off aseptically, washed with sterile water, and divided in half; each half was then placed into a flask containing 100 mL of fresh medium NL 406. Both flasks received 40 μmol of D,L-ethionine each, along with the respective radioactively labeled precursor which was added as a filtration-sterilized aqueous solution. The cultures were harvested 6 days later and the amino acid fraction was isolated by adsorption on Dowex 50 (H^+), elution with NH_4OH, and removal of the alkaloids with chloroform. Purification of the clavicipitic acid was achieved by TLC of an aliquot of the amino acid fraction (silica gel H, solvent 40:9:1 2-propanol–water–concentrated NH_4OH). The clavicipitic acid was eluted with 50% ethanol and further purified by repeated rechromatography on silica gel G plates until scanning of the plates in a radiochromatogram scanner indicated absence of radioactive contaminants or, in the case of double-labeled samples, until the $^3H/^{14}C$ ratio was constant. It was estimated that there was an 80% loss of clavicipitic acid during each separate chromatography and elution. This value was obtained by averaging the loss of radioactivity encountered in subjecting radiochemically pure clavicipitic acid to this purification procedure. The amount of radioactive clavicipitic acid in the original extract could thus be estimated by back calculation, and this figure was employed in determining the approximate percentage of incorporation.

In experiment 4, Table I, approximately 25 μCi of D,L-[2-^{14}C]mevalonic acid and 100 μCi of D,L-[5-^{3}H]mevalonic acid were added to 20 cultures. In this experiment, the workup followed the methods used for the production of unlabeled clavicipitic acid, and the radioactive material was isolated in crystalline form.

Test for Incorporation of Clavicipitic Acid into Elymoclavine. A solution of 0.18 mg of crystalline radioactive clavicipitic acid (8.4 μCi of ^{14}C/mmol) from experiment 4, Table I, in 2% succinic acid was added aseptically through a Millipore filter to a 6-day-old shake culture of *Claviceps* strain SD 58 which had not been treated with ethionine. After another 5 days the cultures were harvested by filtering off the mycelia, and the alkaloid titer in the culture filtrate was determined colorimetrically with van Urk's reagent.[25,26] Elymoclavine was isolated as described previously[27] by extraction from the alkaline culture filtrate into methylene chloride and chromatography on alumina (Brockmann) using methylene chloride with increasing amounts of methanol (0.5%, 2%) as the eluant. It was recrystallized repeatedly from methanol until the material was used up, and at each crystallization stage the specific radioactivity was determined.

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Registry No. IIa, 33062-26-9; IIb, 72690-85-8.

Supplementary Material Available: Fractional coordinates and temperature factors (Table I), bond distances (Table II), bond angles (Table III), and observed and calculated structure factors for clavicipitic acid (15 pages). Ordering information is given on any current masthead page.

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Synthesis of 15-Methyl-*cis*-Δ^4-prostaglandins[1]

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(15*S*)-15-Methyl-*cis*-Δ^4-prostaglandin $F_{1\alpha}$ methyl ester (**4**) and (15*R*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (**5**) were prepared in three steps from keto acetal **1**. First **1** was allowed to react with methylmagnesium bromide, and the product was then hydrolyzed to remove the methoxyl group and, finally, reacted with sodium 4-(triphenylphosphoranylidene)butyrate and diazomethane to give a mixture of **4** and **5**. After separation, **4** was converted to the free acid **6** by saponification, to (15*S*)-15-Me-*cis*-Δ^4-PGE_1 methyl ester (**7**) by selective silylation, oxidation, and deprotection, and to (15*S*)-15-Me-*cis*-Δ^4-PGD_1 methyl ester (**10**) by selective oxidation with Jones reagent at −40 °C. (15*S*)-15-Me-*cis*-Δ^4-PGA_1 methyl ester (**9**) was prepared from **7**. (15*R*)-15-Me-*cis*-Δ^4-PGE_1 methyl ester (**8**) was prepared from **5**. The lactol **3** was oxidized with silver oxide to give lactones **11** and **12**. Spectral properties were used to assign configurations at C-15 in various of the new products.

The prostaglandins found occurring naturally in most mammalian cells are capable of eliciting various powerful biological responses. The exceedingly rapid metabolism of these compounds renders their biological activity of short duration. The two most rapid modes of metabolic attack upon the prostaglandins are, first, the oxidation of the allylic C-15 alcohol accompanied by reduction of the 13,14 double bond, and, second, the oxidative degradation of the carboxylic acid side chain by the processes of β oxidation.[2]

An early objective for the chemical modification of the prostaglandins was the inhibition of these metabolic processes while maintaining the potent biological activities of the molecules. To this end, the preparation of prostaglandins having, for example, a methyl substituent at C-15,[3] dimethyl substitution at C-16,[4] or a phenyl substituent at C-17 (replacing the C_{18-20} carbons)[5] has had the result of effectively blocking or slowing the metabolic attack at the C_{13}–C_{15} allylic alcohol system.[6] Likewise,

(1) A preliminary account of these results was presented at the International Conference on Prostaglandins, Florence, Italy, May 1975. See: Samuelsson, B.; Paoletti, R. *Adv. Prostaglandin Thromboxane Res.* **1976**, *2*, 873.
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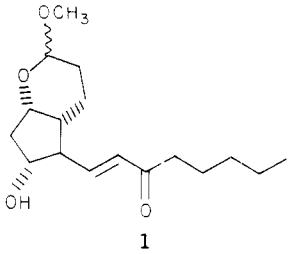
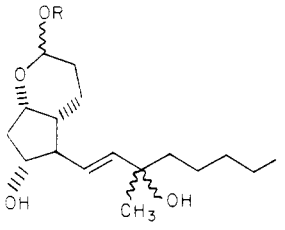
replacement of the normal olefinic carboxylic acid side chain of the 2-series of prostaglandins with, for example, a 3-oxa carboxylic acid[7] may be expected to slow the β-oxidation process. In all these cases the biological activities of the natural prostaglandins were retained in whole or in part.

