11-Deoxy-11α, 12α-methanoprostaglandin E_2, a Potent, Short-Acting Bronchodilator[1]

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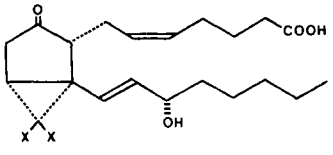
Abstract □ 11-Deoxy-11α,12α-methanoprostaglandin E_2 (**1b**) and the corresponding methyl ester **7a** were highly potent, but short acting, bronchodilators both by the intravenous (80 and 10 times PGE_2, respectively) and aerosol (2 and ~1 times PGE_2) routes, as measured by the Konzett–Rössler assay. The 11β,12β-methano compound **15a** was two orders of magnitude less active than **7a**. In rhesus monkeys anesthetized by aerosol administration, **1b** was 10–50% as potent as, and had a duration of action similar to, PGE_1 in the inhibition of methacholine-induced increases in airway resistance. At doses effective in preventing the methacholine response, **1b** increased the heart rate (≤30%) and precipitated mild upper airway irritation.

The synthesis of 11-deoxy-11α,12α-difluoromethanoprostaglandin E_2 (**1a**) was reported over 10 years ago by Crabbé and Cervantes.[2] This compound was found to be particularly effective in the inhibition of histamine induced increases in airway resistance in guinea pigs, but the level of activity as a bronchodilator in mildly asthmatic humans was discouragingly low.[3] It therefore became of interest to compare the spectrum of activity of this compound with the corresponding 11α,12α-methano compound **1b**, the synthesis and bronchodilator activity of which are described in this paper.

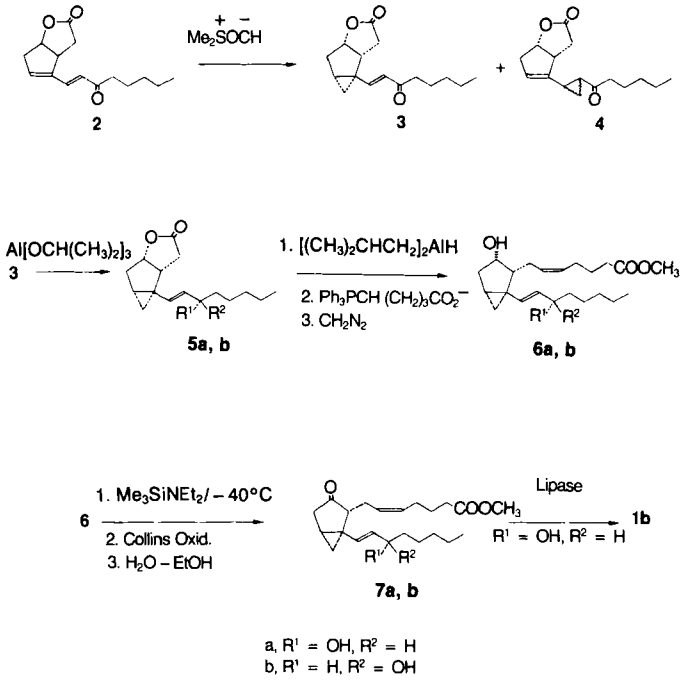


1a, X = F

b, X = H

Results and Discussion

Chemistry—The process which was used to provide access to the title compound was based on the methylenation of the conjugated dienone lactone **2**[3] with dimethylsulfoxonium methylide,[4] a reaction for which there is ample precedent in the steroid field[5] (Scheme I). Under carefully controlled conditions (see *Experimental Section*), a mixture of two products was obtained in low, but reproducible, yield. The major compound (9%) was shown to be the desired enone **3** (see below) while the less abundant (7%) compound **4** (presumably an epimeric mixture) was derived from 1,4–addition of the ylid to the dienone system. There are two noteworthy aspects of this result. First, Radüchel et al.[6] were unable to effect methylenation of **2** under apparently similar conditions. Second, the exclusive formation of the α-methano isomer **3** was unexpected on the basis of steric approach control considerations. A possible rationalization of the apparent stereospecific generation of **3** is that on nearing the less hindered face of the dienone terminus, the ylid preferentially abstracts the acidic, allylic, exo proton with expulsion of the trans coplanar lactonic alkyl oxygen. The cyclopentadiene thus formed would be lost as dimers or polymers. In contrast, attack of the ylid from the endo face of the molecule, though considerably less favorable, can only lead to the observed product.[7]



Scheme I

The transformation of the enone **3** into **1b** was then accomplished as follows. Reduction of **3** with aluminum isopropoxide[8] in refluxing toluene gave an equimolar mixture of the less and more polar 15α (**5a**) and 15β (**5b**) alcohols[9] which were separated by TLC (thin-layer chromatography). The individual alcohols were subjected to reduction with diisobutylaluminum hydride, Wittig olefination with the sodium salt of 5-triphenylphosphoranylpentanoic acid[10] and esterification with diazomethane. The 9,15-diols **6a** and **6b** thus produced were indistinguishable, except for the absence of optical activity, from authentic specimens of the diols synthesized from 11-deoxy-11α-hydroxymethylprostaglandin E_2.[11] Selective silylation of **6a** and **6b** with trimethylsilyldiethylamine followed by Jones oxidation and desilylation[12] gave the epimeric 9-oxo methyl esters **7a** and **7b**. The 15α stereochemistry was assigned to **7a** on the basis of a greater

