Table III. Products of Reaction between *p*-Menthadienol (**1**) and Dimethylheptylresorcinol at 0 and 40°

Reaction time, hr	% composition (glc), C_9-[c]					
	n-CBD	*abn*-CBD	*n*-Δ^8-iso-THC	*n*-Δ^1-THC	*n*-$\Delta^{1(6)}$-THC	*n*-$\Delta^{4(8)}$-iso-THC
3.5	69	31				
17.5[a]	71	22				
20.5	13	3	16	64		
41	3	0	22	72		
159[b]	0		22	61	17	
160					*ca.* 82	*ca.* 18

[a] Fresh $BF_3 \cdot Et_2O$ was added at this time. [b] Fresh $BF_3 \cdot Et_2O$ was added and the mixture was heated at reflux for 1 hr. [c] The *n*-C_5 side chain of the cannabinoids has been replaced by $CH(CH_3)CH(CH_3)C_5H_{11}$.

at 0°. After 20 min an aliquot showed (glc) the presence of only 2- and 4-*p*-mentha-2,8-dien-3-yl-5-(1,2-dimethylheptyl)resorcinols, in a ratio of 70:30, respectively. When no further change had occurred after 17.25 hr, 3 μl of $BF_3 \cdot Et_2O$ was added and the reaction mixture was allowed to stand for 118 hr more at 0°. Aliquots withdrawn during this time showed (glc) the formation of the dimethylheptyl homolog of Δ^1-THC. At this point 1 ml of dichloromethane and 30 μl of $BF_3 \cdot Et_2O$ were added and the reaction mixture was heated at reflux for 1 hr. After quenching and work-up, 51 mg of a cloudy amber resin was obtained which was shown to be 82% 3-(1,2-dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*c*,*d*]pyran-1-ol (nmr, glc, tlc).[6a]

Acknowledgment. This work was carried out with the support of NIDA (Grant No. DA-00574-01). We are grateful to Professor John C. Sheehan for his encouragement of this work and to Dr. Charles E. Hignite of M.I.T. for mass spectral data (NIH Grant No. RR-00317).

Total Synthesis of 15-Methylprostaglandins

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Abstract: A total synthesis of 15-methyl-substituted prostaglandins starting from (−)-2β,4β-dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic acid γ-lactone (**1**) is described. A key synthetic intermediate, (−)-3α,5α-dihydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **6**, is also reported. The following 15-methylprostaglandin analogs as methyl esters are described: (15*S*)-15-methyl-$PGF_{2\alpha}$, -$PGF_{2\beta}$, -PGE_2, -PGA_2, -PGE_1, -$PGF_{1\alpha}$, -PGA_1; 13,14-dihydro-(15*S*)-15-methyl-$PGF_{1\alpha}$, -PGE_1; (15*R*)-15-methyl-$PGF_{2\alpha}$, -$PGF_{2\beta}$, -PGE_2, -PGE_1, -PGA_2. The PGE compounds were prepared from the PGF compounds by selective trimethylsilylation at C-11 followed by oxidation. Preparation of the 15-methylprostaglandins in the PG_1 series involved selective hydrogenation of the 5,6 bond without prior derivativization. The PGA compounds were prepared from the PGE structures by a novel procedure not involving acid treatment. Each 15 epimer of 15-methyl-$PGF_{2\alpha}$ methyl ester and 15-methyl-PGE_2 methyl ester was readily and cleanly epimerized to an equal mixture of both (15*R*) and (15*S*) epimers by treatment with acetic acid at 40°.

Prostaglandins are a family of 20-carbon fatty acids found in virtually all mammalian cells.[1] They are highly active biologically in many systems and have been implicated in mediation of many physiological responses.[2] Their general biology[2] and chemistry[3] have recently been reviewed.

The most rapid mode of metabolism (deactivation) of the natural prostaglandins in man has been shown to be oxidation of the allylic C-15 alcohol, followed by very rapid reduction of the 13,14 double bond.[4] The enzyme responsible for the oxidation, 15-hydroxyprostaglandin dehydrogenase, has been isolated from a variety of tissue preparations.[4,5] Syntheses reported in this and in a related manuscript[6] were initiated to determine whether compounds which were substituted at C-15 with methyl groups could still maintain biological activity. Several 15-methyl-substituted prostaglandins were first reported in 1970.[7] One of these reports included not only a synthetic outline for representative members of this family of prostaglandins but also some preliminary biological assay results.[7a] A communication[8a] outlining a synthetic method for preparation of the 15-methyl members of the PGE_2

(1) (a) S. Bergström, *Science*, **157**, 382 (1967); (b) "Prostaglandins" in Proceedings of the Second Nobel Symposium, Stockholm, June, 1966, S. Bergström and B. Samuelsson, Ed., Almquist and Wiksell, Gebers Forlag AB, Stockholm, 1967.

(2) (a) J. R. Weeks, *Annu. Rev. Pharmacol.*, **12**, 317 (1972); (b) J. W. Hinman, *Annu. Rev. Biochem.*, **41**, 161 (1972).

(3) (a) U. Axen, J. E. Pike, and W. P. Schneider in "Progress in the Total Synthesis of Natural Products," Vol. 1, J. W. ApSimon, Ed., Wiley, New York, N. Y., 1973; (b) G. L. Bundy, *Annu. Rep. Med. Chem.*, **2**, 157 (1972); (c) N. M. Weinshenker and N. H. Andersen in "The Prostaglandins," Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973.

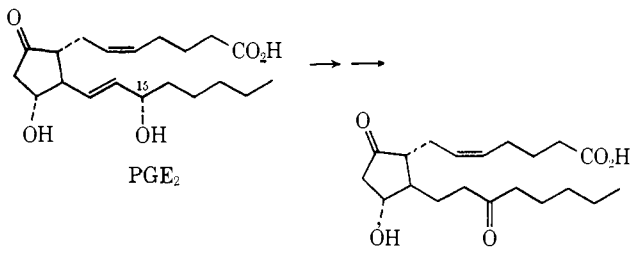
(4) (a) B. Samuelsson, E. Granström, K. Gréen, and M. Hamberg, *Ann. N. Y. Acad. Sci.*, **180**, 138 (1971); (b) B. Samuelsson, *Advan. Biosci.*, **9**, 7 (1973).