More recently it has been reported that the relatively minor structural change of shifting the cis double bond, normally present at the C_5–C_6 position, to the C_4–C_5 position greatly influences the metabolism of the acid side chain.[8] Approximately 10–20% of *cis*-Δ^4-$PGF_{1\alpha}$ administered intravenously to rats is excreted unchanged in the urine, whereas under the same conditions no $PGF_{2\alpha}$ is recovered in the urine. From this it is clear that the C-4 cis double bond greatly inhibits the β oxidation of the acid side chain. Consequently, it was desirable to combine this shift in position of unsaturation with several of the modifications known to retard metabolism of the allylic alcohol system. This report describes the chemical synthesis of prostaglandin analogues combining the cis-Δ^4 structural feature with that of the 15-methyl prostaglandins.

As a starting point for the preparation of this analogue family, we chose intermediate **1**, prepared in our earlier synthesis of several prostaglandin metabolites.[9] Structure **1** is analogous to and is derived from intermediates found



1

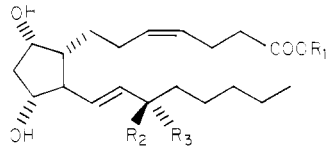


2, R = CH_3
3, R = H

in the total synthesis of the natural prostaglandins.[10] It contains the two features important to introduction of both the cis-Δ^4 and the 15-methyl functionalities. First, the six-membered cyclic acetal contains the potential aldehyde group necessary for attachment of the carboxylic acid side chain via a Wittig reaction. Secondly, the ketone allows introduction of the desired methyl group at the position that ultimately becomes C-15 in the prostaglandin molecule. The reaction of **1** with methylmagnesium bromide was carried out at the temperature of an ice–methanol bath. The reaction was quenched with cold saturated aqueous ammonium chloride and following workup gave an 80% yield of product **2** presumed to be a mixture of epimers at the newly formed tertiary carbinol functionality. These new methyl groups were seen as a single signal (δ 1.28) in the NMR spectrum of the product. That the methyl acetal had survived this treatment was shown by a pair of singlets (δ 3.46 and 3.37) in the NMR spectrum.

Hydrolysis of the acetal functionality, previously a straightforward reaction when the allylic alcohol was secondary,[9] required considerably more delicacy in the case of the tertiary allylic alcohol system of **2**. Reaction of **2** with pH 2 buffer in tetrahydrofuran at room temperature for 20–24 h gave the best yield of desired lactol **3**. Reaction periods shorter than this resulted in incomplete hydrolysis of the acetal while a significantly longer reaction time resulted in loss of **3** due to further side reactions. With this procedure, a 65% yield of lactol **3** was achieved during a large-scale preparation. The most notable spectral property of **3** was the absence of the sharp signals for the methoxyl groups, present in **2**, in the NMR spectrum.

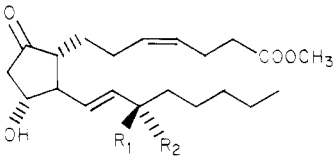
The carboxylic acid side chain was then elaborated by reaction of lactol **3** with the Wittig reagent, sodium 4-(triphenylphosphoranylidene)butyrate. The crude reaction was esterified with diazomethane before purification. Separation of the desired products from the other components of the Wittig reaction gave a yield of 52% of the *R*,*S* isomers. The C-15 epimers can now be separated by chromatography on silica gel. This separation is greatly facilitated by the use of high-pressure liquid chromatography. Following separation of the epimers, there was obtained a 21% yield of the crystalline 15*S* epimer **4** and



4, $R_1 = R_2 = CH_3$; R_3 = OH
5, $R_1 = R_3 = CH_3$; R_2 = OH
6, R_1 = H; $R_2 = CH_3$; R_3 = OH

24% of the 15*R* epimer **5** of 15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester. The free acid, (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ (**6**), was obtained upon saponification of **4**. Esterification of **6** with diazomethane regenerated **4**, which by TLC examination was found to retain epimeric purity at C-15.

The E-series analogues, (15*S*)-15-Me-*cis*-Δ^4-PGE_1 methyl ester (**7**) and (15*R*)-15-Me-*cis*-Δ^4-PGE_1 methyl ester (**8**),



7, $R_1 = CH_3$; R_2 = OH
8, R_1 = OH; $R_2 = CH_3$

were prepared from the PGF compounds **4** and **5**, respectively. In either case, the 11-hydroxyl was protected by the selective preparation of the 11-trimethylsilyl ether derivative.[3] Oxidation of the 9-hydroxyl group to a ketone was then carried out with Collins reagent. Removal of the Me_3Si protecting group gave the desired analogues of the E series.

