Synthesis of 11-Methyl- and 11,11-Dimethylprostaglandins *via* the Wittig Reaction of α-Dienol[1]

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The key intermediates for 11-methyl- and 11,11-dimethylprostaglandins corresponding to Corey's lactone were synthesized *via* the Wittig reaction of dimethyl 2-substituted-4,5-dioxocyclopentane-1,3-dicarboxylate with stable ylides. 11,11-Dimethylprostaglandin E_2 was then synthesized.

Recently, a number of groups have done research on the synthesis of methylprostaglandins (PGs) whose biological activities resemble those of PGEs. 11-Methyl-PGE_2[2] was synthesized by 1,4-addition of ate-complex or diazomethane to the natural PGA_2. We have previously reported the synthesis of 11-deoxy- and natural prostaglandins intermediates[1,3] by the Wittig reaction from enolized α-diketone. We wish to describe the synthesis of the intermediates (**8a** and **8b**) for 11-methylated PGs and a total synthesis of 11,11-dimethyl-PGE_2 (**1b**) starting from **8b**.

The Wittig reaction of one equivalent of dimethyl 4,5-dioxo-2-methylcyclopentane-1,3-dicarboxylate (**2a**) (α-dienol) with two equivalents[4] of (methoxycarbonylmethylene)triphenylphosphorane (**3a**) in chloroform under reflux for 24 h afforded a mixture of the corresponding olefins (**4a**, **4b**, and **4d**). This reaction, however, seemed to proceed differently from the usual Wittig reaction. On addition of the ylide **3a** to α-dienol **2a** in chloroform at room temperature, **2a** was rapidly transformed into a polar intermediate (as monitored by TLC), which was gradually converted into the final olefinic products **4a**, **4b**, and **4d** under reflux. Since the starting material **2a** was quantitatively recovered from the polar intermediate by acid (8% HCl) treatment, the polar intermediate seems to be a phosphonium salt. The formation of the phosphonium salt might be due to the relatively strong acidity[5] of **2a** (pK_{a_1} 6.26 and pK_{a_2} 11.1). The reaction mechanism from the salt to olefins remains unsolved. It is noteworthy that the Wittig reaction proceeded in the case of acidic α-dienols,[3] although under the same conditions cyclopentanone, β-keto ester (**13**), and α-keto enol ethers (**14**) and (**15**) with **3a** gave no products.

The purification of the products was effected by silica gel chromatography and successive fractional recrystallization to give the *exo*-olefins **4a** (mp 82—83.5 °C) and **4b** (mp 96—97.5 °C) in a 25.3% total yield, and the oily *endo*-isomer **4d**[6] in a 25.6% yield. In the NMR spectra vinyl protons of **4a** and **4b** appeared at 6.39 and 6.38 ppm, respectively. The methyl group in **4b** was observed at 1.13 ppm as a doublet, due to a shielding effect of the adjacent methoxycarbonyl group which was larger than that of **4a** at 1.31 ppm. These observations support the stereochemical assignments of the methyl group to the methoxycarbonyl group in **4a** and **4b** as *trans* and *cis*, respectively, except for the geometry of the *exo* double bond. Further confirmation of the stereochemistry of **4a** was made in connection with the stereochemistry of the *trans-trans*-keto diester (**5a**) derived from **4a** by successive catalytic hydrogenation and decarboxylation (*vide infra*). The *endo*-isomer **4d** contains no vinyl proton, but the methyl group appeared at 2.35 ppm as a singlet assignable to an olefinic methyl group. The *endo*-isomer **4d** would be obtained from **4a** and/or **4b** by the migration of the *exo* double bound under the employed reaction conditions.

Catalytic hydrogenation of the *trans-exo*-olefin **4a** over 10% Pd–C in methanol, followed by treatment with NaI–AcOH–diglyme,[7] afforded stereoselectively the *trans-trans*-keto diester **5a** in a 72.7% yield. Its stereochemical assignment was based on the following observations: i) No epimerization of **5a** occurred after treatment with sodium methoxide in methanol, which suggested that **5a** was thermodynamically stable in its configuration. ii) In the NMR spectra the *trans*-methyl group on the cyclopentane ring was generally observed at a lower field than the corresponding *cis*-methyl group, as shown in Table. 1[8] The methyl signal of **5a** at 1.20 ppm was also observed at a lower field than the other two isomers, *i.e.* the *cis-trans*-keto diester (**5b**) (1.13 ppm) and the *cis-cis*-keto diester (**5d**) (0.96 ppm) (*vide infra*). Further chemical transformation of **5a** into 11-methylprostaglandin E_2 confirmed its stereochemical features. On the other hand, for both **4b** and **4d**, catalytic hydrogenation followed by decarboxylation gave a stereoisomeric mixture of **5a** (*trans-trans*), **5b** (*cis-trans*), and **5d** (*cis-cis*), in the ratio of 5: 2: 3.