(5) E. Änggård and B. Samuelsson, *Ark. Kemi*, **25**, 293 (1966).

(6) G. L. Bundy, D. J. Duchamp, C. D. Chidester, and E. W. Yankee, manuscript in preparation.

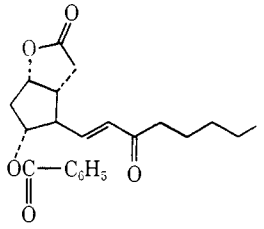
(7) (a) G. Bundy, F. Lincoln, N. Nelson, J. Pike, and W. Schneider, *Ann. N. Y. Acad. Sci.*, **180**, 76 (1971); (b) W. Lippmann, *ibid.*, 332 (1971).

(8) (a) E. W. Yankee and G. L. Bundy, *J. Amer. Chem. Soc.*, **94**, 3651 (1972); (b) S. Iguchi, F. Tanouchi, K. Kimura, and M. Hayashi, *Prostaglandins*, **4**, 535 (1973); (c) J. F. Bagli, T. Bogri, and S. N. Sehgal, *Tetrahedron Lett.*, 3329 (1973).



family followed. Very recently, brief descriptions have appeared[8b,c] of syntheses of certain 15-methyl-PGE and -PGA compounds, isolated only as epimeric mixtures at C-15. The 15-methylprostaglandins are inert to the action of 15-hydroxyprostaglandin dehydrogenase.[9] The methyl esters of $PGF_{2\alpha}$ and 15-methyl-$PGF_{2\alpha}$ have similar potencies *in vitro* on the gerbil colon and *in vivo*, given intravenously, on rat blood pressure.[9] Similarly, the methyl esters of PGE_2 and 15-methyl-PGE_2 are approximately equipotent *in vitro* on the gerbil colon and *in vivo*, both are vasodepressors in the rat.[9] However, both of the 15-methyl analogs exhibit a longer duration of action on rat blood pressure than do the respective parent compounds. Furthermore, the 15-methyl analogs are at least five to ten times more potent in the monkey[10] and up to several hundred times more potent in man[11] when used to terminate pregnancy or to induce labor at term compared to the respective parent prostaglandins. More recently, each C-15 epimer of 15-methyl-PGE_2 methyl ester has shown very potent oral activity as gastric antisecretory agents, both in the dog[12] and man.[13,14]

Because of the promising clinical potential of this class of compounds, development of a total synthetic route for their preparation was highly desirable. The key intermediate in this synthesis was compound **6**, which is analogous, but not identical, to intermediates used by Corey, *et al.*, in their total synthetic routes to natural prostaglandins.[15]

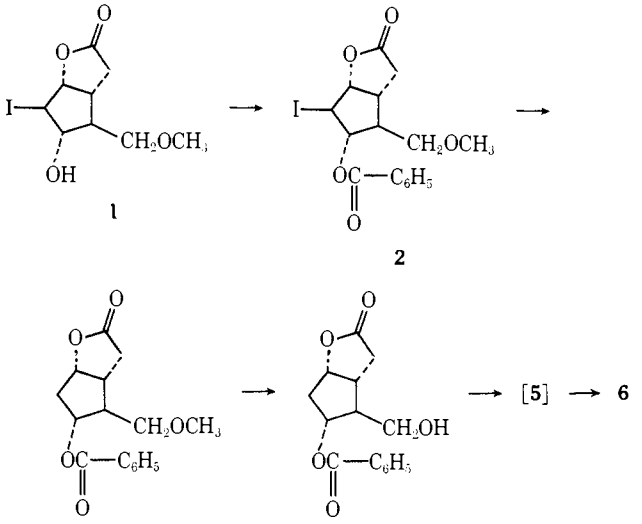


6

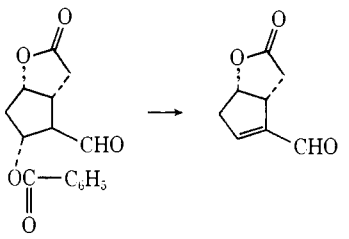
Synthesis

The synthesis of the key intermediate **6** is shown in

Scheme I



Scheme I. Corey, *et al.*, have reported[15b] in a communication the preparation of optically pure iodo lactone **1**. The preparation of **6** from **1** is analogous to that used by those authors in their syntheses[15] of natural prostaglandins. Benzoylation of **1** in pyridine at ambient temperature resulted in conversion to crystalline **2**. Treatment of **2** with tributyltin hydride converted it in high yield to oily **3**. Methyl ether cleavage of **3** with boron tribromide gave crystalline **4** in 79% overall yield from **1**. Oxidation of **4** with Collins reagent[16] gave unstable aldehyde **5**. Although this aldehyde could be obtained crystalline when the oxidation mixture was filtered through silica gel, very poor recoveries resulted. Crystalline aldehyde **5** underwent elimination to what appeared to be aldehyde **7** to an extent of 80% when allowed to stand at ambient temperature for 5 days. Aldehyde **7** has recently been reported in other connections.[17] Treatment of crude **5** without isolation with the ylide prepared from dimethyl (2-oxoheptyl)phosphonate and sodium hydride gave crystalline **6** in 60% yield from **4** after chromatography and recrystallization.



5 **7**

The tertiary methyl group was introduced by treatment of **6** with either methyl Grignard at −78° (in ether or tetrahydrofuran) or with trimethylaluminum in benzene[18] at ambient temperature (Scheme II). Interestingly, conditions could be used which resulted in little or no attack on the lactone ring or the benzoate.