(15*S*)-15-Me-*cis*-Δ^4-PGA_1 methyl ester (**9**) was prepared from **7** via an intermediate 11-acetate which readily undergoes loss of acetic acid by an elimination reaction. This method for the preparation of compounds of the A series has been described previously by Yankee and colleagues.[3] The presence of the unsaturated ketone functionality is clearly seen in the NMR spectrum of **9**.

The D analogue, (15*S*)-15-Me-*cis*-Δ^4-PGD_1 methyl ester (**10**), was prepared from **4** by selective oxidation of the 11-hydroxyl group with Jones reagent at −40 °C.[11] Under conditions where some starting material is recovered

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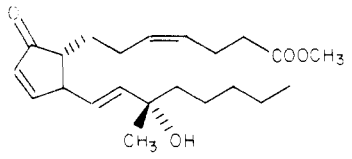
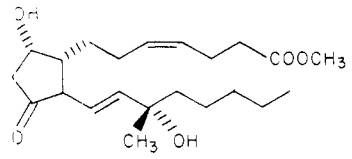


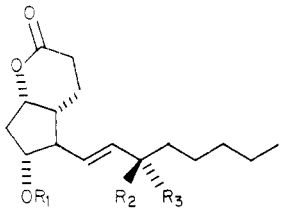
9



10

(17%), the yield of **10** is 49% while 13% of **7**, the corresponding E compound, is formed.

Lactones **11** and **12** were desired and were easily prepared from lactol **3** by oxidation with silver oxide.[9] Preparation of **11**, the 15*S* diastereomer of the lactone



11, R_1 = H; R_2 = CH_3; R_3 = OH
12, R_1 = H; R_2 = OH; R_3 = CH_3
13, R_1 = COC_6H_5; R_2 = CH_3; R_3 = $OCOC_6H_5$
14, R_1 = COC_6H_5; R_2 = $OCOC_6H_5$; R_3 = CH_3

structure, makes available by synthesis one of the mammalian metabolites of either (15*S*)-15-Me-$PGF_{2\alpha}$[6] or (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$.[12] Lactones **11** and **12** have been used in the present work for the preparation of the corresponding 11,15-dibenzoate esters **13** and **14**.

The circular dichroism (CD) spectra of the dibenzoate derivatives **13** and **14** have been measured. Correlation of these CD spectra with those of prostaglandin benzoates of known absolute configurations[13] confirm the assignments of configuration at C-15 used throughout this report. As in the previous work, one diastereomer has a positive band at 255 nm ([Θ] +2860) in the CD spectrum while the other has a weak, negative band at 269 nm ([Θ] −2100). The former is consistent with the 15*S* configuration and the latter with the 15*R* configuration.

Finally, we note that we have confirmed the configuration at C-15 in final products **4** and **5** by correlation of the ^{13}C NMR chemical shifts of the 15-methyl group with those reported previously by Sih and Nash.[14] Compound **4** has a signal at 27.3 ppm in its ^{13}C NMR spectrum (see Table I) for the C-15 methyl group whereas compound **5** has the signal for that carbon at 28.3 ppm. By analogy to the previous assignments, **4** must have the 15*S* configuration and **5** the 15*R* configuration. Similar signals are seen in the spectra of lactones **11** and **12** and are tabulated in Table I.

Table I. ^{13}C NMR Signals for C_{15} Methyl Carbons

compd	signal, ppm 15*S*-CH_3	15*R*-CH_3
15*S*-15-Me-$PGF_{2\alpha}$ methyl ester[a]	27.3	
15*R*-15-Me-$PGF_{2\alpha}$ methyl ester[a]		28.1
15*S*-15-Me-2,3-dinor-$PGF_{2\alpha}$ methyl ester[a]	27.0	
15*R*-15-Me-2,3-dinor-$PGF_{2\alpha}$ methyl ester[a]		28.3
4	27.3	
5		28.3
11	26.8	
12		28.4

[a] Data from ref 14.

Experimental Section

2α,4α-Dihydroxy-5-(3′ε-hydroxy-3′ε-methyl-1′-*trans*-octenyl)cyclopentane-1α-propionaldehyde δ-Lactol Methyl Ether (2). A solution of the ketone **1** (10 g, 33.7 mmol) in ether (1.5 L) was chilled with an ice–methanol bath. The stirred solution was treated by the dropwise addition of methylmagnesium bromide (ethereal, 3 M, 22.5 mL, 67.4 mmol) from a 50-cm^3 syringe. The addition, performed under a dry nitrogen atmosphere, required 10 min. The ice bath was removed, and the mixture was stirred at ambient temperature under nitrogen. The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1). After 3 h, the reaction was again chilled, and another 22.5 mL of methylmagnesium bromide was added. The ice bath was removed, and the reaction was found to be complete after 1 h by TLC evidence. The mixture was poured into an ice-cold saturated ammonium chloride solution (500 mL plus ice). The resulting mixture was extracted with ether. The combined ether layers were washed with brine and dried (Na_2SO_4), and the ether was removed to give 10.6 g (100%) of a pale yellow oil.