TABLE 1. NMR OF METHYL CYCLOPENTANES CHEMICAL SHIFT AND J VALUE OF METHYL SIGNALS

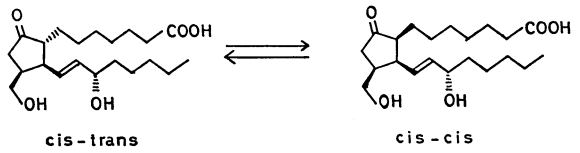
trans δ (JHz)	cis δ (JHz)	trans δ (JHz)	cis δ (JHz)
 1.20 (5)	 1.04 (6)	 1.17 (5)	 1.03 (6)
 1.10 (5)	 0.97 (7)	 1.06 (4)	 0.98 (6)
 1.07 (4)	 0.97 (6)	 1.21 (6)	 1.15 (6)
 1.14 (6)	 1.00 (6)	 —	 1.09 (6)

The *cis-exo*-olefin **4b** was found to be isomerized to the *endo* double bond in **4d** by treatment with activated 10% Pd–C in methanol under argon atmosphere. The formation of the mixture of **5a**, **5b**, and **5d** from **4b** was thus explained on the assumption that **4b** was

isomerized to **4d** prior to hydrogenation.

Separation of these isomers by silica gel or alumina column chromatography was unsuccessful. HPL chromatography, however, gave the pure isomer **5b** and a mixture of **5a** and **5d**. In the NMR spectra, methyl signals of **5a**, **5b**, and **5d** appeared at 1.20 (doublet, J=5 Hz), 1.13 (doublet, J=8 Hz), and 0.96 ppm (doublet, J=8 Hz). These NMR data indicate that the methyl group of **5d** was more shielded by other substituents on the cyclopentane ring, *i.e.*, methoxycarbonyl and methoxycarbonylmethyl groups, than were the methyl groups of **5a** and **5b**. Therefore, the less shielded isomer **5b** may be assigned as *cis-trans* and the most shielded one **5d** as *cis-cis*.

These assignments are supported by the facts that the *cis-trans*-isomer **5b** readily isomerizes to an equilibrium mixture of **5b** and **5d** in the ratio of 2: 3 under decarboxylation conditions, *i.e.*, NaI–AcOH–diglyme at 120 °C, whereas the *trans-trans*-isomer **5a** underwent no isomerization under the same conditions. The equilibration between *cis-trans*- and *cis-cis*-isomers on the cyclopentanone ring has already been observed: *cis-trans*-PGE_1s and/or *cis-cis*-PGE_1s underwent isomerization to their equilibrium mixture by treatment with bases such as K_2CO_3 or NaOH.[9]



Scheme 1.