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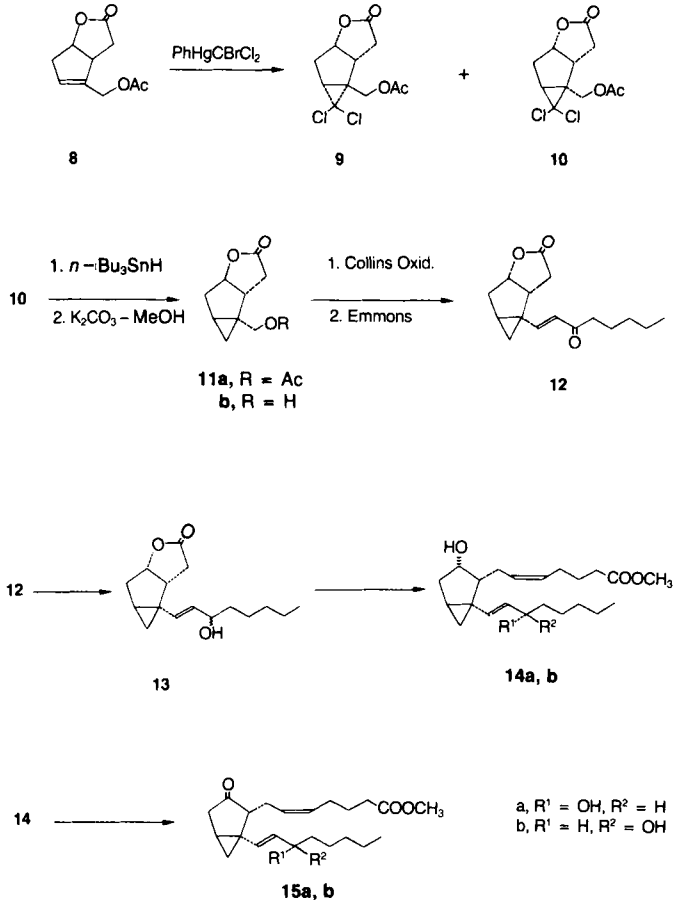
inhibition (intravenous administration) of the histamine induced bronchoconstriction in anesthetized guinea pigs[13] (Table I). The conversion of **7a** into the carboxylic acid **1b**[14] was effected enzymatically with a lipase from a Candida species.

The synthesis of the 11β,12β-methano isomers **15a** and **15b** of **7a** and **7b** was based on the dichloromethylenation of the bicyclic allylic acetate 8 (Scheme II). Thus, when a benzene solution of phenyl(bromodichloromethyl)mercury[15] and 8 (2.7:1 organomercurial:olefin ratio) was heated at reflux temperature (71°C in Mexico City) a 65:1 mixture of the β- and α-adducts **10** and **9** was isolated in nearly quantitative yield. The β-configuration of the cyclopropane ring in **10** was assigned on the basis of the NMR chemical shifts of the 8β- and 9β-hydrogen atoms (prostaglandin numbering) which appeared as multiplets at δ 3.24 and 4.84 ppm, considerably upfield from the 8β (δ 3.79 ppm) and 9β (δ 5.17 ppm) protons in **9**. These chemical shifts are similar to those previously observed for the products of the addition of chlorofluoro carbene to the enone **2**.[16] The dechlorination of **10** was accomplished with tri-*n*-butyltin hydride in refluxing toluene (102°C in Mexico City)[17] and the acetate **11a** so obtained was converted into the primary alcohol **11b** with methanolic potassium carbonate. Oxidation of the alcohol with Collins reagent[18] gave the aldehyde which was condensed, without purification, with dimethyl 2-oxoheptylphosphonate. The physical properties of the enone **12** thus formed were distinctly different from those of the 11α,12α-methano compound **3**. In particular, the former was crystalline whereas the latter was an oil. Furthermore, as expected, the NMR absorption for the H-8 and H-9 protons (δ 3.12 and 4.73 ppm) of **12** were at higher field than the corresponding protons in **3** (δ 3.23 and 4.98 ppm). The enone **12** was then converted into **15a** and **15b** by a reaction sequence identical to that used for the synthesis of **7a** and **7b** except that the separation of the epimeric 15-hydroxy compounds was carried out after the introduction of the upper side chain. Compound **15a**, derived from the less polar diol **14a**, was assumed to possess the 15α-configuration because of its superior intravenous bronchodilator activity (Table I).

Table I—Relative Bronchodilator Potency of 11,12-Methano Prostanoic Acids

Compound	Relative Potency in Guinea Pigs	
	Intravenous	Aerosol
(−)-PGE_2	1	1
1a	4	1
1b	80	2
7a	10	0.5-1
7b	0.08	N.T.[a]
15a	~0.1	N.T.
15b	<0.05[b]	N.T.

[a] N.T. = not tested. [b] Inactive at 20 μg.



Scheme II

Bronchodilator Activities—The bronchodilator activities of the 9-oxoprostaglandins were evaluated initially by the intravenous route using a Konzett–Rössler type assay[13] in guinea pigs bronchoconstricted with histamine (see the *Experimental Section*). Compounds **1b** and **7a** were exceedingly active in this assay being ~80 and 10 times as effective (Table I) as PGE_2 for the inhibition of the response to histamine (measured 1 min post-histamine challenge). These potencies are, to our knowledge, the greatest ever documented for this assay,[19] but the duration of action is relatively short as indicated by the responses to histamine challenges after 6 and 11 min (Table II). The 11β,12β-methano compound **15a** was about two orders of magnitude less active than **7a**.