(9) (a) J. R. Weeks, D. W. DuCharme, W. E. Magee, and W. L. Miller, *J. Pharmacol. Exp. Ther.*, **186**, 67 (1973); (b) G. L. Bundy, E. W. Yankee, J. R. Weeks, and W. L. Miller, *Advan. Biosci.*, **9**, 125 (1973).

(10) K. T. Kirton and A. D. Forbes, *Prostaglandins*, **1**, 319 (1972).

(11) (a) S. M. M. Karim and S. D. Sharma, *J. Obstet. Gynacol. Brit. Commonw.*, **79**, 737 (1972); (b) M. Bygdeman, F. Béguin, M. Toppozada, and N. Wiqvist in "The Prostaglandins—Clinical Applications in Human Reproduction," E. M. Southern, Ed., Futura Publishing Co., Inc., Mount Kisco, N. Y., 1972; (c) M. Bygdeman, F. Béguin, M. Toppozada, W. Wiqvist, and S. Bergström, *Lancet*, **1**, 1336 (1972).

(12) (a) A. Robert and B. J. Magerlein, *Advan. Biosci.*, **9**, 247 (1973), (b) A. Robert and E. W. Yankee, *Proc. Soc. Exp. Biol. Med.*, in press.

(13) (a) S. M. M. Karim, D. C. Carter, D. Bhana, and P. A. Ganesan, *Advan. Biosci.*, **9**, 255 (1973); (b) *Brit. Med. J.*, **1**, 143 (1973).

(14) A. Robert, B. Nylander, and S. Andersson, *Life Sci.*, **14**, 533 (1974).

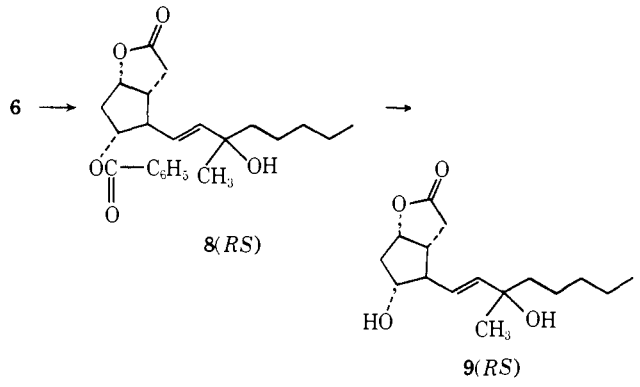
(15) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5677 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelleker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (c) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).

(16) (a) R. Radcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970); (b) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(17) (a) R. C. Kelly, I. Schletter, and R. L. Jones, *Prostaglandins*, **4**, 653 (1973); (b) P. Crabbé and A. Cervantes, *Tetrahedron Lett.*, 1319 (1973).

(18) (a) H. M. Neumann, J. Laemmle, and E. C. Ashby, *J. Amer. Chem. Soc.*, **95**, 2597 (1973); (b) E. C. Ashby and S. Yu, *Chem. Commun.*, 351 (1971); (c) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Amer. Chem. Soc.*, **90**, 5179 (1968).