The analytical sample was obtained by the chromatography of 238 mg of material on 20 g of silica gel. The column was packed as a slurry with CH_2Cl_2–Skelly B–acetone (1:1:1) and eluted with the same. Fractions with a volume of 4 mL each were collected. The product was obtained in fractions 19–22 (46 mg), 23–32 (115 mg), and 33–52 (39 mg) (total 200 mg, 84%). Fractions 23–32 were used for analysis: IR (liquid film) ν_{OH} 3400, $\nu_{C=C}$ 1660, $\nu_{trans\text{-}CH=CH}$ 908 cm^{-1}; NMR ($CDCl_3$) δ 5.51 (m, 2 H, CH=CH), 4.68 (m, 0.7 H, O—CH—O), 4.33–3.67 (m, 3.3 H, 2 OCH<, 0.3 O—CHOCH$_3$, OH?), 3.46, 3.37 (2 s, 3 H, OCH_3), 1.28 (s, 3 H, 15-CH_3), 0.89 (t, 3 H, J = 5 Hz, CH_3); ORD (in MeOH, plain negative curve) $[\Theta]_{260}$ about +1000, $[\Theta]_{220}$ about −1400; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{24}H_{48}Si_2O_4$ m/e 456.3091, found m/e 456.3114, other peaks m/e 441, 425, 424, 409, 385, 366, 295, 263, 143.

2α,4α-Dihydroxy-5-(3′ε-hydroxy-3′ε-methyl-1′-*trans*-octenyl)cyclopentane-1α-propionaldehyde δ-Lactol (3). A solution of the lactol ether **2** (940 mg, 3.1 mmol) in THF (50 mL) was treated with 50 mL of a pH 2 buffer solution (50 mL of 0.2 M KCl plus 13 mL of 0.2 M HCl) and stirred at room temperature. The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1). The optimal ratio of product to side products and starting material was achieved after 24 h. The reaction was terminated by adding saturated NaCl solution and extracting with methylene chloride. The combined methylene chloride extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to give 918 mg (99%) of a pale yellow oil.

The material obtained (918 mg) was chromatographed on 100 g of silica gel. The column was packed as a slurry and eluted with ethyl acetate, collecting fractions with a volume of 25 mL each. The product was obtained in fractions 38–39 (26 mg), 40–44 (110 mg), and 46–80 (312 mg) for a total of 448 mg of **3** (48.5% of theory) as a colorless oil: NMR ($CDCl_3$) δ 5.51 (m, 2 H, CH=CH), 1.28 (s, 3 H, 15-CH_3), 0.88 (t, 3 H, J = 5 Hz, CH_3), no signal for methoxyl protons.

When this preparation was carried out on a large scale with 91.24 g (0.29 mol) of **2**, there was obtained after chromatography 57.09 g (65%) of **3** as well as 22.97 g of starting material (**2**). The latter was contaminated with approximately 25% of a UV-absorbing impurity.

(15*S*)-15-Methyl-*cis*-Δ^4-prostaglandin $F_{1\alpha}$ Methyl Ester (4) and (15*R*)-15-Methyl-*cis*-Δ^4-prostaglandin $F_{1\alpha}$ Methyl Ester (5). A. Preparation of the *RS* Mixture. Lactol **3** (5.18 g, 0.0174 mmol) was allowed to react with the ylide prepared from 3-(carboxypropyl)triphenylphosphonium bromide (22.4 g, 0.0522

(12) (a) Tarpley, W. G.; Sun, F. F. *J. Med. Chem.* **1978**, *21*, 288. (b) Hansson, G., submitted for publication.
(13) Johnson, R. A.; Krueger, W. C.; Nidy, E. G.; Pschigoda, L. M.; Garry, M. J. *J. Org. Chem.*, in press.
(14) Sih, J. C.; Nash, S. A. *Prostaglandins* **1977**, *14*, 407.

mol) and sodium hydride (4.24 g, 0.104 mol) according to literature procedures.[3] Following workup, the resulting amber oil was dissolved in ether, methylene chloride, and methanol and treated with excess ethereal diazomethane to give after evaporation 6.21 g of a yellow oil. The crude product was chromatographed on 620 g of silica gel packed as a slurry with 40% acetone in Skelly B and eluted with the same solvent system. Fractions with a volume of 250 mL each were collected. Fractions 14 (476 mg), 15 and 16 (873 mg), 17 and 18 (530 mg), and 19–21 (336 mg) contained a total of 2.21 g (33%) as a mixture of C-15 epimers. TLC mobility on silica gel plates developed with acetone–CH_2Cl_2 (45:55) for the 15*S* ester was R_f 0.28 and for the 15*R* ester was R_f 0.34.

A large-scale preparation using 43.5 g (0.145 mol) of **3** gave 29.0 g (0.076 mol, 52%) of the *RS* mixture (methyl ester) following chromatography. It should be noted that upon workup of the Wittig reaction mixture, the organic layers containing the carboxylic acid must be washed thoroughly to remove traces of acid and thereby prevent the formation of elimination products.