The bronchodilator activities of **1b** and **7a** were also studied in guinea pigs via aerosol administration. By this route, **1b** was about twice as potent as PGE_2 while the ester **7a** approached the potency of the standard. Neither **1b** nor **7a** were particularly long acting by this route. In contrast, the difluoromethano compound **1a** at comparable doses (e.g., 1

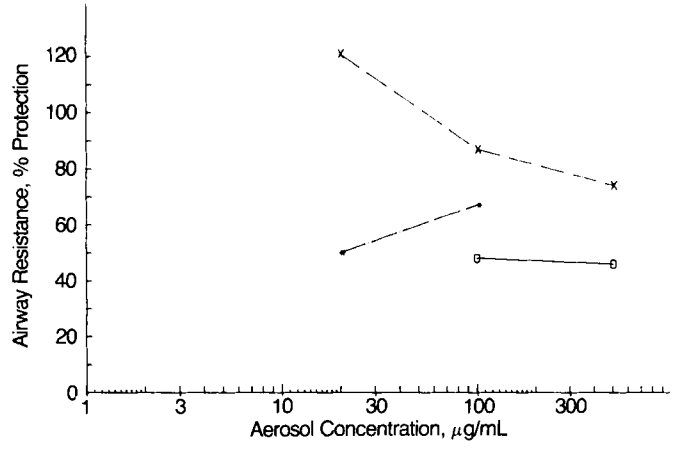


Figure 1—*Effect of aerosolized 11-deoxy-11α, 12α-methano PGE_2 on the pulmonary airway resistance of three anesthetized and spontaneously breathing rhesus monkeys challenged with aerosol inhalations of methacholine. Key: (*) rhesus monkey #453; (×) rhesus monkey #447; (○) rhesus monkey #446.*

Table II—Inhibition of Histamine Induced Increased Airway Resistance in Guinea Pigs by 11,12-Methano Prostanoic Acids

Compound	Intravenous Dose, μg	Aerosol Conc., μg/3 mL	No. of Animals	Mean Percent Inhibition Histamine Response		
				Initial	6 min	11 min
(−)-PGE_2	0.5		4	15(0–27)[a]	0	
	1		5	41(25–60)	0	
	2		4	82(69–94)	0	
	4		4	82(74–93)	0	
	8		2	86(82,89)	0	
		1	2	38(20,55)	16(13,18)	0
		3	2	81(71,91)	60(29,91)	69(64,73)
1a	0.063		2	19(31,6)	0	
	0.125		2	33(23,43)	11(0,22)	
	0.25		2	50(66,33)	0	
	0.5		2	64(58,70)	36(37,35)	38(32,43)
		1	2	32(0,63)	47(43,50)	48(57,38)[b]
		3	2	44(42,45)	53(42,64)	61(67,55)[c]
1b	0.005		2	0		
	0.01		2	4(0,8)	0	
	0.02		4	76(62,90)	0	
	0.04		2	76(71,80)	0	
	0.2		2	100	58(35,80)	18(0,35)
		0.1	2	0		
		0.3	4	8(0,21)		
		1	5	76(60–88)	36(0–73)	28(0–67)
7a	0.04		5	16(0–50)	3(0–13)	
	0.08		6	43(0–65)	14(0–35)	13(0–45)
	0.16		4	68(54–85)	14(0–50)	3(0–12)
	0.32		3	75(71–77)	54(46–62)	39(29–54)
	0.63		1	67	20	0
	1.25		1	61	78	0
	2.5		2	86(75,96)	44(10,77)	27(0,53)
		0.1	2	11(0,22)	6(0,11)	0
		1	3	34(19–55)	24(19–27)	23(9–36)
		10	3	88(63–100)	79(63–88)	44(33–56)
15a	2		2	0		
	20		3	78	0	

[a] Individual responses or range of measured responses. [b] At 16 min, percent inhibition was 34(43,25). [c] At 16 min, percent inhibition was 66(67,64).

μg/3 mL; Table II) still showed substantial inhibition 16 min after the methacholine challenge. The carboxylic acid **1b** was also subjected to preliminary evaluation by aerosol inhalation in anesthetized, spontaneously breathing, adult rhesus monkeys bronchoconstricted with methacholine and connected to a recorder to measure pulmonary compliance, airway resistance, respiration, and heart rates. As judged by the inhibition of the methacholine induced airway resistance changes (Fig. 1), **1b** was 10–50% as potent as, and had a duration of activity similar to, PGE_1[20] (~1 h). At doses which protected against the methacholine responses, mild cardiac stimulation (≤30%) and relatively minor increases in respiration rate (≤57%) were observed. This latter response was interpreted as evidence of mild upper airway irritation. It is noteworthy that in one monkey (#447) the baseline respiratory function was improved even in the absence of the challenge. This is usually the hallmark of a potent bronchodilator.

Experimental Section

Bronchodilator Assays in Guinea Pigs (Histamine Challenge)—*Intravenous*—This assay was conducted according to published procedures.[13] Female guinea pigs weighing 400–500 g were anesthetized with urethane (1 g/kg ip), and both the trachea and jugular vein were cannulated. The tracheal cannula (plastic tube) was attached to a Harvard ventilator and pressure transducer to measure changes in respiratory resistance. The jugular cannula (a 22-gauge needle) permitted injection of the intravenously administered materials. Recordings were made with a Harvard Biograph. A standard histamine challenge was given to determine the sensitivity of the animals to histamine. Five minutes later the test material was given intravenously followed by a second histamine challenge after dosing with the test material. Repeated histamine challenges were given to determine the duration of action of the test substance.