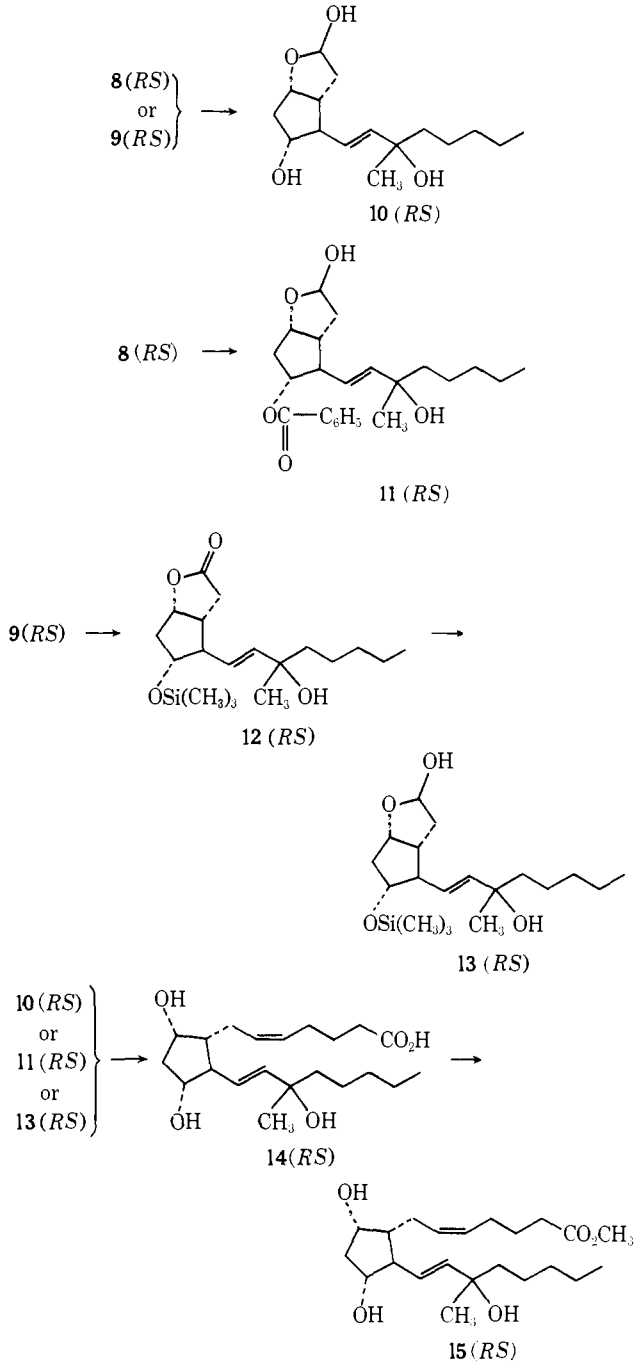
Scheme II



No thin-layer chromatographic solvent system was found which would distinguish the two expected epimers in **8**(*RS*). The 60-MHz nmr spectrum of **8**(*RS*) in chloroform-*d* also failed to show two epimers, with a single methyl singlet at δ 1.3 being obtained. However, incremental addition of the lanthanide shift reagent tris(dipivaloylmethanato)europium(III)[19] to a chloroform-*d* solution of **8**(*RS*) showed, in the 60-MHz spectrum, a resolution and downfield shift of the tertiary signal to give two singlets. Using this technique, different runs of **6** → **8**(*RS*) utilizing either methyl Grignard or trimethylaluminum were shown to result in very similar (nearly 1 : 1) epimeric ratios in **8**(*RS*). Use of trimethylaluminum seemed to favor slightly the (*S*) epimer (*vide infra* for stereochemical assignments), but this could not be quantitated.[20] Treatment of **8**(*RS*) with sodium methoxide in methanol at ambient temperature rapidly and cleanly cleaved the benzoate group to give oily **9**(*RS*). As with **8**(*RS*), the two expected epimers in **9**(*RS*) could not be distinguished by thin-layer chromatography[21] with several solvent systems or by 60-MHz nmr.

As shown in Scheme III, several alternative routes for conversion of intermediates **8**(*RS*) and **9**(*RS*) to prostaglandins **14**(*RS*) were investigated. Reduction of **9**(*RS*) with excess diisobutylaluminum hydride (Dibal-H) in tetrahydrofuran at −78° cleanly gave oily lactols **10**(*RS*). These same lactols could be obtained from **8**(*RS*) with Dibal-H at −20°, although in the latter case some overreduction occurred. However, treatment of **8**(*RS*) with the hydride reagent at −78° cleanly gave lactol benzoates **11**(*RS*) without significant ester cleavage. Alternatively, **9**(*RS*) was silylated with trimethylsilyldiethylamine to give monotrimethylsilyl ether **12**(*RS*) which could be treated with Dibal-H at −78° to give lactol silyl ether **13**(*RS*). Treatment of each of these lactols (*i.e.*, **10**(*RS*), **11**(*RS*), **13**(*RS*)) with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide and sodium methylsulfinylmethide gave prostaglandins **14**(*RS*) which after esterification with diazomethane gave chromatographically pure oily **15**(*RS*) in overall yields from ketone **6** of 28–37%. It is interesting to note that in the conditions used for the Wittig

Scheme III



reaction and product isolation, cleavage of the benzoate in the sequence **11**(*RS*) → **14**(*RS*) as well as the trimethylsilyl in sequence **13**(*RS*) → **14**(*RS*) occurred.

The epimers in **15**(*RS*) are clearly distinguishable by thin-layer chromatography. They are also preparatively separable by column chromatography on silica gel, as reported previously.[7a] The two epimers are in every way identical with the compounds prepared by a different route,[6,7a] the (**15***R*) (less polar) epimer being an oil and the (**15***S*) (more polar) epimer being crystalline. The assignment of configuration at C-15 was originally[7a] based on comparisons of tlc mobilities and biological activities of several prostaglandin C-15 epimeric pairs. More recently, the assignment was confirmed by X-ray crystallography of the corresponding *p*-bromophenacyl ester of **15**(*S*).[6,22]

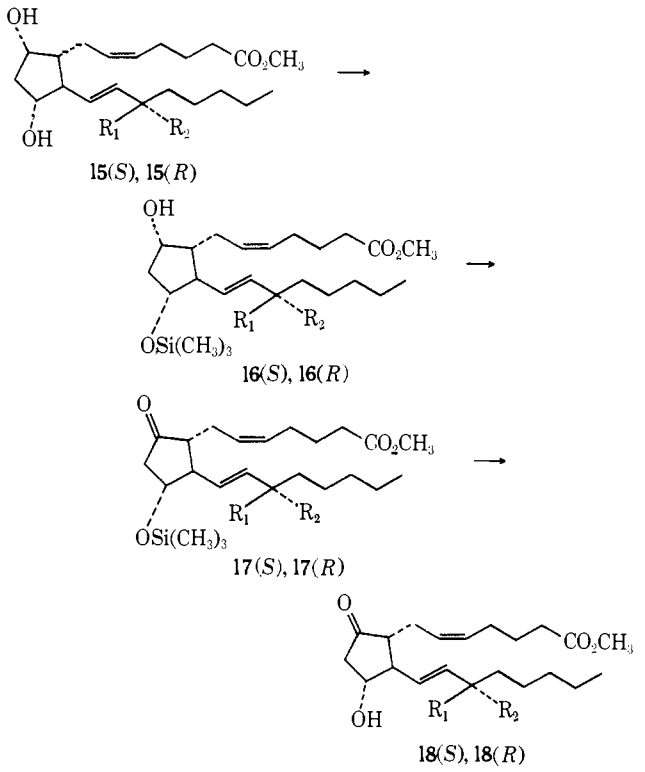
(19) K. J. Eisentraut and R. B. Sievers, *J. Amer. Chem. Soc.*, 87, 5254 (1965).

(20) S. Mizsak of The Upjohn Co. has observed that the ^{13}C nmr spectrum of 8(*RS*) in chloroform-*d* shows the tertiary methyl to consist of two signals at δ 28.0 and 28.4 downfield from internal TMS.

(21) Dr. J. M. McCall of The Upjohn Co. has demonstrated that the epimers of 9(*RS*) are separable by high-pressure liquid chromatography using a Waters Model A100 liquid chromatograph, with a 6 ft × 1/8 in. column packed with Corasil II, 10% acetone in methylene chloride (v/v), at a flow of 1.5 ml/min.

(22) C. G. Chidester and D. J. Duchamp, Abstracts of the American Crystallographic Association, Winter Meeting, 1974, Vol. 2, Series 2, p 34.

