and δ 5.67 (H-9, $J_{9,10}$ = 6.3, $J_{8,9}$ = 2.3) and the doublets (SFORD) of olefinic carbons at 138.52 ppm (C-10) and 132.21 ppm (C-9) offered clear evidence of the new 9,10 position established for the double bond, while the formation from the α side of the acetalic tetrahydrofuran ring was supported by the resonances of the hemiacetal proton (δ 4.81, H-13) and of the AB system (2H-11′, δ 3.92 and 3.80, J_{AB} = 9.3) of methylene linked to the new chiral center C-11, bearing the β methoxy group. The stereochemistry at the C-11 and C-12 centers of **6** was also proved by the formation of lactone **i** (see later).

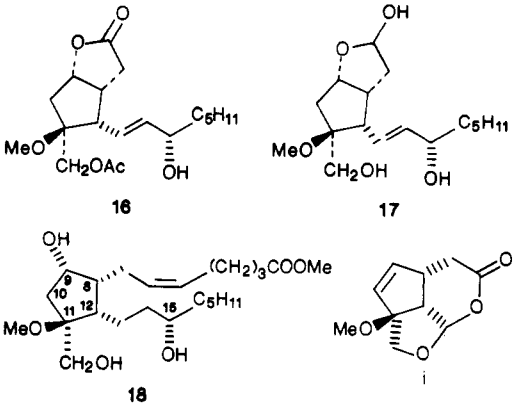
Methyl acetal **6** is an excellent starting material for synthesis of 11-deoxy-$PGF_{2\alpha}$ as the double bond of the cyclopentene ring is γ,δ to the carbomethoxy function for use in securing lactone ring closure, and the acetal function can be cleaved to provide both the formyl group at C-12 for introduction of the lower chain and the final substituents at C-11 position.[12]

Basic hydrolysis of **6** gave acid **9** which was subjected to the classical iodolactonization procedure (I_2/KI).[13] The iodo lactone **10** was successively deiodinated (tributyltin hydride)[14] to tricyclic methyl acetal **11** ($y_{6 \to 11}$ = 60%).[15]

Selective cleavage of the acetal protecting group with 0.05 N HCl in H_2O/MeCN (1:1)[18] gave the free hemiacetal **12**,[19] which was subjected to an Emmons–Horner reaction with the sodium salt of dimethyl (2-oxoheptyl)phosphonate[20] to provide the expected enone **13** accompanied by cyclic ether **14** in a 7:3 ratio.[21] The mixture was converted—under acetylation conditions—into acetyl enone **15**,[21] while still retaining the original chirality at C-12. The α orientation of the side chain at C-12 was proved by the value of the coupling constant $J_{12,13}$ (10.5 Hz) which agrees with the values (10.6, 11.0 Hz) found in analogous cis (12,13) enones (8.0, 8.8 Hz for trans (12,13) enones).[22]

The prochiral unsaturated carbonyl compound **15** was enantioselectively reduced with (*S*)BINAL-H,[24] a chiral aluminum hydride reagent with exceptionally high chiral recognition ability,[26] giving the 15*S* allylic alcohol **16**.[27]

Lactone **16** was reduced with diisobutylaluminum hydride (DIBAH) in CH_2Cl_2 at −60 °C to lactol **17**, which was



condensed, without isolation, with a Wittig reagent derived from (4-carboxybutyl)triphenylphosphonium bromide[29] affording, after esterification with diazomethane, the Me ester **18** (yield of **15** → **18** = 11%) of a 11-deoxy-12-*epi*-$PGF_{2\alpha}$, with a new substitution model (β-OMe, α-CH_2OH) at C-11.

The structure and stereochemistry of Me ester **18** were in agreement with its ^1H NMR spectrum (300 MHz): the

(7) Best yields were obtained with the procedure described in Experimental Section (anhydrous MeOH/HCl). Other catalytic conditions (pTSA or strongly acidic resin "Ionenaustaucher I" Merck) gave lower yields.