Aerosol—Female guinea pigs (400–500 g) were anesthetized, cannulated, etc., as described above, except that a Monaghan ultrasonic nebulizer was inserted in series between the ventilator and the animal. A standard histamine challenge was given to determine the sensitivity of the animals to histamine. Five minutes thereafter the test substance was given by aerosol followed by a second histamine challenge after dosing with the test material. Repeated histamine challenges were given to determine the duration of action of the test material.

Rhesus Monkey Bronchodilator Test (Methacholine Aerosol Challenge)—The experiments were carried out with adult female rhesus monkeys (6–9 kg). Each animal was sedated with ketamine, the trachea was intubated with a Murphy type inflatable endotracheal tube, and then the animal was placed under methoxyflurane anesthesia for the duration of the experiment (the breathing being spontaneous). The respiratory airflow was monitored via a screen type (Hewlett-Packard) pneumotachograph. An air-filled polyethylene cannula was introduced into the pleural space. The pleural pressure was measured by connecting one end of a Statham PC 131

differential pressure transducer into the cannula, the other end of the tube led to the mouth. The tidal volume, respiration rate, pulmonary compliance (zero flow method), and airway resistance (isovolumetric technique) were calculated electronically on a breath-to-breath basis by an on-line analog computer. The heart rate was obtained from the EKG recordings. The respiratory challenge consisted of aerosolized methacholine inhalations administered at 30-min intervals. The test compound was given 5 min prior to the challenge. Aerosols were generated by a Monaghan ultrasonic nebulizer. The test compound was dissolved in Sorensen's phosphate buffer (pH 6–8). The effect of the test compound was calculated as the percent protection according to Dennis et al.[21]

Chemistry—All melting points were determined in a Mel-Temp apparatus and are uncorrected. The IR spectra were measured on a Perkin-Elmer model 267 grating IR spectrophotometer in chloroform solution (unless stated otherwise). The NMR spectra were recorded with a Varian T-60 NMR spectrometer or a Varian HA-100 NMR spectrometer in $CDCl_3$ solution. The chemical shifts are expressed in parts per million (δ) from internal Me_4Si. The high resolution MS were measured on TLC pure compounds with a Varian-MAT 311A mass spectrometer.

The term "dried" signifies that the solution was dried over anhydrous $MgSO_4$ or Na_2SO_4. The term "worked up in the usual way" means that the solution was washed with saturated NaCl solution, and after drying, the solution was evaporated under reduced pressure. All TLC separations were effected on silica gel plates. All oils were colorless and not distillable without extensive decomposition (even under high vacuum).

Reaction of Dienone 1 with Dimethylsulfoxonium Methylide—A dispersion of sodium hydride in mineral oil (50%, 0.048 g, 1.00 mmol) was washed free of the carrier with dry hexane in an atmosphere of argon, and then anhydrous Me_2SO (2 mL) was added to the washed sodium hydride. The suspension was cooled in an ice–salt bath and trimethyl sulfoxonium iodide (0.022 g, 1.00 mmol) was added with stirring. The cooling bath was removed and after 30 min at room temperature, when the evolution of hydrogen was complete, a solution of the dienone 1 (0.250 g, 1.00 mmol) in dry Me_2SO (2 mL) was added. Agitation at room temperature was continued for 15 min and the mixture was poured into cold, dilute, aqueous oxalic acid solution. The products were extracted into ethyl acetate, the extract was washed to neutrality with saturated NaCl solution, and then dried. The solvent was removed under reduced pressure and the residue was subjected to preparative TLC using hexane:ethyl acetate (7:3) as the developing solvent. In this way the methano compounds 3 (0.025 g, 9%) and 4 (0.018 g, 7%) were obtained together with a small amount (0.010 g) of the starting material. The 11α,12α-methano compound 3 was an oil; IR: 1775, 1688, 1663, and 1613 cm^{-1}; ^1H NMR: δ 0.92–1.87 (m, 14), 2.31–2.75 (m, 4), 3.04–3.42 (m, 1), 4.98 (m, 1, H-9), 6.05 (d, 1, J = 15.7 Hz, H-14), and 6.58 ppm (d, 1, J = 15.7 Hz, H-13); MS: calc. for $C_{16}H_{22}O_3$ (molecular ion) *m/z* 262.1569, found *m/z* 262.1576.

The 13,14-methano compound 4 also was an oil; IR: 1773, 1694, and 1613 cm^{-1}; ^1H NMR: δ 0.44 (m, 1), 0.87 (t, 3, J = 6.5 Hz, CH_3), 0.95–2.18 (m, 10), 2.35–2.75 (m, 4), 3.00 (m, 1), 3.41 (m, 1), 5.06 (m, 1, H-9), and 5.25 ppm (m, 1, H-11); MS: calc. for $C_{16}H_{22}O_3$ (molecular ion) *m/z* 262.1569, found *m/z* 262.1579.