Scheme IV



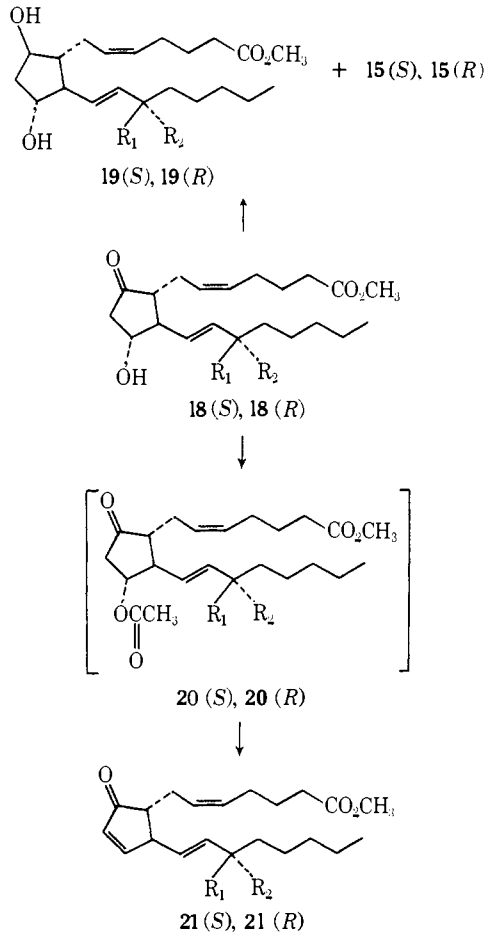
(*S*) isomers, $R_1 = CH_3$; $R_2 = OH$

(*R*) isomers, $R_1 = OH$; $R_2 = CH_3$

Scheme IV outlines conversion of the PGF compounds to their respective PGE structures. Part of this has been reported in a prior communication.[8] Selective monosilylation of the PGF compounds was accomplished using trimethylsilyldiethylamine in acetone at −45°. This reagent has been reported to be very sensitive to the steric environment of hydroxyl groups.[23] The conversion of **15**(*S*) and **15**(*R*) to their respective 11-trimethylsilyl ether derivatives apparently depends on the different steric environments of the C-11 and C-9 hydroxyl groups. The hydroxyl at C-9 is cis to the side chain at C-8 whereas the C-11 hydroxyl is trans to the C-12 side chain. Although varying amounts of 9,11-bis(trimethylsilyl) ethers could be formed, depending on reaction temperature, no mono-9-trimethylsilyl ethers were ever observed. The hydroxyl at C-15, being tertiary, is much less accessible to the silylating reagent. Even when C-15 is secondary (as in the natural prostaglandins), the hydroxyls at C-11 and C-15 can both be silylated preferentially over that at C-9.[24] Oxidation of the crystalline monosilyl derivatives **16**(*S*) or **16**(*R*) with Collins reagent[16] gave the corresponding PGE structures **17**(*S*) or **17**(*R*) which, without purification, were converted to **15**(*S*)-15-methyl-PGE_2 methyl ester, **18**(*S*), or **15**(*R*)-15-methyl-PGE_2 methyl ester, **18**(*R*), under mild acidic conditions. Compounds **18**(*S*) and **18**(*R*) are distinguishable (with difficulty) by thin-layer chromatography. It was established that the conditions required to remove the trimethylsilyl protecting groups (methanol, water, with a trace of acetic acid, ambient temperature) did not effect epimerization at C-15 in **18**(*S*), **18**(*R*), **15**(*S*), or **15**(*R*). This is in direct contrast to the results obtained using conditions required to remove tetrahydropyranyl groups (acetic acid, water, tetrahydrofuran, 40°) where complete epimerization occurred within 3 hr with little apparent formation of other products.

Conversion of the PGE_2 structures **18**(*S*) and **18**(*R*) to the remaining members of the 15-methyl-PG_2 family is outlined in Scheme V. Reduction of **18**(*S*) or **18**(*R*) with sodium borohydride in methanol at −15° gave the expected[3] PGF compounds **19**(*S*) and **15**(*S*) or **19**(*R*) and **15**(*R*), respectively. The C-9 epimers were separated preparatively by column chromatography on silica gel. Treatment of **18**(*S*) and **18**(*R*) each with excess acetic anhydride in pyridine at ambient temperature gave the unstable 11-acetates **20**(*S*) and **20**(*R*). Without purification, these were converted to the chromatographically pure PGA prostaglandins **21**(*S*) and **21**(*R*) in 90 and 84% overall yields respectively from **18**(*S*) and **18**(*R*). Although the C-11 acetates of the corresponding enantiomeric prostaglandins[25] were isolated (not characterized) and then successfully subjected to elimination conditions (methanol, potassium acetate, ambient temperature), the overall PGE → PGA conversion was more efficiently carried out by *in situ* elimination. This involved dilution of the pyridine

Scheme V



(*S*) isomers, $R_1 = CH_3$; $R_2 = OH$

(*R*) isomers, $R_1 = OH$; $R_2 = CH_3$

(23) I. Weisz, K. Felföldi, and K. Kovács, *Acta Chim. Acad. Sci. Hung.*, 58, 189 (1968).

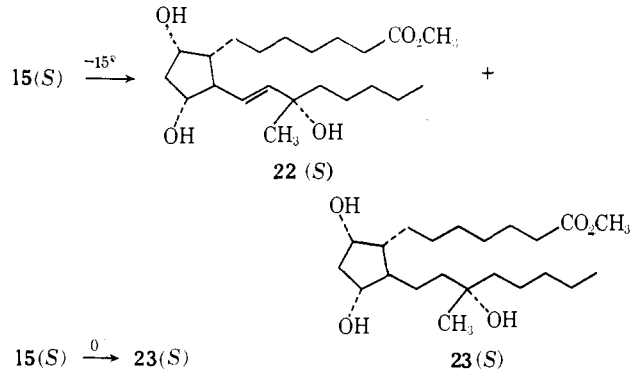
(24) E. W. Yankee, C. H. Lin, and J. Fried, *J. Chem. Soc., Chem. Commun.*, 1120 (1972).