(8) This product was previously described,[9] with poor ^1H NMR analysis, in the work on the structure elucidation of aucubin.

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(11) All new compounds gave satisfactory elemental analyses while corresponding ^1H and ^{13}C NMR data were reported in the Experimental Section.

(12) Attempts to modify the conditions of step **5** → **6** to replace the OMe at C-11 with other alkoxy functions (e.g., *i*-PrO, $PhCH_2O$) or to dealkylate tertiary OMe of **6** (e.g., BBr_3, ITMS, Birch reaction, catalytic hydrogenation) were unsuccessful.

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(15) Various attempts to obtain **11** from **9** by other lactone closure procedures, e.g., BF_3–Et_2O[16] or *p*-TSA in C_6H_6,[17] afforded quantitatively the lactone **i** (^1H NMR data in Experimental Section).

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(19) Note that before compound **12**, all synthetic steps were carried out without chromatographic purification of single compounds.

(20) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, V.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.

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(22) Contrary to literature data[4i,q] regarding Wittig-type reactions of hemiacetals in DME, in this case the inversion of C-12 center did not occur. On the other hand, practical difficulties[23] prevented us from effecting the epimerization (e.g., TsOH in AcOH at 105 °C)[4c] of the α side chain.

(23) Our stock of **15** was destroyed in a fire together with our laboratory. The synthesis was completed by utilizing only the sample (30 mg) sent to NMR service.

(24) Prepared according to the procedure of Noyori[25] by successive mixing of lithium aluminum hydride with equimolar amounts of EtOH and optically pure (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthyl.

(25) Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.

(26) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(27) It is well-known that C-15 epimeric carbinols give chromatographycally separable mixtures and may be recognized on the basis of their TLC behavior (15*S* isomer more polar).[28] The unicity of **16** and the enantioselectivity of the reduction with (*S*)-BINAL-H are therefore well corroborated by its single spot on TLC with various solvent systems.

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clean doublet of doublets at δ 5.43 ($J_{13,14}$ = 15.3, $J_{12,13}$ = 9.3)[30] is assignable to the olefinic H-13 on the basis of detailed homonuclear double resonance experiments carried out on the broad triplet at δ 2.77 (clearly attributable to the β H-12 cyclopentane ring proton) and by comparison of chemical shift, multiplicity, and J values of analogous PG's[4o,31]

The other significant resonances are those of the remaining three olefinic protons H-5, H-6, and H-14 (overlapping signals in the range of δ 5.62–5.53), of H-9 (multiplet at δ 4.80), of H-15[34] (multiplet at δ 4.10), of carbomethoxy (singlet at δ 3.49), and angular methoxy (singlet at δ 3.24) groups.

Summary and Conclusion

The preparation of the new 11-deoxy-12-*epi*-$PGF_{2\alpha}$ methyl ester **18** from aucubin (**1**) confirms the important role that iridoids may play as natural chirons in a synthetic approach to bioactive cyclopentanoid compounds. Syntheses of other biologically active compounds, utilizing 1 or other iridoid glucosides as chiral starting material, are in progress.

Experimental Section

General Procedures. Routine ^{1}H NMR spectra were recorded at 60 MHz on a Varian EM 360 instrument. High field spectra were recorded on a Varian XL 300 instrument. ^{1}H NMR data are reported as parts per million (δ) downfield from Me_4Si, with the multiplicities, assignments, and J values (Hz) in parentheses. All spectra were determined in deuteriochloroform.

^{13}C NMR spectra were recorded at 25 MHz on a Varian CFT 20 in deuteriochloroform with Me_4Si as internal standard and are reported in parts per million (ppm) downfield from Me_4Si. Values with same superscript are interchangeables.

PG numbering was used for all compounds with the exception of **5** and **i** (iridoid numbering).