Reduction of the Enone 3 with Aluminum Isopropoxide—A solution of the methano compound 3 (0.700 g, 2.66 mmol) in anhydrous toluene (25 mL), containing freshly distilled aluminum isopropoxide (1.63 g), was heated at reflux temperature for 4 h. The cooled solution was diluted with ethyl acetate and then a saturated aqueous solution of sodium tartrate (28 mL) was added. The mixture was stirred for 10 min, and the organic phase was separated and worked up in the usual way. The residual mixture of **5a** and **5b** was separated by TLC using hexane:ethyl acetate (3:2) as the developing solvent. This process gave the less polar alcohol **5a** (0.290 g, 41%) and the more polar alcohol **5b** (0.296 g, 42%). The less polar isomer **5a** was an oil; IR (KBr): 3460, 1773, and 1668 cm^{-1}; ^1H NMR: δ 0.57–0.94 (m, 5, CH_3 and 1α,12α CH_2), 1.18–1.50 (m, 8), 1.65–2.93 (m, 6), 3.17 (m, 1), 4.01 (m, 1, H-15), 4.90 (m, 1, H-9), and 5.40 ppm (m, 2, H-13,14); MS: calc. for $C_{16}H_{24}O_3$ (molecular ion) *m/z* 264.1725, found *m/z* 264.1730.

The more polar alcohol was obtained as an oil which crystallized on standing. After crystallization from ether:hexane it had a melting point of 63–65°C; IR (KBr): 3535, 3330, 1770, and 1665 cm^{-1}; ^1H NMR: δ 0.30–0.57 (m, 1), 0.65–0.93 (m, 4), 1.10–1.47 (m, 8), 1.77–2.93 (m, 6), 3.19 (m, 1), 4.02 (m, 1), 4.89 (m, 1), and 5.38 ppm (m, 1); MS: calc. for $C_{16}H_{24}O_3$ (molecular ion) *m/z* 264.1725, found *m/z* 264.1730.

Methyl 9α,15α-Dihydroxy-11-deoxy-11α,12α-methanoprosta-5-*cis*-13-*trans*-dienoate (6a)—A toluene solution of diisobutylaluminum hydride [1.07 mL (1.51 mmol) of a solution made from the commercial reagent (1 mL; Aldrich Chem. Co.) and dry toluene (3 mL)] was added to a stirred solution of the less polar alcohol **5a** (0.200 g, 0.756 mmol) in anhydrous toluene (10 mL) cooled to −60°C. After 15 min at −60°C, the excess hydride reagent was destroyed by the addition of a few drops of methanol and, 10 min thereafter, the gel which had formed was diluted with ether (30 mL). After a further 30 min stirring, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give the crude lactol (0.200 g) which was used immediately as described below. A 2 M solution of sodium methylsulfinyl carbanion in Me_2SO (3.58 mL) was added to a stirred solution of 5-triphenylphosphoranylpentanoic acid (1.67 g, 3.77 mmol) in dry Me_2SO. After 10 min, the above lactol, dissolved in the same solvent (3.2 mL), was added and the solution was stirred for 3 h. The reaction was quenched with water and the solution was extracted with a 1:1 ethyl acetate:ether solution (discarded). The aqueous solution was cooled in ice, made acidic to pH 6.5 with saturated aqueous oxalic acid and the solution was extracted with a 1:1 pentane:ether mixture (5 × 10 mL). The extract was worked up in the usual way. The residue was esterified with excess ethereal diazomethane. The crude ester was purified by TLC using CH_2Cl_2:ether (4:1) as the developing solvent. A specimen of **6a** (0.176 g, 64%) that showed one spot on TLC was obtained as an oil; IR: 3625, 3515, 1743, and 1665 cm^{-1}; ^1H NMR: δ 0.58–0.72 (m, 1), 0.88 (m, 3, CH_3), 1.13–1.55 (m, 11), 1.61–1.86 (m, 5), 2.03–2.38 (m, 8), 3.64 (s, 3, OCH_3), 4.01 (m, 1, H-15), 4.24 (m, 1, H-9), and 5.24–5.64 ppm (m, 4, H-5,6,13,14); MS: calc. for $C_{22}H_{36}O_4$ (molecular ion) *m/z* 364.2614, found *m/z* 364.2602.

Methyl 9α,15β-Dihydroxy-11-deoxy-11α,12α-methanoprosta-5-*cis*-13-*trans*-dienoate (6b)—This compound was prepared (32% yield) in the same manner as described for **6a**. A specimen that showed one spot on TLC was obtained as an oil; IR: 3625, 3520, 1733, and 1665 cm^{-1}; ^1H NMR: δ 0.50–0.71 (m, 1), 0.88 (m, 3), 1.12–1.48 (m, 11), 1.55–1.86 (m, 5), 2.03–2.38 (m, 8), 3.65 (s, 3), 4.01 (m, 1), 4.25 (m, 1), and 5.25–5.64 ppm (m, 2); MS: calc. for $C_{22}H_{36}O_4$ (molecular ion) *m/z* 364.2614, found *m/z* 364.2606.