(25) E. L. Cooper and E. W. Yankee, *J. Amer. Chem. Soc.*, **96**, 5876 (1974).

solutions of the acetates (containing excess acetic anhydride) with methanol. Compounds **21**(*S*) and **21**(*R*) were indistinguishable by thin-layer chromatography as well as by spectral techniques.

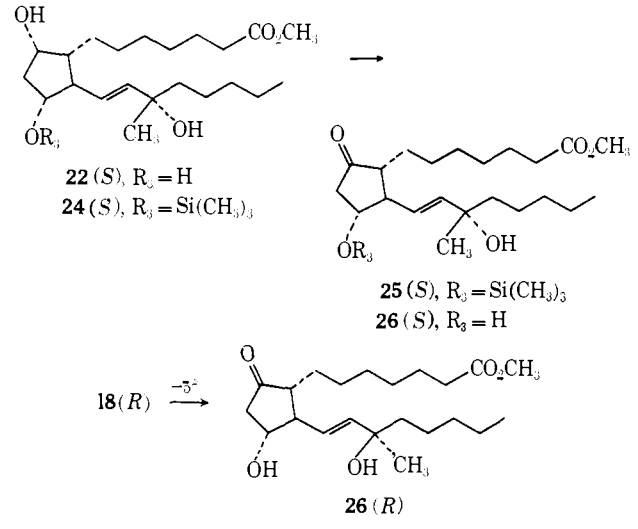
Although the above synthetic route leads to compounds in the PG_2 series, 15-methylprostaglandins in the PG_1 as well as the dihydro-PG_1 series are readily accessible by direct hydrogenation. As shown in Scheme VI, the 5,6 double bond in **15**(*S*) could be

Scheme VI



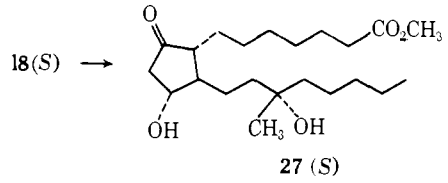
selectively hydrogenated to crystalline **22**(*S*) using 1 atm of hydrogen and palladium on charcoal at −15° in ethyl acetate. These conditions are essentially identical with those first reported[26] by Samuelsson using tritium to reduce the parent prostaglandins. Both Corey, *et al.*,[27] and Lincoln, *et al.*,[28] have also used similar conditions to selectively hydrogenate derivatives of prostaglandins. One interesting and significant difference here is that the 15-methyl compounds require no derivativization with blocking groups (such as THP) on the C-11 and C-15 hydroxyls for high selectivity. Unfortunately (as with the parent prostaglandin derivatives[27,28]), even though good selectivity could be achieved for the 15-methyl compounds under these conditions, the reactions required frequent monitoring by thin-layer chromatography using silver nitrate impregnated silica gel to avoid significant overreduction

Scheme VII

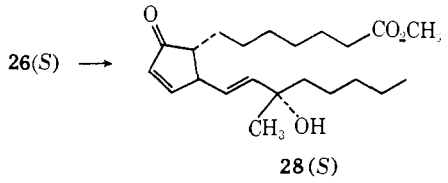


to the dihydro compounds. As shown, crystalline **23**(*S*) was also prepared directly from **15**(*S*) by hydrogenation at a higher temperature.

The 15-methyl-PGE_1 compounds could be prepared by either of two methods as shown in Scheme VII. The method for conversion of **22**(*S*) to crystalline **24**(*S*) was essentially identical with that used for the 15-methyl-PG_2 series (*vide supra*). Oxidation of **24**(*S*) followed by hydrolysis gave crystalline **26**(*S*) in overall yield of 40% from **22**(*S*). Selective hydrogenation at −5° directly on **18**(*R*) gave oily **26**(*R*) in 75% yield after chromatography. That this selectivity also was temperature dependent was shown by the hydrogenation of **18**(*S*) directly to give oily **27**(*S*) at 10°.



Using the method described above, (15*S*)-15-methyl-PGE_1 methyl ester, **26**(*S*), was converted to (15*S*)-15-methyl-PGA_1 methyl ester, **28**(*S*), in 95% yield.



Experimental Section

General. All melting points are corrected. All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with ir spectra being obtained either on neat samples (oils) or on mulls (crystalline samples) and 60-MHz nmr spectra on chloroform-*d* solutions containing internal tetramethylsilane. Thin-layer chromatography (tlc) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μ). Plates for silver nitrate silica gel tlc were prepared by dipping the Analtech plates in a saturated solution of ethonolic silver nitrate followed by brief drying on a hot plate at 200°. Where mixed solvents are used for tlc, the composition is expressed as a per cent by volume of the former in the latter or as a ratio by volume. The solvent system A-IX[29] is the organic layer from an equilibrated mixture of 90 ml of ethyl acetate, 20 ml of acetic acid, 50 ml of 2,2,4-trimethylpentane, and 100 ml of water. The plates were visualized first by uv light (using a UVS-12 lamp) then by spraying with a vanillin–phosphoric acid solution, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). Anhydrous solvents were generally prepared by drying over molecular sieves (Linde), size 3A or 4A. All reagents were used as purchased and were reagent grade where available.