Analytical and preparative TLC were performed on silica gel 60 F-254 plates (E. Merck). Compounds were visualized by spraying with 2 N H_2SO_4 and heating on a hot plate until spots developed.

All products described as oils were purified for analytical purposes by chromatography on "washed silica gel" (70–230-mesh silica gel (Merck) treated with dilute HCl, then washed with hot H_2O to eliminate Cl^- ions, dried, and activated at 120 °C for 8 h) by eluting with the same solvent used for TLC controls.

Dimethyl sulfoxide and methylene chloride were dried over calcium hydride, distilled (Me_2SO, in vacuo), and stored over 4-Å molecular sieves; MeOH and benzene were distilled over lithium aluminum hydride; *N*-bromosuccinimide (NBS) was recrystallized from water; sodium hydride was employed as an 80% oil dispersion, which was washed with dry hexane immediately before use.

Tributyltin hydride, α,α'-azobis(isobutyronitrile), and (4-carboxybutyl)triphenylphosphonium bromide were purchased from Fluka; dimethyl (2-oxoheptyl)phosphonate, and (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthyl, and diisobutylaluminum hydride (DIBAH) were purchased from Janssen.

Aucubin (1). Aucubin was isolated from *Aucuba japonica* as previously described.[3] About 100 g of aucubin were obtained from 5 kg of fresh plant and recrystallized from EtOH as colorless crystals.

Preparation of Lactone 5. To a solution of **4** (10 g, 16.72 mmol) in Me_2SO/H_2O (100 mL, 50:1) was added NBS (3.12 g, 18.1 mmol) at 0–5 °C with stirring. The reaction was monitored on TLC (Et_2O) and after 30 min, EtOAc (800 mL) was added; then Me_2SO was removed by washing the solution with H_2O (5 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give a solid residue (12.5 g) containing two products at lower R_f values than **4** (TLC in Et_2O). Without purification, the solid was dissolved in Me_2CO (100 mL) and Jones reagent (40 mL) was slowly added over a period of 4 h with stirring. The green solution resulting after *i*-PrOH addition was carefully neutralized with saturated Na_2CO_3 solution and then concentrated. The final solution was extracted with EtOAc (5 × 150 mL), dried (Na_2SO_4), and concentrated to 200 mL. Then AcOH (100 mL) and powdered Zn (1 g) were added, with stirring. After 1 h, the salts were filtered on a Gooch funnel and washed with Et_2O. The organic phase was washed with a saturated Na_2CO_3 solution until neutral and then with water, dried (Na_2SO_4), and concentrated under reduced pressure to leave 8.7 g (85%) of desired lactone **5** as white crystals: mp 174–175 °C (lit.[4e] mp 174–174.5 °C); ^{13}C NMR 170.01, 169.43, 169.11 (s, C-3 and acetyl C=O), 142.86 (s, C-8), 129.19 (d, C-7), 97.35 (d, C-1 and C-1′), 84.58 (d, C-6), 72.63 (d, C-3′ and C-5′), 70.89 (d, C-2′), 68.06 (d, C-4′), 61.63 (t, C-6′), 60.73 (t, C-10), 47.94 (d, C-9), 39.44 (d, C-5), 33.00 (t, C-4), 20.98, 20.60 (q, *Me*CO); ^{1}H NMR (60 MHz) 5.90 (bs, 1 H, H-7), 5.64 (d, 1 H, H-1, $J_{1,9}$ = 2.8), 5.32 (bs, 1 H, H-6, partly overlapped), 4.72 (bs, 2 H, 2H-10), 3.82 (bs, 1 H, H-9), 3.38 (bs, 1 H, H-5), 2.78 (bs, 2 H, 2H-4), 2.1–1.8 (18 H, AcO).