Methyl 9-Oxo-15α-hydroxy-11-deoxy-11α,12α-methanoprosta-5-*cis*-13-*trans*-dienoate (7a)—Trimethylsilyldiethylamine (2.8 mL) was added to a stirred, cooled (−40°C) solution of the "less polar" diol **6a** (0.160 g, 0.43 mmol) in reagent grade acetone (3 mL). After 5 h at −40°C and 4 h at −20°C, anhydrous methanol (2.2 mL) was added, the solution was left to reach room temperature and the solvent was removed under reduced pressure. The crude 15-trimethylsilyl compound (0.177 g), dissolved in anhydrous CH_2Cl_2 (5 mL), was added to a stirred mixture of Celite (1.7 g, dried at 125°C for 24 h) and the chromium trioxide–pyridine complex[17] (0.87 g, 3.2 mmol) in dry CH_2Cl_2 (20 mL) at 0°C. After 10 min at this temperature, the mixture was filtered through a pad of anhydrous $MgSO_4$ and the filtrate was evaporated under reduced pressure at <10°C. The crude 15-trimethylsilyloxy ketone was dissolved in ethanol (5.6 mL) containing water (2.7 mL) and, after 1 h at room temperature, the ethanol was removed under reduced pressure. Ether was added to the residue and the ether phase was worked up in the usual way. The crude product was purified by TLC using hexane:ethyl acetate (7:3) as the developing solvent. Pure **7a** (0.083 g, 56%) was obtained as an oil; IR: 3625, 3505, 1738, 1673, and 951 cm^{-1}; ^1H NMR: δ 0.42 (dd, 1, J_{trans} = 4.5 Hz, J_{gem} = 6.0 Hz, endo methano H), 0.95 (m, 3, CH_3), 1.05 (dd, 1, J_{cis} = 7.5 Hz, J_{gem} = 6.0 Hz, exo methano H), 1.26–1.61 (m, 10), 1.62–1.83 (m, 3), 2.00–2.44 (m, 8), 2.53–2.93 (m, 2), 2.67 (s, 3, OCH_3), 4.13 (m, 1, H-15), and 5.24–5.77 ppm (m, 4, H-5,6,13,14); MS: calc. for $C_{22}H_{34}O_4$ (molecular ion) *m/z* 362.2457, found *m/z* 362.2460.

Methyl 9-Oxo-15β-hydroxy-11-deoxy-11α,12α-methanoprosta-5-*cis*-13-*trans*-dienoate (7b)—The "more polar" 15β-alcohol **7b** was prepared (16% yield) in exactly the same manner as described for **7a**. It was an oil; IR: 3610, 1738, 1669, and 951 cm^{-1}; ^1H NMR: δ 0.55 (dd, 1, J_{trans} = 4.7 Hz, J_{gem} = 6.1 Hz), 0.90 (t, J = 6 Hz, 3), 0.94–1.17 (m, 1), 1.27–1.62 (m, 10), 1.70–1.87 (m, 3), 2.01–2.45 (m, 8), 2.55–2.97 (m, 1), 3.67 (s, 3), 4.15 (m, 1), and 5.25–5.78 ppm (m, 4); MS: calc. for $C_{22}H_{34}O_4$ (molecular ion) *m/z* 362.2457, found *m/z* 362.2450

9-Oxo-15α-hydroxy-11-deoxy-11α,12α-methanoprosta-5-*cis*-13-*trans*-dienoic acid (1b)—A mixture of the ester **7a** (0.020 g), Type VII lipase (0.10 g, from *Candida cylindracea*, Sigma) and pH 7 phosphate buffer (15 mL) was sonicated briefly (1–2 min, Branasonic

12 bath sonicator) and then stirred for 3 h at room temperature (argon atmosphere), and the progress of the reaction was followed by TLC (hexane:ethyl acetate; 6:4, plus trace HOAc). The product was extracted with ethyl acetate and the extract was worked up in the usual way. The residue was purified by centrifugally accelerated TLC (model 7924 Chromatotron, Harrison Research, Palo Alto, CA) on silica gel using hexane:ethyl acetate (4:1). The carboxylic acid (0.016 g) was obtained as an oil; ^{1}H NMR: δ 0.50 (dd, 1, J_{gem} = 6.0 Hz, J_{trans} = 4.6 Hz, endo methano H), 0.89 (t, 3, J = 6.6 Hz, CH_3), 0.99 (dd, J_{gem} = 6.0 Hz, $J_{cis} \simeq$ 7.5 Hz, exo methano H), 1.26–1.40 (m, 8), 1.43–1.75 (m, 6), 2.02–2.22 (m, 6), 2.27–2.38 (m, 3), 4.13 (m, 1, H-15), and 5.34–5.68 ppm (m, 4); MS: calc. for $C_{21}H_{32}O_4$ (molecular ion) *m/z* 348.2301, found *m/z* 348.2296.

Reaction of Phenyl(Bromodichloromethyl)mercury with the Allylic Acetate (8)—A mixture of the allylic acetate 8 (12.0 g, 61.1 mmol) and phenyl(bromodichloromethyl)mercury[15] (73.4 g, 166 mmol) in anhydrous benzene (192 mL) was stirred at reflux temperature for 20 h. The mixture was cooled, filtered, the solid was washed with benzene, and the combined filtrate and washings were evaporated under reduced pressure. The residue was slurried with ether (100 mL), and the insoluble phenylmercuric bromide was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was crystallized from ether to give the 11β,12β-dichloromethano compound **10** (11.96 g). The mother liquor was subjected to column chromatography on silica gel (180 g); the fraction that was eluted with CH_2Cl_2:hexane (1:1) contained more phenylmercuric bromide. Elution with hexane:ethyl acetate (9:1) gave an additional amount of **10** (4.20 g). A mixture of **9** and **10** (~1 g) was removed from the column with hexane:ethyl acetate (7:3). This mixture was subjected to TLC using hexane:ethyl acetate (3:2) as the developing solvent. This process provided a further quantity (0.38 g) of **10** (total 16.54 g or 97% yield) and a small amount of (0.256 g, 1.5% yield) the α-adduct **9**. Crystallization of **9** from methanol gave solid material, mp 150–155°C; IR: 1783 and 1751 cm^{-1}; ^{1}H NMR: δ 2.13 (s, 3, CH_3CO), 2.50–2.87 (m, 5), 3.79 (m, 1, H-8), 4.42 (q, 2, J = 12.3 Hz, CH_2O), and 5.17 ppm (m, 1, H-9).