B. Separation of the *RS* Mixture. A total of 29.0 g of (15*RS*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester was chromatographed on a 2 in. × 15 ft column containing 4 kg of silica gel. The material was divided into two lots of 21.55 and 7.45 g and chromatographed separately. The solvent system used for elution was acetone–methylene chloride–Skellysolve B (27:50:23) and increased in polarity to 40:50:10 in increments. The individual *R* and *S* epimers were subjected to additional chromatography separately to remove minor solvent impurities. There was obtained a total of 13.60 g of *R* epimer (**5**) and 11.97 g of *S* epimer (**4**).

A 9.83-g center cut of the *S* epimer (**4**) was crystalline and was recrystallized by dissolving in ether (~200 mL). The ether solution was chilled to 8 °C, treated with cold (8 °C) pentane (~150 mL), and seeded. The solution was then maintained at 8 °C. After crystallization commenced, additional pentane was added. A first crop of white crystals (4.49 g), mp 54–55 °C, was obtained. A second crop of 2.75 g, mp 53–54 °C was obtained.

The rest of the *S* epimer plus the mother liquids obtained from the recrystallization were chromatographed again and then pooled with the second crop of crystals (2.75 g) to give 6.34 g of material which was crystallized from ether–pentane. This gave 5.6 g of (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (**4**) as white crystals: mp 54–56 °C; $[\alpha]_D$ +18° ($CHCl_3$); IR (liquid film) ν_{OH} 3310, $\nu_{C=O}$ 1745, $\nu_{trans\text{-}CH=CH}$ 975 cm^{-1}; NMR ($CDCl_3$) δ 5.51 (m, 2 H, *trans*-CH=CH), 5.40 (m, 2 H, *cis*-CH=CH), 4.38–3.74 (m, 2 H, 2 OCH<), 3.68 (s, 3 H, $C(O)OCH_3$), 2.36 (m, 2 H, $CH_2C(O)O$), 1.28 (s, 3 H, 15-CH_3), 0.88 (t, 3 H, J = 5 Hz, CH_3); ORD (in MeOH, plain negative curve) $[\theta]_{300}$ about +90 $[\theta]_{257}$ about 0 $[\theta]_{235}$ about −270; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{31}H_{62}Si_3O_5$ *m/e* 598.3905, found *m/e* 598.3907, other peaks *m/e* 583, 567, 527, 508, 493, 477, 455, 437, 418, 392, 365, 275, 217, 191, 147, 75, 73.

Anal. Calcd for $C_{22}H_{38}O_5$ (mol wt 382.52): C, 69.07; H, 10.01. Found: C, 69.20; H, 9.94.

(15*R*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (5) was a colorless oil; IR (neat oil) ν_{OH} 3390, $\nu_{C=O}$ 1740 cm^{-1}; ORD (plain negative Cotton curve) $[\theta]_{300}$ about +140 $[\theta]_{246}$ about 0, $[\theta]_{234}$ about −30; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{32}H_{62}Si_3O_5$ *m/e* 598.3905, found *m/e* 598.3899, other peaks *m/e* 583 ($M^+ - CH_3$), 567 ($M^+ - OCH_3$), 527 ($M^+ - C_5H_{11}$), 508 ($M^+ - HOSiMe_3$), 493 ($508^+ - CH_3$), 477 [$M^+ - (HOSiMe_3 + C_5H_{11})$], 418 ($M^+ - 2\ HOSiMe_3$), 217 ($Me_3SiO$ + CH=CHCH=CHOSiMe$_3$); NMR ($CDCl_3$) δ 5.49 (m, 2 H, *trans*-CH=CH), 5.40 (m, 2 H, *cis*-CH=CH), 4.35–3.75 (m, 2 H, 2 OCH<), 3.66 (s, 3 H, $C(O)OCH_3$), 2.35 (m, 2 H, $CH_2C(O)O$), 1.28 (s, 3 H, 15-CH_3), 0.88 (t, 3 H, J = 5 Hz, CH_3).

Anal. Calcd for $C_{22}H_{38}O_5$ (mol wt 382.52): C, 69.07; H, 10.01. Found: C, 68.40; H, 10.09.

(15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ (6). (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (**4**; 0.250 g, 0.655 mmol) was saponified in methanol (6 mL) with 0.6 mL of 50% sodium hydroxide and 2 mL of water. Following workup, the product (**6**; 0.229 g, 95%) was obtained as a colorless oil: IR (liquid film) ν_{OH} 3360, ν_{CH} 2920, 2860, $\nu_{OH(acid)}$ 2640, $\nu_{C=O(acid)}$ 1710, $\nu_{trans\text{-}CH=CH}$ 975 cm^{-1}; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{33}H_{68}Si_4O_5$ *m/e* 656.4144, found *m/e* 656.4167, other peaks *m/e* 641, 585, 566, 551, 450, 217. The acid was homogeneous in three TLC systems, and a sample that was reesterified with diazomethane (to give **4**) likewise was homogeneous in TLC systems that separate the 15-position epimers.