Methanolysis of Lactone 5 to 6. To a stirred suspension of **5** (8.7 g, 14.2 mmol) in anhydrous MeOH (100 mL) was added dropwise a solution of dry gaseous HCl (5.3 g) in anhydrous MeOH (100 mL). The brown reaction mixture was stirred overnight at room temperature and then neutralized with a saturated Na_2CO_3 solution. After concentration under reduced pressure, the aqueous residue was transferred on a liquid–liquid apparatus and continuously extracted with Et_2O. The Et_2O extracts, dried (Na_2SO_4) and evaporated in vacuo, afforded 2.92 g (85%) of **6** as slightly impure oil (TLC in Et_2O/hexane, 6:4): ^{13}C NMR 174.76 (s, C-6), 138.52 (d, C-10), 132.21 (d, C-9), 106.08 (d, C-13), 99.65 (s, C-11), 74.02 (t, C-11′), 54.64 (q, COO*Me*), 52.56 (q, OMe-11), 52.03 (d, C-8), 51.80 (q, OMe-13), 42.78 (d, C-12), 35.64 (t, C-7); ^{1}H NMR (300 MHz) 5.89 (dd, 1 H, H-10, $J_{9,10}$ = 6.3, $J_{8,10}$ = 1.8), 5.67 (dd, 1 H, H-9, $J_{9,10}$ = 6.3, $J_{8,9}$ = 2.3), 4.81 (s, 1 H, H-13), 3.92 (d, 1 H, H_A-11′, J_{AB} = 9.3), 3.80 (d, 1 H, H_B-11′, J_{AB} = 9.3), 3.72 (s, 3 H, COO*Me*), 3.48 (m, 1 H, H-8), 3.34 (s, 3 H, OMe-11), 3.22 (s, 3 H, OMe-13), 2.74 (d, 1 H, H-12, $J_{8,12}$ = 9.3), 2.53 (dd, 1 H, H_A-7, $J_{A,8}$ = 8.4, J_{AB} = 16.0), 2.42 (dd, 1 H, H_B-7, $J_{B,8}$ = 8.3, J_{AB} = 16.0).

Hydrolysis of 6: Acid 9. To a solution of **6** (2.92 g) in MeOH (10 mL) was added a saturated solution (50 mL) of $Ba(OH)_2$ with stirring. After 1 h at room temperature, the solution was extracted with Et_2O to eliminate neutral impurities. The pH of the aqueous solution was adjusted to 7 with 2 N H_2SO_4 until perfect balance of Ba^{2+} and SO_4^{2-} ions. The final suspension was extracted with EtOAc (5 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated to give 2.58 g (94%) of **9** as oil, unitary on TLC (Et_2O/hexane, 8:2): ^{1}H NMR (60 MHz) 9.50 (bs, 1 H, COO*H*), 5.92 (dd, 1 H, H-10, $J_{9,10}$ = 6.0, $J_{8,10}$ = 1.0), 5.62 (dd, 1 H, H-9, $J_{9,10}$ = 6.0, $J_{8,9}$ = 2.2), 4.86 (s, 1 H, H-13), 3.88 (dd, 2 H, 2H-11′, J_{AB} = 10.0), 3.5–3.1 (m, 1 H, H-8, masked by OMe), 3.32 (s, 3 H, OMe-11), 3.22 (s, 3 H, OMe-13), 2.76 (d, 1 H, H-12), 2.50 (m, 2 H, 2H-7).