Anal.—Calc. for $C_{11}H_{12}Cl_2O_4$: C, 47.35; H, 4.34; Cl, 25.42. Found: C, 47.23; H, 4.18; Cl, 25.33.

The β-adduct **10** had a melting point of 80°C; IR: 1786 and 1750 cm^{-1}; ^{1}H NMR: δ 1.98–2.93 (m, 5), 2.10 (s, 3, CH_3CO), 3.24 (m, 1, H-8), 4.47 (s, 2H, CH_2O), and 4.84 ppm (m, H-9).

Anal.—Calc. for $C_{11}H_{12}Cl_2O_4$: C, 47.35; H, 4.34; Cl, 25.42. Found: C, 47.34; H, 4.34; Cl, 25.14.

Reductive Dechlorination of 10 with Tri-*n*-butyltin Hydride—A solution of **10** (5.5 g, 19.7 mmol) in anhydrous toluene (100 mL), containing tri-*n*-butyltin hydride (28.7 g, 98.5 mmol) and azobisisobutyronitrile (0.795 g), was stirred at reflux temperature for 22 h. The solvent was removed under reduced pressure and a 1:1 ethyl acetate:ether mixture (1 L) was added to the residue. The mixture was washed successively with 5% NaOH, water, and saturated sodium chloride. The organic phase was dried, evaporated under reduced pressure, and the residue was crystallized from ether to give the acetate **11a** (2.63 g). The mother liquor was subject to column chromatography on silica gel (100 g) and an additional amount (0.42 g, total of 3.05 g or 74% yield) of the product was eluted with hexane:ethyl acetate (85:15). Compound **11a** had a melting point of 62°C; IR: 1782 and 1743 cm^{-1}; ^{1}H NMR: δ 0.39 (m, 1, endo H), 0.89 (m, 1, exo H), 1.65 (m, 1, H-11), 2.02–3.22 (m, 5), 2.08 (s, 3, CH_3CO), 4.12 (q, 2, J = 12 Hz, CH_2O), and 4.72 ppm (q, 1, J = 6.5 Hz, H-9).

Anal.—Calc. for $C_{11}H_{14}O_4$: C, 62.91; H, 6.72. Found: C, 62.85; H, 6.80.

Hydrolysis of the Acetate 11a—A solution of the acetate **11a** (3.17 g, 15 mmol) in methanol (26.5 mL) containing anhydrous K_2CO_3 (2.09 g, 15 mmol) was stirred at room temperature for 45 min. The mixture was cooled to 0°C and 1 M HCl (30.2 mL) was added with stirring for 5 min. The methanol was evaporated under reduced pressure, and the residual solution was extracted with ethyl acetate. The extract was worked up in the usual way to give the primary alcohol **11b** (2.46 g, 97%), which, on crystallization from ether, had a melting point of 50°C; IR: 3580, 3450, and 1768 cm^{-1}; ^{1}H NMR: δ 0.32 (t, 1, $J_{gem} \simeq J_{trans} \simeq$ 5.7 Hz, endo H), 0.74 (dd, 1, J_{gem} = 5.7 Hz, J_{cis} = 7.3 Hz, exo H), 1.42 (m, 1, H-11), 1.98 (m, 1, 10β-H), 2.20 (dd, 1, J_{gem} = 13.8 Hz, $J_{9\beta,10\alpha}$ = 7.2 Hz, $J_{10\alpha,11} \simeq$ 0 Hz, 10α-H), 2.66 (m, 2, H-7α and H-7β), 3.04 (m, 1, H-8), 3.64 (q, 2, J_{AB} = 11.6 Hz, CH_2O), and 4.70 ppm (q, 1, $J \simeq$ 7 Hz, H-9).

Anal.—Calc. for $C_9H_{12}O_3$: C, 64.35; H, 7.20. Found: C, 64.18; H, 7.12.

Synthesis of the Enone 12—A solution of the alcohol **11b** (2.36 g, 15 mmol) in dry CH_2Cl_2 (30 mL) was added to a stirred suspension of Collins reagent[17] (32 g) and Celite (64 g, dried at 125°C for 24 h) at 0°C. Twenty minutes after the addition was completed, $NaHSO_4$ (64 g) was added and, after an additional 10 min agitation period, the mixture was filtered through a pad of anhydrous $MgSO_4$. The solid was washed with CH_2Cl_2, the combined filtrate and washings were evaporated under reduced pressure at a temperature <10°C, and the crude oily aldehyde [2.32 g (IR: 2720, 1783, and 1709 cm^{-1})] was used directly as described below. Dimethyl 2-oxoheptylphosphonate (3.36 g, 15 mmol) in dry dimethoxyethane (73 mL) was added, at room temperature, to a stirred suspension of sodium hydride [prepared from 50% sodium hydride in mineral oil (0.73 g, 15 mmol) washed free of the carrier with hexane] in dry dimethoxyethane (176 mL, argon atmosphere). After 1 h, a gelatinous mass had formed, and the crude aldehyde dissolved in dry dimethoxyethane (70 mL) was added thereto. The mixture was stirred for 2 h at room temperature and the reaction was quenched with glacial acetic acid (4 mL). Ethyl acetate and water were added to the mixture, the organic phase was separated, and worked up in the usual way. The residue was subjected to preparative TLC using hexane:ethyl acetate as the developing solvent. The enone **12** was obtained as a solid (2.45 g, 67%) which on crystallization from ether had a melting point of 50°C; IR: 1783, 1693, 1668, and 1617 cm^{-1}; ^{1}H NMR: δ 0.67–2.77 (m, 18), 3.12 (m, 1, H-8), 4.73 (q, 1, $J \simeq$ 7 Hz, H-9), and 6.35 ppm (q, 2, J_{AB} = 16.4 Hz, H-13,14).