(15*S*)-15-Me-*cis*-Δ^4-PGE_1 Methyl Ester (7). A. Preparation of the Me_3Si Derivative. A solution of (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (**4**, 0.10 3 g) in acetone (4 mL) in a two-necked, 25-mL, round-bottomed flask equipped with a nitrogen inlet and drying tube was cooled to −40 to −45 °C (dry ice) under N_2 and maintained at that temperature while 1.0 mL of (trimethylsilyl)diethylamine was added. Cooling was continued. After 30 min the reaction was monitored by TLC in 50% ethyl acetate–Skelly B (spotted directly on the silica gel plate and put quickly in the tank). The reaction was essentially complete, with the mono Me_3Si derivative having an R_f of 0.63. The reaction was then diluted with 12 mL of precooled (−78 °C) ether. The resulting solution was added to 20 mL of half-saturated $NaHCO_3$ solution in a separatory funnel. The mixture was shaken and separated. The aqueous layer was extracted four times with ether. The ether extracts were combined and shaken two times with brine. The ether layer was dried (Na_2SO_4) and the ether removed at 40 °C under reduced pressure. The residue was azeotroped twice with benzene and cooled to room temperature under nitrogen. The product (113 mg) was an oil.

B. Oxidation and Removal of Me_3Si. The product (113 mg) from the preceding section was oxidized with chromium trioxide–pyridine complex according to standard procedures.[15] Following workup, a dark brown oil (77 mg) was obtained. The oil was dissolved in 5 mL of methanol and cooled to 10 °C. The solution was treated with a mixture of 2.5 mL of water and 0.3 mL of glacial acetic acid. The reaction was stirred at room temperature for 45 min. The reaction was quenched by adding it to a mixture of 0.1 M $NaHSO_4$ (10 mL), ether (5 mL), and ice. The mixture was shaken and separated. The aqueous layer was extracted five more times with ether (5-mL portions). The combined ether extracts were washed with water (to pH 5–7), with $NaHCO_3$ (saturated), and with brine followed by drying (Na_2SO_4). The ether was evaporated under reduced pressure at 40 °C and azeotroped two times with benzene. The residue was cooled to room temperature under a nitrogen stream. An oil (64 mg) was obtained. The oil obtained was chromatographed on 6 g of silica gel. The column was packed as a slurry with 50% ethyl acetate–hexane. The sample was applied in CH_2Cl_2, and the column was eluted with 80% ethyl acetate–hexane. Fractions of 3 mL each were collected. The product was obtained in fractions 12–32 (33 mg); IR (liquid film) ν_{OH} 3390, $\nu_{C=O}$ 1735, $\nu_{trans\text{-}CH=CH}$ 975 cm^{-1}; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{28}H_{52}Si_2O_5$ *m/e* 524.3354, found *m/e* 524.3367, other peaks *m/e* 509, 493, 453, 434, 381.

(15*R*)-15-Me-*cis*-Δ^4-PGE_1 Methyl Ester (8). The procedure used above for preparation of **7** was applied to the conversion of **5** (0.512 g, 1.34 mmol) to **8** (0.211 g, 0.55 mmol, 41%). The product (**8**) was a colorless oil: IR (liquid film) ν_{OH} 3430, $\nu_{C=O}$ 1740, $\nu_{trans\text{-}CH=CH}$ 975 cm^{-1}; CD max (in dioxane) $[\theta]_{304}$ −9900 ± 200, $[\theta]_{298}$ −10 000 ± 200; NMR ($CDCl_3$) δ 5.69 (m, 2 H, *trans*-CH=CH), 5.34 (m, 2 H, *cis*-CH=CH), 4.36–3.80 (m, 1 H, >CHO), 3.65 (s, 3 H, OCH_3), 1.29 (s, 3 H, 15-CH_3), 0.89 (t, 3 H, CH_3, J = 5 Hz); high-resolution mass spectrum of $(Me_3Si)_2$ derivative, theory for $C_{28}H_{52}Si_2O_5$ *m/e* 524.3353, found *m/e* 524.3321, other peaks *m/e* 509, 493, 453, 434, 309.

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 68.97; H, 9.28.

(15*S*)-15-Me-*cis*-Δ^4-PGA_1 Methyl Ester (9). By the use of the method of Yankee and co-workers,[3] a sample of **7** (0.172 g, 0.45 mmol) was converted to **9**. After workup of the reaction, there was obtained 160 mg of a yellow oil. The oil was chromatographed on 22 g of analytical-grade silica gel by using 50% ethyl acetate–Skelly B to elute the column. Fractions with a volume of 10 mL each were collected. The product was found in fractions 8–15 which gave 129 mg of a pale yellow oil: IR (liquid film) ν_{OH} 3480, $\nu_{=CH}$ 3020, $\nu_{C=O}$ 1740, 1710, $\nu_{C=C(ring)}$ 1585 cm^{-1}; NMR ($CDCl_3$) δ 7.51 (m, 1 H, C_{11}=CH), 6.17 (m, 1 H, C_{10}=CH), 5.69 (m, 2 H, *trans*-CH=CH), 5.40 (m, 2 H, *cis*-CH=CH), 3.65 (s, 3 H, OCH_3), 1.26 (s, 3 H, C_{15} CH_3), 0.89 (t, 3 H, CH_3, J = 5 Hz);

(15) (a) Radcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000. (b) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1973**, 1319.

CD max $[\Theta]_{325}$ -6900 (n → π*), $[\Theta]_{234}$ 60 800 (π → π*); high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{25}H_{42}SiO_4$ *m/e* 434.2852, found *m/e* 434.2879.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.69; H, 9.46.