Preparation of Iodolactone 10. **9** (2.58 g) was dissolved in H_2O (3.5 mL) and $NaHCO_3$ (1.13 g) was added with stirring. A solution of I_2 (6.5 g) and KI (14 g) in 45 mL of H_2O was added and stirring was continued for 2 days in the dark. I_2 excess was reduced with Na_2SO_3 and the solution extracted with Et_2O (3 × 300 mL). The organic phase, washed with brine, dried (Na_2SO_4), and concentrated to dryness, afforded 2.90 g (72%) of almost pure **10** (TLC in Et_2O): ^{13}C NMR 174.91 (s, C-6), 105.78 (d, C-13), 94.25 (s, C-11), 91.13 (d, C-9), 68.28 (t, C-11′), 55.00 (q, OMe-11), 52.93 (q, OMe-13), 51.88 (d, C-12), 38.28 (d, C-8), 35.28 (d, C-10), 30.09 (t, C-7); ^{1}H NMR (300 MHz) 5.20 (dd, 1 H, H-9, $J_{9,10}$ = 5.4, $J_{8,9}$ = 8.8), 4.83 (s, 1 H, H-13), 4.37 (d, 1 H, H-10, $J_{9,10}$ = 5.4), 4.09 (d, 1 H, H_A-11′, J_{AB} = 10.0), 3.77 (d, 1 H, H_B-11′, J_{AB} = 10.0),

(30) Although there are very few cases of $J_{12,13}$ values for 12-*epi*-PG's in the literature ($J_{12,13}$ = 9.8 Hz),[31] the value found for **18** seems completely out of the range of $J_{12,13}$ values (7.5–8.3 Hz)[4c,i,o,q,32,33] found for trans (12,13) PG's.

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(34) The very small chemical shift differences found[4o,32] for the H-15 of epimeric carbinols 15*R* and 15*S* render them indistinguishable. The single, clean double doublet for the H-13 of **18**, on the other side, is a spectroscopic confirmation of its unicity and consequently of the marked enantioselectivity of the reduction.

3.5–3.3 (m, H-8, masked by OMe), 3.38# (s, 3 H, OMe-11), 3.36# (s, 3 H, OMe-13), 2.89 (d, 1 H, H-12, $J_{8,12}$ = 10.8), 2.60 (d, 2 H, 2H-7, $J_{7,8}$ = 8.4).

Deiodination of 10: Lactone 11. To **10** (2.90 g) dissolved in 20 mL of distilled C_6H_6 were added 2.37 g (2.19 mL) of (*n*-Bu)$_3$SnH and 50 mg of α,α'-azobis(isobutyronitrile). The reaction, monitored on TLC (Et_2O), was complete in 3 days. The solution was adsorbed on "washed silica gel" and the silica gel layer was successively washed with petroleum ether (40–70 °C) to eliminate hydride and with Et_2O. The Et_2O solution, concentrated to dryness, afforded 1.65 g (88%) of chromatographycally pure **11**: ^{13}C NMR 175.98 (s, C-6), 105.98 (d, C-13), 94.74 (s, C-11), 85.37 (d, C-9), 73.06 (t, C-11′), 55.69 (d, C-12), 54.90# (q, OMe-11), 52.56# (q, OMe-13), 42.72 (t, C-10), 40.35 (d, C-8), 30.69 (t, C-7); ^{1}H NMR (300 MHz) 5.04 (q, 1 H, H-9, J = 7.0), 4.79 (s, 1 H, H-13), 4.05 (d, 1 H, H$_A$-11′, J_{AB} = 9.0), 3.85 (d, 1 H, H$_B$-11′, J_{AB} = 9.0), 3.4–3.2 (m, 1 H, H-8, masked by OMe), 3.37# (s, 3 H, OMe-13), 3.28# (s, 3 H, OMe-11), 2.70 (d, 1 H, H-12, $J_{8,12}$ = 9.9), 2.6–2.5 (o, 2 H, 2H-10, overlapped by H-7), 2.60 (d, 2 H, 2H-7, J = 6.6).