(+)-2β,4β-Dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 4-Benzoate (2). To a stirred solution at 20° of 75 g (0.24 mol) of (−)-2β,4β-dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic acid γ-lactone, **1**, mp 101–102°, $[\alpha]D$ −50° (*c* 0.98, $CHCl_3$), in 135 ml of dry pyridine was added 30.4 ml (0.26 mol) of benzoyl chloride over a period of 5 min. After 30 min, 250 ml of toluene was added and the resulting solution evaporated to near dryness under reduced pressure. This was repeated. The residue was dissolved in 1000 ml of ethyl acetate. The organic solution was washed in sequence with 200 ml of aqueous 10% sulfuric acid and 200 ml of brine. The aqueous solutions were backwashed each with 200 ml of ethyl acetate. The ethyl acetate solutions were dried (sodium sulfate) and evaporated under reduced pressure to give 95 g (95%) of oil which crystallized. The crude

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(28) F. H. Lincoln, W. P. Schneider, and J. E. Pike, *J. Org. Chem.*, 38, 951 (1973).
(29) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, 241, 257 (1965).

product was recrystallized from ethanol to give a total of 90 g (90%) of white solid, mp 84–86°, $[\alpha]D$ +5° (*c* 1.03, $CHCl_3$). The ir showed bands at 1768, 1722, 1600, 1570, 1490, 1275, 1265, 1180, 1125, 1090, 1060, 1030, and 710 cm^{-1}. The nmr showed ($CDCl_3$) δ 2.1–3.45 (mult, 4), 4.3–4.5 (mult, 1), 3.30 (s, 3), 3.50 (d, 2), 4.3–4.5 (mult, 1), 5.0–5.2 (mult, 1), 5.51 (t, 1, 5 Hz), 7.18–7.58 (t, 3), 7.83–8.05 (mult, 2).

Anal. Calcd for $C_{16}H_{17}O_5I$: C, 46.12; H, 4.12. Found: C, 46.05; H, 4.10.

(−)-3α,5α-Dihydroxy-2β-(methoxymethyl)cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (3). To a stirred solution of 4.2 g (0.11 mol) of lithium aluminum hydride in 420 ml of ether under a nitrogen atmosphere and cooled in an ice bath was added dropwise a solution of 99 g (0.34 mol) of tributyltin chloride in 210 ml of ether over a period of 20–30 min.[30] The cooling bath was removed and stirring continued at ambient temperature for 1.5 hr. The solution was then cooled again in an ice bath. To this was cautiously added 260 ml of water causing vigorous hydrogen evolution at first which slowly subsided. The resulting mixture was transferred to a separatory funnel, equilibrated, and separated. (Caution: very hazardous chemical; use of rubber gloves in all handling operations is strongly urged.) The organic solution which contained the tributyltin hydride was washed twice with ice–water (2 × 200 ml) and dried (magnesium sulfate).

To a solution of 60 g (0.14 mol) of (+)-2β,4β-dihydroxy-3α-iodo-5α-(methoxymethyl)cyclopentane-1β-acetic acid γ-lactone 4-benzoate, **2**, in 240 ml of benzene cooled to 15° was added slowly the ethereal tributyltin hydride solution prepared above. After addition was complete, the solution was evaporated at 40° under reduced pressure to give an oil. The oil was stirred with 600 ml of Skellysolve B and 600 ml of water for 30 min. The mixture was separated, the product being dispersed in the aqueous layer and on the side of the vessel. The organic layer was extracted twice with water (2 × 60 ml). The aqueous solutions were combined, saturated with salt, and extracted with 450 ml of ethyl acetate, using a portion of the ethyl acetate to rinse the glassware. The aqueous solution was extracted three times more with ethyl acetate (3 × 175 ml). The ethyl acetate solutions were combined, dried (magnesium sulfate), and evaporated at reduced pressure to give 39 g (93%) of almost colorless oil. Tlc using cyclohexane–ethyl acetate (1:1) showed one spot, R_f 0.28. (Starting material shows R_f 0.48 in this system.) This material was used without further purification.

An analytical sample was prepared by washing a 2-g portion of the product twice with Skellysolve B (2 × 25 ml) followed by drying under vacuum. The ir showed bands at 1775, 1715, 1600, 1585, 1490, 1315, 1275, 1180, 1110, 1070, 1055, 1025, and 715 cm^{-1}. The nmr showed ($CDCl_3$) δ 2.15–3.0 (mult, 6), 3.25 (s, 3), 3.34 (d, 2, 6 Hz), 4.84–5.17 (mult, 1), 5.17–5.4 (mult, 1), 7.1–7.5 (mult, 3), 7.8–8.05 (mult, 2). The mass spectrum exhibited peaks at *m/e* 290 (M^+), 168 (M − 122), 105, and 77.

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65.49; H, 6.39.

(−)-3α,5α-Dihydroxy-2β-(hydroxymethyl)cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (4). To a vigorously stirred solution of 20 g (69 mmol) of crude (−)-3α,5α-dihydroxy-2β-(methoxymethyl)-cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **3**, in 320 ml of methylene chloride under a nitrogen atmosphere and cooled in an ice bath was added dropwise over a period of 50 min a solution of 24.8 ml (99 mmol) of boron tribromide in 320 ml of methylene chloride. After the addition was complete, the solution was kept cold and stirred an additional 1 hr. To the cold solution was cautiously added a solution of 78 g of sodium carbonate monohydrate in 200 ml of water over a period of 30 min. After addition, the mixture was stirred an additional 15 min. To this mixture was added 66 g of solid sodium chloride and stirring continued for 20 min. With the aid of ethyl acetate, the mixture was transferred to a separatory funnel, equilibrated, and separated. The aqueous phase (bottom) was extracted three times more with ethyl acetate (3 × 200 ml). The organic solutions were combined, washed with brine, dried (sodium sulfate), and evaporated under reduced pressure to give 18.1 g (95%) of oil which crystallized readily.

The product was recrystallized from 25 ml of methylene chloride and 25 ml of carbon tetrachloride to give a total of 16.9 g (89%) of crystalline material, mp 116–118°, $[\alpha]D$ −79° (*c* 0.89, $CHCl_3$). The ir showed bands at 3460, 1735, 1708, 1600, 1580, 1490, 1325, 1315, 1280, 1205, 1115, 1090, 1070, 1035, 1025, 730, and 720 cm^{-1}. The nmr showed absorptions at ($CDCl_3$) δ 2.1–3.0 (mult, 6), 3.58 (d, 2, 5.5 Hz), 4.83–5.12 (mult, 1), 5.2–5.45 (mult, 1), 7.15–7.55 (mult, 3), and 7.8–8.0 (mult, 2).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.70; H, 5.87.