(15*S*)-15-Me-*cis*-Δ^4-PGD$_1$ Methyl Ester (10). A solution of (15*S*)-15-Me-*cis*-Δ^4-$PGF_{1\alpha}$ methyl ester (200 mg, 0.524 mmol) in acetone (10 mL) was cooled to -40 °C and oxidized with Jones reagent.[16] Following workup, the crude product (0.2 g) was chromatographed on 22 g of analytical-grade silica gel via high-pressure chromatography. The column was eluted with 15% acetone–methylene chloride. Fractions with a volume of 10 mL each were collected. The product (**10**) was found in fractions 14–26 (98 mg, 49% of theory), (15*S*)-15-Me-*cis*-Δ^4-PGE_1 methyl ester (**7**) in fractions 36–50 (25 mg, 13% of theory) and starting material (**4**) after eluting with 300 mL of 60% acetone–CH_2Cl_2 (34 mg, 17%): IR (liquid film) ν_{OH} 3440, $\nu_{C=O's}$ 1750, $\nu_{trans\text{-}CH=CH}$ 980 cm^{-1}; NMR ($CDCl_3$) δ 5.92–5.13 (m, 4 H, 2 CH=CH), 4.56 (m, 1 H, >CHO), 3.66 (s, 3 H, OCH_3), 1.27 (s, 3 H, OCH_3), 0.90 (t, 3 H, CH_3, *J* = 5 Hz); CD max (in dioxane) $[\Theta]_{306}$ -6200 ± 43, $[\Theta]_{297}$ -5300 ± 43; high-resolution mass spectrum of Me_3Si derivative, calcd for $C_{28}H_{52}Si_2O_5$ *m/e* 524.3353, found *m/e* 524.3364, other peaks *m/e* 509, 506, 453, 434, 363.

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.08; H, 9.63.

(15*S*)-15-Methyl-2,3,4,5-tetranorprostaglandin $PGF_{1\alpha}$ δ-Lactone (11) and (15*R*)-15-Me-2,3,4,5-tetranor-$PGE_{1\alpha}$ δ-Lactone (12). The lactol **3** (3.78 g, 12.7 mmol) was oxidized with silver oxide (prepared from 4.3 g of $AgNO_3$) according to a previously described procedure.[9]

The crude product (2.18 g) was divided into two lots of 0.77 and 1.41 g each which were chromatographed on three, series-connected, Merck size B Lobar columns. The columns were eluted by high-pressure chromatography using 50% acetonitrile–methylene chloride as the solvent mixture. A total of 447 mg of the less polar *R* isomer contaminated with a trace of an impurity with a higher R_f was obtained. The more polar *S* isomer was obtained in a 506-mg yield which was one spot on thin-layer chromatography.

The 15*S* lactone **11** had the following properties: IR (liquid film) ν_{OH} 3400, $\nu_{C=O}$ 1735, ν_{C-O} 1250, 1190, 1170, 1095, 1040 cm^{-1}; ORD min (in methanol) $[\Theta]_{230}$ about -3900 ± 50; high-resolution mass spectrum of $(Me_3Si)_2$ derivative, calcd for $C_{23}H_{44}Si_2O_4$ *m/e* 440.2778, found *m/e* 440.2762, other peaks *m/e* 425 ($M^+ - CH_3$), 369 ($M^+ - C_5H_{11}$), 279 [$M^+ - (C_5H_{11} + Me_3SiOH)$]; NMR ($CDCl_3$) δ 5.55 (m, 2 H, CH=CH), 4.71 (m, 1 H, C-9), 3.87 (m, 1 H, HC—O), 1.28 (s, 3 H, 15-CH_3), 0.88 (t, 3 H, CH_3, *J* = 5 Hz).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.23; H, 9.74.

The 15*R* lactone **12** was rechromatographed on two Merck size B prepacked columns connected in series. The column was eluted with ethyl acetate and fractions with a volume of 25 mL each were collected. Fraction 29 contained 33 mg of impure *R* isomer (a less polar impurity), and fractions 30–52 contained 338 mg of the pure *R* isomer which solidified to give a white solid, mp 71–73 °C. The solid was recrystallized from ether–hexane to give 213 mg of a white solid: mp 73–74 °C; IR ν_{OH} 3480, 3180, $\nu_{C=O}$ 1705, ν_{OCH} 980 cm^{-1}; ORD (in methanol) $[\Theta]_{230}$ -3900 ± 60; high-resolution mass spectrum of $(Me_3Si)_2$ derivative, calcd for $C_{23}H_{44}Si_2O_4$ *m/e* 440.2778, found *m/e* 440.2749, other peaks *m/e* 425 ($M^+ - CH_3$), 396 ($M^+ - CO_2$), 369 ($M^+ - C_5H_{11}$), 350 ($M^+ - Me_3SiOH$), 335 [$M^+ - (Me_3SiOH + CH_3)$], 279 [$M^+ - (C_5H_{11} + Me_3SiOH)$]; NMR ($CDCl_3$) δ 5.56 (m, 2 H, CH=CH), 4.70 (m, 1 H, C-9), 3.88 (m, 1 H, HC—O), 1.28 (s, 3 H, CH_3), 0.89 (t, 3 H, CH_3, *J* = 5 Hz).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.44; H, 9.71.