Hydrolysis of 11: Hemiacetal 12. To a solution of **11** (1.65 g) in H_2O/MeCN (1:1) (30 mL) was added 2 N HCl (1 mL). The reaction mixture, monitored on TLC (EtOAc/Et_2O, 7:3), was stirred at 40 °C for 5 days. The solution was neutralized with a saturated $NaHCO_3$ solution and continuously extracted in a liquid–liquid apparatus with EtOAc. The extract was dried (Na_2SO_4) and concentrated to leave 1.30 g of an oily residue containing **12** contaminated by unreacted **11** (TLC in EtOAc/Et_2O, 7:3). Chromatography of the residue afforded 1.16 g (75%) of pure **12**: ^{13}C NMR 181.63 (s, C-6), 99.91 (d, C-13), 96.00 (s, C-11), 88.68 (d, C-9), 75.52 (t, C-11′), 56.48 (d, C-12), 53.13 (q, OMe-11), 40.44 (d, C-8), 39.06 (t, C-10), 31.93 (t, C-7); ^{1}H NMR (60 MHz) 5.45 (s, 1 H, H-13), 5.20 (m, 1 H, H-9), 4.16 (dd, 2 H, 2 H-11′, J_{AB} = 10.0), 3.5–3.1 (m, 1 H, H-8), 3.30 (s, 3 H, OMe-11), 3.0–2.6 (m, 2 H, 2H-7), 2.90–2.40 (m, 3 H, 2H-10 and H-12).

Preparation of 15. A solution of 2.40 mL (2.57 g) of dimethyl (2-oxoheptyl)phosphonate in 3 mL of DME was injected under a nitrogen atmosphere into a stirred suspension of NaH (280 mg) in DME (4 mL). Stirring was continued for 1 h while a voluminous white precipitate was formed. After cooling in an ice bath, a solution of **12** (1.16 g, 5.4 mmol) in DME (2 mL) was injected and stirring was continued for 30 min with ice cooling and then for 12 h at room temperature. The reaction mixture was neutralized with AcOH and concentrated under reduced pressure. A TLC preparative plate, eluted with Et_2O/EtOAc (3:7), showed a narrow strip with positive UV reaction which was carefully scraped. The resulting silica gel powder was eluted with EtOAc, affording 650 mg of an oily mixture of enone **13** and cyclic ether **14** (total yield 40%), in a ratio 7:3 established by ^{1}H NMR analysis of the mixture. The mixture was directly acetylated (Ac_2O (10 mL), CF_3COOH (0.3 mL), 50 °C, 5 h), giving a unique compound (TLC, Et_2O). After dilution with EtOAc, the organic phase was washed with saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the residue by chromatography on "washed silica gel" (Et_2O) afforded 518 mg (70%) of **15**: ^{13}C NMR 199.35 (s, C-15), 176.07 (s, C-6), 138.99 (d, C-13), 135.73 (d, C-14), 87.98 (s, C-11), 83.75 (d, C-9), 62.69 (t, C-11′), 52.00 (q, OMe-11), 50.20 (d, C-12), 41.49 (d, C-8), 39.85# (t, C-10), 38.37# (t, C-16), 31.36* (t, C-7), 30.80* (t, C-18), 23.67 (t, C-17), 22.42 (t, C-19), 20.62 (q, *Me*CO), 13.83 (q, C-20); ^{1}H NMR (300 MHz) 6.32 (dd, 1 H, H-13, $J_{12,13}$ = 10.5, $J_{13,14}$ = 16.0), 6.12 (d, 1 H, H-14, $J_{13,14}$ = 16.0), 5.03 (se, 1 H, H-9), 4.08 (dd, 2 H, 2H-11′, J_{AB} = 12.0), 3.4–3.0 (m, 1 H, H-8), 3.20 (s, 3 H, OMe-11), 3.04 (dd, 1 H, H-12, $J_{8,12}$ = 8.0, $J_{12,13}$ = 10.5), 2.65 (dd, 1 H, H$_A$-10′, J_{AB} = 18.0, $J_{9,10}$ = 12.0), 2.8–1.9 (m, 2 H, 2H-7), 2.47 (t, 2 H, 2H-16), 2.31 (d, 1 H, H$_B$-10′, J_{AB} = 18.0), 2.06 (s, 3 H, *Me*CO), 1.55 (t, 2 H, 2H-17), 1.25 (m, 4 H, 2H-18 and 2H-19), 0.85 (t, 3 H, 3H-20).