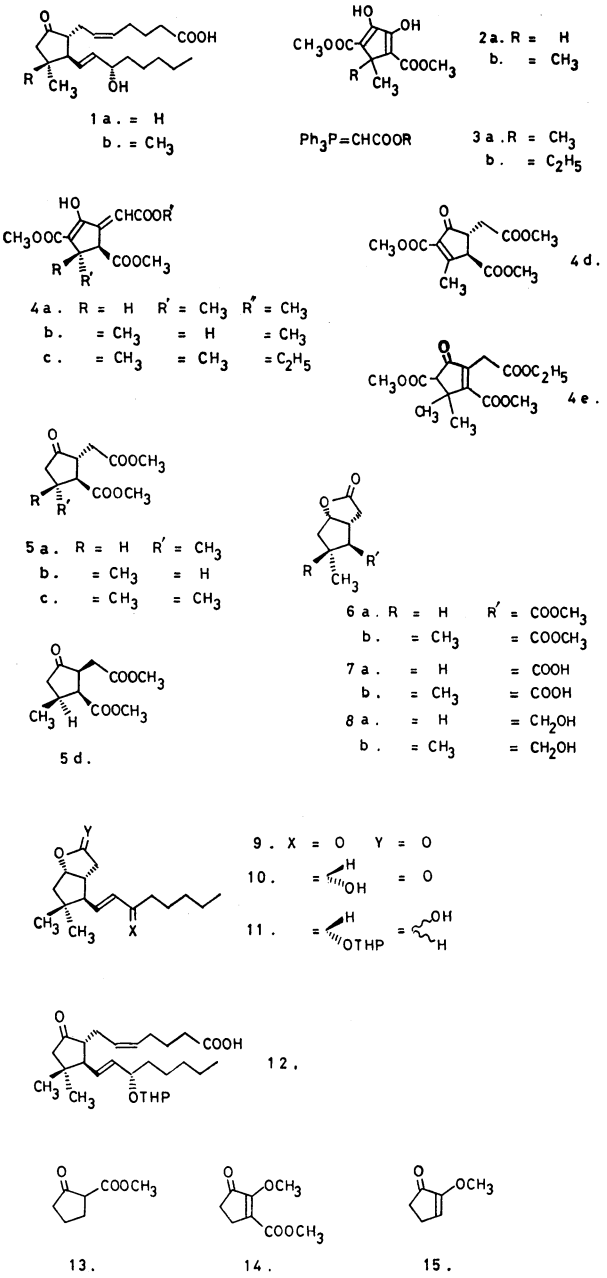
Treatment of a stereoisomeric mixture of **5** with a strong base such as NaOMe furnished predominantly the *trans-trans*-isomer **5a**. Ultimately, the stable isomer **5a** was obtained in a 46.4% yield starting from the α-dienol **2a**, without separation of the products in each step.

The reduction of the keto diester **5a** with potassium tri-*s*-butylborohydride gave the lactone (**6a**) in a 67.8% yield. By hydrolysis with concd hydrochloric acid, crystalline lactone acid (**7a**) (65.5%, mp 116—117 °C) was obtained. On reduction with $NaBH_4$ after conversion into the mixed anhydride ($ClCOOEt$–Et_3N), **7a** gave the key intermediate lactone alcohol (**8a**), which may be easily converted into 11-methyl-PGs by established methods.

11,11-Dimethyl-PGE_2 (**1b**) was obtained from the α-dienol (**2b**) by the same method. The Wittig reaction of **2b** (pK_{a_1} 6.61 and pK_{a_2} 11.1) with stable ylide (**3b**) gave a mixture of the corresponding olefins (**4c** and **4e**) (*ca.* 3: 7) in a 25.4% yield. Catalytic hydrogenation of the mixture over 10% Pd–C, followed by treatment with concd hydrochloric acid, gave the decarboxylated product. This was reesterified with diazomethane to give the keto diester (**5c**) in a 78.5% yield. The keto diester **5c** was stereoselectively reduced with potassium tri-*s*-butylborohydride to give the lactone ester (**6b**) (46.7%, mp 69.5—71 °C). Acid-hydrolysis of **6b** with hydrochloric acid gave the lactone acid (**7b**) (71%, mp 179.5—181 °C); this was reduced *via* the mixed anhydride to the lactone alcohol (**8b**) in a 73.6% yield.

Both side chains required for the prostaglandins were introduced into **8b** by the usual method. The Collins oxidation of **8b** followed by the Wittig reaction gave the enone (**9**), which was reduced with $NaBH_4$ to an epimeric mixture of (**10**) and its 15-OH epimer. By preparative layer chromatography the less polar compound **10** was obtained. This was tentatively assigned as the 15α-OH(*S**) epimer. Treatment of **10** with dihydropyran in the presence of *p*-TsOH, followed by reduction with diisobutylaluminium hydride, provided the lactol (**11**). The Wittig reaction of **11** with sodium 5-(triphenylphosphoranylidene)pentanoate, followed by the oxidation with the Collins reagent, afforded 15-tetrahydropyranyloxy-11,11-dimethyl-PGE_2 (**12**). Removal of the protecting group of **12** with aqueous AcOH afforded 11,11-dimethyl-PGE_2 **1b**.