(15*S*)-15-Methyl-2,3,4,5-tetranorprostaglandin $F_{1\alpha}$ δ-Lactone 11,15-Dibenzoate (13). A solution of the (15*S*)-15-methyl δ-lactone **11** (99 mg, 0.34 mmol; containing ca. 15% of the *R* isomer **12**) in pyridine (10 mL) was chilled in an ice–water bath and treated with 2.5 mL of benzoyl chloride (3.0 g, 0.022 mol). Following workup, the crude reaction product was chromatographed once on a Merck size B column with 2% acetone–methylene chloride. The product fractions were pooled and rechromatographed on a Merck size B column with 25% acetone–hexane. The product (58 mg) was obtained as a colorless oil: IR (liquid film) similar to that of the *R* isomer **14** described below; high-resolution mass spectrum, very weak M^+, found *m/e* 382.2131 ($M^+ - PhCO_2H$), calcd for $C_{24}H_{30}O_4$ *m/e* 382.2144, other peaks *m/e* 399 ($M^+ - C_6H_5C{=}O$), 391 [$M^+ - (C_5H_{11} + CH_2CO)$], 260 ($M^+ - 2\ PhCO_2H$), 122 ($PhCO_2H^+$), 105 ($C_6H_5C{=}O^+$), 77 ($C_6H_5^+$); NMR ($CDCl_3$) δ 7.69 (m, 10 H, aromatic), 5.96 (d, 1 H, $J_{trans\text{-}H}$ 16 Hz, H-14), 5.57 (dd, 1 H, $J_{H_{12}}$ = 7 Hz, $J_{trans\text{-}H}$ = 16 Hz, H-13), 5.18 (four-line pattern, 1 H, H-11), 4.78 (m, 1 H, H-9), 1.63 (s, 3 H, C-15 methyl), 0.79 (t, 3 H, CH_3).

Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.78; H, 7.19. Found: C, 73.44; H, 7.36.

(15*R*)-15-Methyl-2,3,4,5-tetranorprostaglandin $F_{1\alpha}$ δ-Lactone 11,15-Dibenzoate (14). (15*R*)-15-Methyl δ-lactone **12** (0.166 g, 0.56 mmol) was benzoylated with benzoyl chloride (4.85 g) in pyridine (15 mL). Following workup, the crude product was obtained as a viscous oil. The crude product was chromatographed on silica gel with 2% acetone–methylene chloride, and then the product fractions were rechromatographed with 30% acetone–hexane. The product fractions were pooled to give 132 mg of an oil: high-resolution mass spectrum, very weak M^+, found *m/e* 382.2127 ($M^+ - PhCO_2H$), calcd for $C_{24}H_{30}O_4$ *m/e* 382.2144, other peaks *m/e* 399 ($M^+ - C_6H_5CO$), 391 [$M^+ - (C_5H_{11} + CH_2CO)$], 360 ($M^+ - 2\ C_6H_5CO_2H$), 204.1148 [(calcd 204.1150) $PhC(O)O^+{=}CC_5H_{11}$)], 122 ($C_6H_5CO_2H^+$), 105 ($C_6H_5C{=}O^+$), 77 ($C_6H_5^+$); IR (liquid smear) $\nu_{C=O}$ 1750, 1720, $\nu_{C=C}$ 1605, 1585, ν_{C-O} 1275, 1250, 1115, $\nu_{\delta\text{-}CH}$ 710; NMR ($CDCl_3$) δ 7.70 (m, 10 H, aromatic), 6.00 (d, 1 H, $J_{trans\text{-}H}$ = 16 Hz, H-14), 5.56 (dd, 1 H, $J_{H_{12}}$ = 7 Hz, $J_{trans\text{-}H}$ = 16 Hz, H-13), 5.18 (four-line pattern, 1 H, H-11), 4.77 (m, 1 H, H-9), 1.64 (s, 3 H, C-15 methyl), 0.78 (t, 3 H, CH_3, *J* = 5 Hz).

Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.78; H, 7.19. Found: C, 73.85; H, 7.21.

Registry No. **1**, 72776-98-8; **2**, 72726-73-9; **3**, 72726-74-0; **4**, 64223-05-8; **4** ($(Me_3Si)_3$ derivative), 72726-75-1; **4** (Me_3Si derivative), 72726-76-2; **5**, 72749-03-2; **5** ($(Me_3Si)_3$ derivative), 72726-77-3; **6**, 72726-78-4; **6** ($(Me_3Si)_4$ derivative), 72726-79-5; **7**, 67749-12-6; **7** ($(Me_3Si)_2$ derivative), 72749-08-7; **8** ($(Me_3Si)_2$ derivative), 72749-09-8; **8** ($(Me_3Si)_2$ derivative), 72749-10-1; **9**, 72726-80-8; **9** (Me_3Si derivative), 72726-81-9; **10**, 64223-06-9; **10** ($(Me_3Si)_2$ derivative), 69079-66-9; **11**, 66616-80-6; **11** ($(Me_3Si)_2$ derivative), 72778-01-9; **12**, 72776-99-9; **12** ($(Me_3Si)_2$ derivative), 72726-82-0; **13**, 72726-83-1; **14**, 72777-00-5; sodium 4-(triphenylphosphoranylidene)butyrate, 69552-58-5.

(16) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.