Preparation of 11-Deoxy-11β-methoxy-11α-(hydroxymethyl)-12-*epi*-PGF$_{2\alpha}$ Methyl Ester (18) from 15. To a stirred solution of **15** (30 mg)[23] in THF (5 mL) at −100 °C was added 3 equiv of (*S*)-BINAL-H[24] (0.97 M solution in THF). Stirring was continued for 2 h at −100 °C and then for 1 h at −78 °C. The reaction mixture was quenched by addition of moist ether, filtered, and evaporated under reduced pressure. A TLC control (EtOAc/Et_2O, 7:3) showed a unique spot with R_f slightly lower than that of **15** and negative reaction to 2,4-DNF spray reagent. The residue (**16**, 25 mg) was dissolved in anhydrous CH_2Cl_2 (10 mL) and reduced with DIBAH (20% solution in hexane, 1.2 mL) at −60 °C under nitrogen for 30 min. The reaction was stopped with MeOH (2 mL), diluted with H_2O (20 mL), and extracted with EtOAc (5 × 20 mL). The organic phase was dried (Na_2SO_4) and evaporated, affording 20 mg of crude **17**, which was a single spot by TLC (EtOAc). A mixture of NaH in mineral oil (80%, 100 mg) and anhydrous Me_2SO (10 mL) was stirred under nitrogen at 70–75 °C for 45 min and then cooled to 5 °C. After addition of (4-carboxybutyl)triphenylphosphonium bromide (95 mg) in anhydrous Me_2SO (3 mL), the resulting dark-red solution was stirred for 30 min at room temperature. To this solution was added the crude lactol **17** (20 mg) in anhydrous Me_2SO (3 mL). After 12 h the reaction mixture was poured into ice–water, acidified with AcOH, and extracted with Et_2O (4 × 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give an oily residue which was dissolved in Et_2O (10 mL) and treated with an ether solution of CH_2N_2 until the yellow color persisted. Removal of the solvent gave 12 mg of a residue which was purified by chromatography with $CHCl_3$/MeOH (95:5) to give 4 mg ($y_{15 \rightarrow 18}$ = 11%) of **18** as an oil: ^{1}H NMR (300 MHz) 5.62–5.53 (m, 3 H, H-5, H-6, and H-14), 5.43 (dd, 1 H, H-13, $J_{13,14}$ = 15.3, $J_{12,13}$ = 9.3), 4.80 (bt, 1 H, H-9, $J_{9,10A}$ = 8.6, $J_{9,10B}$ = 3.2), 4.10 (m, 1 H, H-15), 3.49 (s, 3 H, COO*Me*), 3.24 (s, 3 H, OMe-11), 2.77 (bt, 1 H, H-12, $J_{12,13}$ = 9.3), 2.22 (dd, 1 H, H$_A$-10, J_{AB} = 14.5, $J_{A,9}$ = 8.6), 1.74 (dd, 1 H, H$_B$-10, J_{AB} = 14.5, $J_{B,9}$ = 3.2), [1.60 (m), 1.30 (m), 1.25 (m), 14 H, aliphatic chains], 0.83 (t, 3 H, 3H-20).

Lactone i: ^{1}H NMR (300 MHz) 5.90 (s, 2 H, H-6, and H-7), 5.90 (d, 1 H, H-1, $J_{1,9}$ = 4.2), 4.20 (dd, 2 H, 2H-10, J_{AB} = 9.8), 3.38 (m, 1 H, H-5), 3.18 (s, 3 H, OMe-8), 3.11 (dd, H-9, $J_{1,9}$ = 4.2, $J_{5,9}$ = 9.6), 2.66 (dd, 1 H, H$_A$-4, J_{AB} = 10.3, $J_{A,5}$ = 2.9), 2.49 (dd, 1 H, H$_B$-4, J_{AB} = 10.3, $J_{B,5}$ = 6.0).

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