11,11-Dimethyl-PGE_2 **1b** showed *anti*-ulcer activity



nearly equal to 11-methyl-PGE_1.

Experimental

The melting points were determined on a Micro Melting Point Apparatus (Yanagimoto) and are uncorrected. The infrared spectra were recorded in Nujol mull or neat on a JASCO Model A-2. The NMR spectra were obtained on a Varian T-60 spectrometer with TMS as an internal standard.

The starting materials **2a** and **2b** were prepared from oxalyl ester and dimethyl 3-methyl- or 3,3-dimethylglutarate.[10]

*Dimethyl 2-Hydroxy-3-methoxycarbonylmethylene-*trans*-5-methyl-1-cyclopentene-1,4-dicarboxylate* ***4a****, Its* cis*-Isomer* ***4b****, and* endo*-Olefinic Isomer* ***4d****.* A solution of **2a** (9.15 g) and **3a** (26.8 g) in chloroform was stirred at 60 °C for 24 h. The reaction mixture was washed with 8% HCl and the solvent was evaporated *in vacuo*. The residue was added to hexane–benzene and extracted well with 10% aqueous K_2CO_3. The basic aqueous extracts were combined, acidified with dil HCl, and extracted with ether. The ethereal extracts were washed with water, dried over Na_2SO_4, and evaporated to give a dark oil. The crude product was chromatographed on an acid-washed silica gel to give a mixture of crystalline *exo*-olefins as the less polar fraction, which consisted of two stereoisomers **4a** and **4b** (2.86 g ratio **4a**: **4b**=1: 1), and an oily *endo*-olefin as the more polar fraction **4d**. Recrystallization from ethanol afforded pure **4a** and **4b**. **4a**: Mp 82—83.5 °C; MS: *m/e* 284 (M^+); IR: 3350, 1715, 1705, 1645, and 1610 cm^{-1}; NMR ($CDCl_3$): 9.98 (1H, bs, OH), 6.39 (1H, d, J=2 Hz, olefin), 3.7 (1H, m, >CH–COO), 3.06 (1H, dq, J=2 and 6 Hz, >CH–Me), and 1.31 (3H, d, J=6 Hz, CH_3). Found: C, 54.87; H, 5.57%. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67%. **4b**: mp 96—97.5 °C; IR: 3360, 1735, 1715, 1710, 1645, and 1610 cm^{-1}; NMR ($CDCl_3$): 10.02 (1H, s, OH), 6.38 (1H, d, J=2 Hz, olefin), 4.20 (1H, q, J=8 Hz, >CH–COO), 3.36 (1H, dq, J=7 and 8 Hz, >CH–Me), and 1.13 (3H, d, J=7 Hz, CH_3). Found: C, 54.64; H, 5.38%; Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67%. **4d**: oil; IR: 1730 and 1630 cm^{-1}; NMR ($CDCl_3$): 3.77, 3.66, and 3.60 (3× 3H, s, $COOCH_3$), 3.7 (1H, m, >CH–COO), 3.2—2.6 (3H, m), and 2.35 (3H, s, CH_3). Found: C, 54.75; H, 5.43%. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67%.

Hydrogenation and Decarboxylation of ***4a****,* ***4b****, and* ***4c*** *to* ***5****.* A solution of **4a** (0.426 g) in methanol was hydrogenated in the presence of 5% Pd–C under hydrogen atmosphere at room temperature. After removal of the catalyst and evaporation of the solvent, the hydrogenated product was heated at 120—140 °C for 1 h in a mixture of diglyme (6 ml), acetic acid (0.4 ml), and sodium iodide (0.2 g). The reaction mixture was poured into water and extracted with ether. The ethereal extracts were evaporated to dryness and the residue was chromatographed on silica gel to give **5a** (0.27 g), which was homogeneous in TLC, gas chromatography, and HPLC. **5a**; IR: 1740 cm^{-1}; NMR ($CDCl_3$): 3.63 and 3.73 (2× 3H, s, $COOCH_3$) and 1.20 (3H, d, J=5 Hz, CH_3); Found: C, 58.18; H, 7.14%. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%.