Anal.—Calc. for $C_{16}H_{23}O_3$: C, 73.20; H, 8.44. Found: C, 73.19; H, 8.50.

Reduction of the Enone 12 with Aluminum Isopropoxide—This reaction was effected in the same manner as described for the reduction of the enone **3**, except that a 4:1 molar ratio of reducing agent to enone **12** was used. The crude product was purified by column chromatography on silica gel (60:1 w/w) using hexane:ethyl acetate (9:1) to elute the product (85% yield). The mixture of alcohols **13** was obtained as an oil; IR: 3625, 3480, 1782, 1672 and 958 cm^{-1}; ^{1}H NMR: δ 0.54 (m, 2, H_{endo} and H_{exo}), 0.90 (m, 3, CH_3), 1.14–2.72 (m, 13), 3.18 (m, 1, H-8), 4.19 (m, 1, H-15), 4.69 (q, 1, $J \simeq$ 6.5 Hz, H-9), and 5.51 ppm (m, 2, H-13, 14); MS: calc. for $C_{16}H_{24}O_3$ (molecular ion) *m/z* 264.1725, found *m/z* 264.1732.

Methyl 9α,15α-Dihydroxy-11-deoxy-11β,12β-methanoprosta-5-*cis*-13-*trans*-dienoate (14a) and Methyl 9α,15β-Dihydroxy-11-deoxy-11β,12β-methanoprosta-5-*cis*-13-*trans*-dienoate (14b)—The mixture of alcohols **13** was subjected to reaction conditions identical to those used to prepare **6a** and **6b**. The crude mixture of alcohols was separated by TLC using CH_2Cl_2:ether (4:1) as the developing solvent. This process gave the less polar 15α-alcohol **14a** (29%) and the more polar 15β-isomer **14b** (31%). The less polar diol **14a** was an oil; IR: 3625, 3545, 1736, 1670, and 957 cm^{-1}; ^{1}H NMR: δ 0.59 (m, 2, H_{endo} and H_{exo}), 0.87 (m, 3, CH_3), 1.24–2.36 (m, 20), 3.61 (s, 3, OCH_3), 3.90–4.16 (m, 2, H-9,15), 5.29 (dd, 1, $J_{13,14}$ = 15.6 Hz, $J_{14,15}$ = 6.8 Hz, H-14), 5.41 (m, 2, H-5,6), and 5.99 ppm (d, 1, $J_{13,14}$ = 15.6 Hz, H-13); MS: calc. for $C_{22}H_{36}O_4$ (molecular ion) *m/z* 364.2613, found *m/z* 364.2627.

The more polar 15β-alcohol **14b** also was an oil; IR: 3625, 3475, 1783, 1670, and 957 cm^{-1}; ^{1}H NMR: δ 0.58 (m, 2), 0.87 (m, 3), 1.24–2.36 (m, 20), 3.62 (s, 3), 3.90–4.15 (m, 2), 5.28 (dd, 1, $J_{13,14}$ = 15.4 Hz, $J_{14,15}$ = 7.2 Hz), 5.47 (m, 2), and 5.99 ppm (d, 1, $J_{13,14}$ = 15.4 Hz); MS: calc. for $C_{22}H_{36}O_4$ (molecular ion) *m/z* 364.2613, found *m/z* 364.2620.

Methyl 9-oxo-15α-hydroxy-11-deoxy-11β,12β-methanoprosta-5-*cis*-13-*trans*-dienoate (15a)—This compound was prepared in the same manner as described for **7a**. The crude product was purified by TLC using CH_2Cl_2:ether (95:5) as the developing solvent. The pure ketone **15a** (50% yield) was obtained as an oil; IR: 3620, 3500, 1740, and 958 cm^{-1}; ^{1}H NMR: δ 0.27 (m, 2, H_{endo} and H_{exo}), 0.87 (m, 3, CH_3), 1.03–2.72 (m, 20), 3.62 (s, 3, OCH_3), 4.07 (m, 1, H-15), 5.44 (m, 3, H-5,6,14), and 6.03 ppm (d, 1, J = 15 Hz, H-13).

Anal.—Calc. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.66; H, 9.64.

Methyl 9-Oxo-15β-hydroxy-11-deoxy-11β,12β-methanoprosta-5-*cis*-13-*trans*-dienoate (15b)—This compound was prepared in the same manner (58% yield) as the isomeric 15-α compound except that CH_2Cl_2:ether (9:1) was used as the TLC developing solvent. Compound **15b** was an oil; IR: 3625, 3520, 1741, and 958 cm^{-1}; ^{1}H NMR: δ 0.27 (m, 2), 0.89 (m, 3), 1.02–2.75 (m, 20), 3.63 (s, 3), 4.05 (m, 1), 5.46 (m, 3), and 6.03 ppm (d, 1, J = 15 Hz).

Anal.—Calc. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.62; H, 9.51.

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