Similarly, **4b** and **4c** were hydrogenated and decarboxylated. In each case there was only one spot on TLC, but the NMR spectra of the methyl group showed three components. These mixtures were separated into two fractions by HPLC. The first fraction showed a doublet signal at 1.13 ppm assignable to the methyl of **5b**, the second fraction two doublet signals at 1.20 and 0.96 ppm, to which were assigned **5a** and **5d**, respectively.

A Mixture of Dimethyl 5,5-Dimethyl-3-ethoxycarbonylmethylene-2-hydroxy-1-cyclopentene-1,4-dicarboxylate ***4c*** *and Its Olefinic Isomer* ***4e****.* A solution of **2b** (25.1 g) and **3b** (72.3 g) in chloroform was stirred at 60 °C for 5 days. After evaporation of the solvent *in vacuo*, the residue was added to ether and the precipitate of the unreacted **3b** was filtered off. The filtrate was washed with 8% HCl and then 10% aqueous K_2CO_3, and evaporated *in vacuo*. The residue was redissolved in diisopropyl ether and stored in a refrigerator to give triphenylphosphine oxide. After removal of Ph_3PO by filtration, evaporation of the filtrate gave a reddish oil which was chromatographed on acid-washed silica gel to give a mixture of **4c** (*exo*) and **4e** (*endo*) (8.21 g). MS: *m/e* 312 (M^+); IR: 1740, 1710, and 1655 cm^{-1}; NMR ($CDCl_3$): 10.5 (s, OH) and 6.4 (d, olefin).

Methyl t*-2-Methoxycarbonyl-*c*-3-methyl-5-oxocyclopentane-*r*-1-acetate* ***5a*** *and 3,3-Dimethyl Derivative* ***5c****.* A solution of the crude Wittig products, obtained from α-dienol **2a** (6.84 g) and 10% Pd–C (4.0 g) in methanol was hydrogenated under atmospheric pressure. After filtration and evaporation *in vacuo*, the oily residue was refluxed in concd HCl for 3 h. The reaction mixture was evaporated to dryness *in vacuo*, and reesterified with CH_2N_2 in ether to give crude **5a** which was equilibrated with NaOMe in methanol at room temperature for 12 h. The chromatography of the crude oil on a silica gel column gave the oil **5a** (3.17 g). MS: *m/e* 228 (M^+); IR: 1740 cm^{-1}; NMR ($CDCl_3$): 3.75 and 3.66 (2× 3H, s, $COOCH_3$) and 1.20 (3H, d, J=5 Hz, CH_3). Found: C, 57.69; H, 7.14%; Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%.

A similar procedure starting from the crude Wittig products **4c** and **4e** (8.20 g) afforded **5c** (5.03 g), which was homogeneous in TLC; no isomerization was observed after the treatment of **5c** with NaOMe–methanol. MS: *m/e* 242 (M^+); IR: 1740 cm^{-1}; NMR ($CDCl_3$): 1.40 and 1.00 (2× 3H, s, CH_3). Found: C, 59.23; H, 7.42%. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%.

*c-5-Hydroxy-*t*-2-methoxycarbonyl-*c*-3-methylcyclopentane-*r*-1-acetic Acid γ-Lactone* ***6a*** *and 3,3-Dimethyl Derivative* ***6b****.* To a stirred solution of **5a** (2.28 g) in tetrahydrofuran at 0 °C under argon was added dropwise a solution of 0.5 M/L potassium tri-*s*-butylborohydride in tetrahydrofuran (22 ml). The mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of 4% HCl. The resulting mixture was diluted with brine and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude oil. The oil was chromatographed on silica gel to give **6a** (1.34 g). IR: 1775, 1740, and 1735 cm^{-1}; NMR ($CDCl_3$): 5.0 (1H, m, lactone), 3.71 (3H, s, $COOCH_3$), and 1.10 (3H, d, J=5.5 Hz, CH_3). Found: C, 60.37; H, 7.25%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

A similar procedure starting from **5c** (5.53 g) afforded **6b** (2.27 g). Mp 69.5—71 °C; MS: *m/e* 212 (M^+); IR: 1775, 1765, and 1730 cm^{-1}; NMR ($CDCl_3$): 4.96 (1H, dt, J=7 and 5 Hz, lactone), 3.70 (3H, s, $COOCH_3$), 1.24 and 0.90 (2× 3H, s, CH_3). Found: C, 62.40; H, 7.61%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

t*-2-Carboxy-*c*-5-hydroxy-*c*-3-methylcyclopentane-*r*-1-acetic Acid γ-Lactone* ***7a*** *and 3,3-Dimethyl Derivative* ***7b****.* A solution of **6a** (1.32 g) in concd HCl was refluxed for 2 h. The resulting solution was evaporated *in vacuo* and the residue was recrystallized from benzene–diisopropyl ether to give the lactone acid **7a** (0.803 g). Mp 116—117 °C; NMR ($CDCl_3$): 10.7 (1H, s, COOH), 5.00 (1H, m, lactone), and 1.17 (3H, d, J=5 Hz, CH_3). Found: C, 58.43; H, 6.35%. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%.

Similarly, **6b** (2.27 g) was converted by the same procedure into **7b** (1.51 g). Mp 179.5—181 °C; MS: *m/e* 198 (M^+); NMR (acetone-d_6): 8.2 (1H, bs, COOH), 5.0 (1H, dt, J=7 and 5 Hz, lactone), 1.32 and 0.93 (2× 3H, s, CH_3). Found: C, 60.34; H, 7.17%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

*c-5-Hydroxy-*t*-2-hydroxymethyl-*c*-3-methylcyclopentane-*r*-1-Acid*

γ-Lactone 8a and 3,3-Dimethyl Derivative 8b. To a solution of **7a** (0.75 g) and triethylamine (0.572 g) in tetrahydrofuran at 0 °C under argon was added ethyl chloroformate (0.61 g) in tetrahydrofuran. After 1 h, the precipitate was filtered off from the reaction mixture. To the filtrate was added dropwise a solution of $NaBH_4$ (0.643 g) in water at 0 °C and the mixture was stirred at ambient temperature for an additional 1 h. After cooling to 0 °C, 8% HCl was added to the reaction mixture, and extraction was carried out with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude oil. This was chromatographed on silica gel to afford the lactone alcohol **8a** (0.552 g). MS: *m/e* 170 (M^+); IR: 3500 and 1770 cm^{-1}; NMR ($CDCl_3$): 4.90 (1H, m, lactone), 3.4—4.0 (3H, m), and 1.07 (3H, d, J=6 Hz, CH_3). Found: C, 63.47; H, 8.18%; Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Similarly, **7b** (1.50 g) was converted by the same procedure into the oil **8b** (1.03 g). MS: *m/e* 184 (M^+); IR: 3450 and 1770 cm^{-1}; NMR ($CDCl_3$): 4.92 (1H, dt, J=7 and 5 Hz, lactone), 3.3—4.0 (3H, m), 1.16 and 0.82 (2× 3H, s, CH_3). Found: C, 65.03; H, 8.72%; Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

*3,3-Dimethyl-*c*-5-hydroxy-*t*-2-(3-oxo-*trans*-1-octenyl)cyclopentane-*r*-1-acetic Acid γ-Lactone* **9**. To a stirred solution of the Collins reagent prepared from CrO_3 (4.04 g) and pyridine (6.25 ml) in dichloromethane at 0 °C under argon was added a solution of **8b** (1.03 g) in dichloromethane. The resulting solution was stirred at 0 °C for 5 min and then at ambient temperature for 20 min, and added to ether. The precipitate was filtered and the filtrate was washed with 4% sodium hydroxide, water, 4% HCl, water, 3% $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated to give a crude aldehyde (0.92 g). To the solution of this aldehyde in ether was added a solution of (2-oxoheptylidene)tributylphosphorane (2.32 g) in dry ether. The mixture was stirred at ambient temperature for 6 h under argon. After evaporation of the solvent, the residual oil was chromatographed on silica gel to give the enone **9** (1.18 g). IR: 1775, 1700, 1675, and 1630 cm^{-1}; NMR ($CDCl_3$): 6.7 (1H, dt, J=16 and 8 Hz, olefin), 6.1 (1H, d, J=6 Hz, olefin), 5.0 (1H, dt, lactone), and 0.9 (2X 3H, s, CH_3). Found: C, 73.37; H, 9.44%. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%.

*3,3-Dimethyl-*c*-5-hydroxy-*t*-2-[(3S*)-hydroxy-*trans*-1-octenyl)]-cyclopentane-*r*-1-acetic Acid γ-Lactone* **10**. A solution of **9** (1.37 g) and $NaBH_4$ (0.205 g) in absolute methanol was stirred at 0 °C for 1 h under argon. The reaction mixture was quenched by addition of aqueous acetic acid. The resulting solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give a crude oil. The oil was separated into a less polar oil (0.655 g) and a more polar crystalline part (mp 53—54 °C) (0.562 g) by preparative thin layer chromatography. The former was assigned tentatively as the 15*S**-hydroxy lactone **10** and the latter as the 15*R**-hydroxy epimer. **10**: MS: *m/e* 280 (M^+); IR: 3450 and 1770 cm^{-1}; NMR ($CDCl_3$): 5.4—5.6 (2H, m, olefin), 5.0 (1H, m, lactone), 4.1 (1H, m, >CH–O), 1.0 and 0.8 (2× 3H, s, CH_3). Found: C, 72.88; H, 9.91%; Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%.

*3,3-Dimethyl-*c*-5-hydroxy-*t*-2-[(3S*)-(tetrahydropyranyloxy)-trans-1-octenyl]cyclopentane-*r*-1-acetaldehyde γ-Lactone* **11**. A solution of **10** (0.641 g), dihydropyran (0.5 ml), and a catalytic amount of *p*-toluenesulfonic acid in dry dichloromethane was stirred at 0 °C for 20 min. After the addition of a few drops of pyridine, the reaction mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give an oil. This oil was chromatographed on aluminum oxide (Woelum grade III) to give a tetrahydropyranylated lactone (0.864 g). NMR ($CDCl_3$): 4.6 (1H, m, O–CH–O). To a stirred solution of the tetrahydropyranylated lactone in toluene at −70 °C under argon was added a solution of 25% diisobutylaluminium hydride (4 ml) in toluene. After 1.5 h the reaction was quenched by addition of methanol. The resulting mixture was allowed to warm to ambient temperature with stirring and water was added. The mixture was filtered through celite, and washed with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude oil. The oil was chromatographed on silica gel to give **11** (0.612 g). MS: *m/e* 366 (M^+); IR: 3425 cm^{-1}; NMR ($CDCl_3$): 5.2—5.7 (3H, m), 1.0 and 0.8 (2× 3H, s, CH_3). Found: C, 71.78; H, 10.48%; Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45%.

11,11-Dimethyl-15-(tetrahydropyranyloxy)prostaglandin E_2 **12**. To a solution of sodium 5-(triphenylphosphoranylidene) pentanoate prepared from (4-carboxybutyl)triphenylphosphonium bromide (3.82 g) and NaH (0.78 g) in DMSO under argon was added **11** (0.592 g) in DMSO. The mixture was allowed to stand at room temperature for 2 h. The reaction mixture was poured into ice–water, acidified with acetic acid, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give a crude oil. To a solution of the Collins reagent (2.32 g) in dichloromethane at 0 °C under argon was added a solution of the crude oil in dichloromethane. The resulting mixture was stirred at ambient temperature for 30 min and added to ether. The mixture was then filtered through celite. The filtrate was washed with 4% HCl and evaporated to give an oily residue. The residue was chromatographed on silica gel to give **12** (0.467 g). IR: 1740, 1710, and 1020 cm^{-1}; NMR ($CDCl_3$): 10.0 (1H, bs, COOH), 5.0—5.7 (4H, m, olefin), 1.2 and 0.9 (2× 3H, s, CH_3). Found: C, 71.99; H, 9.92%; Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89%.

11,11-Dimethylprostaglandin E_2 **1b**. A solution of **12** (0.467 g) in acetic acid, water, and tetrahydrofuran (20: 10: 3) was heated at 40 °C for 6 h. The solvent was evaporated azeotropically with toluene *in vacuo*. The residue was added to water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give an oily residue. The crude product was chromatographed on an acid-washed silica gel to give **1b** (0.267 g). MS: *m/e* 364 (M^+); IR: 3450 and 1740 cm^{-1}; NMR ($CDCl_3$): 6.9 (2H, bs, COOH and OH), 5.1—5.7 (4H, m, olefin), 4.1 (1H, m, $C_{15}H$), 1.1 and 0.9 (2× 3H, s, CH_3). Found: C, 72.62; H, 9.80%; Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96%.

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