(−)-3α,5α-Dihydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (6). To a stirred mixture of 1.75 g (0.15 mmol) of sodium hydride (50% dispersion in mineral oil) and 250 ml of tetrahydrofuran under an atmosphere of nitrogen and cooled in an ice bath was added 8.0 g (36 mmol) of dimethyl (2-oxoheptyl)phosphonate in portions over a period of about 2–3 min. The cooling bath was removed and the ylide mixture stirred at ambient temperature for 2 hr and then cooled to 0° again. A thick white precipitate formed within 30 min at ambient temperature.

To a stirred mixture of 11 g (0.11 mol) of anhydrous chromium trioxide and 150 ml of methylene chloride under a nitrogen atmosphere and cooled in an ice bath was added 17 g (0.22 mol) of anhydrous pyridine. This mixture was stirred an additional 15 min at 0°, at ambient temperature for 2 hr, then at 0° again. A solution of 5.0 g (18 mmol) of (−)-3α,5α-dihydroxy-2β-(hydroxymethyl)-cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **4**, in 150 ml of methylene chloride was cooled to 10° then added rapidly to the cold Collins oxidant solution. The resulting black mixture was stirred an additional 5 min. After addition of 100 ml of benzene, the mixture was filtered through Celite, washing well with benzene. The filtrate was concentrated to 50 ml under reduced pressure at 30° and then diluted with 100 ml of benzene. This solution was added to the cold ylide mixture from above. The resulting dark mixture was stirred for 1.5 hr at ambient temperature. After dropwise addition of 3 ml of acetic acid the mixture was concentrated under reduced pressure almost to dryness. The residue was dissolved in 400 ml of ethyl acetate. The solution was washed twice with water (2 × 80 ml) and then with brine. The aqueous solutions were backwashed with 100 ml of ethyl acetate. The organic solutions were combined, dried (sodium sulfate), and evaporated to give a dark oil. Tlc using ethyl acetate showed one major product, R_f 0.6.

The crude product was chromatographed on 500 g of silica gel, packed in methylene chloride. Taking 500-ml fractions, elution was with 7.5 l. of 25% and 5 l. of 30% ethyl acetate in Skellysolve B (v/v). Fractions 11–19 contained pure product, as analyzed by tlc (4.0 g (60%) of oil which crystallized). Recrystallization from ethyl acetate and Skellysolve B gave a total of 3.2 g (48%) of white needles, mp 63–63.8°, $[\alpha]D$ −113° (*c* 1.18 in chloroform). The uv (ethanol) showed λ_{max} 228 (26,150), 268 sh (899), 273 (1000) and 281 (829). The ir showed bands at 1765, 1715, 1690, 1625, 1600, 1585, 1495, 1320, 1275, 1165, 1115, 1075, 1030, 985, 975 and 715 cm^{-1}. The nmr showed absorptions at ($CDCl_3$) δ 0.7–1.9 (mult, 9), 2.2–2.3 (mult, 8), 4.9–5.4 (mult, 2), 6.17 (d, 1, 16 Hz), 6.71 (d of d, 1, 16 Hz, 6.5 Hz), 7.2–7.6 (mult, 3), 7.8–8.1 (mult, 2). The mass spectrum showed *m/e* 370 (M^+), 314 (M − 56), 248, 192, and 177.

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.10; H, 7.09.

Isolation of 3α,5α-Dihydroxy-2β-formylcyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (5). One-fifth of a 5-g run oxidation mixture was filtered through 3 in. of silica gel (washing well with ethyl acetate) after the black mixture had been stirred for 5 min but prior to addition of benzene. The resulting clear filtrate was evaporated to give 0.20 g of oil which crystallized on trituration with ether. The material exhibited mp ~115° dec and nmr absorption at ($CDCl_3$) δ 1.8–3.7 (mult, 6), 4.9–5.2 (mult, 1), 5.54–5.77 (mult, 1), 7.2–7.6 (mult 3), 7.7–8.0 (mult, 2), and 9.80 (mult, 1). The crystalline sample on standing at room temperature decomposed slowly to give what appeared be the unsaturated aldehyde 1-formyl-4α-hydroxycyclopentene-5α-acetic acid, γ-lactone, **7**.

Preparation of 1-Formyl-4α-hydroxycyclopentene-5α-acetic Acid γ-Lactone (7). The oxidation mixture of a 2-g run of **4** was filtered through Alumina Adsorption (Fisher) with the aid of tetrahydrofuran after the black mixture had been stirred for 5 min but prior to addition of benzene. The colorless filtrate appeared to contain only one substance which by tlc using ethyl acetate moved just behind compound **5**. The nmr of the material showed absorptions at ($CDCl_3$) δ 2.6–3.0 (mult, 4), 3.4–3.8 (mult, 1), 4.98–5.28 (mult, 1), 6.7–6.9 (mult, 1), 8.92 (mult, 1). Aldehyde **7** appeared quite stable at 0° in solution (tetrahydrofuran) but decomposed to unknown products when kept neat.

(−)-3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate [8(*RS*)] from Trimethylaluminum. To a stirred solution of 1.0 g (2.7 mmol)

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of (−)-3α,5α-dihydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **6**, in 50 ml of benzene at ambient temperature under nitrogen was added 0.6 ml of trimethylaluminum giving an intense yellow color. After 15 min, the color had faded significantly. Tlc (50% EtOAc–SSB) of an aliquot quenched in ether–ammonium chloride showed the reaction to be complete with one main spot. The reaction was quenched by dropwise addition of 30 ml of saturated aqueous ammonium chloride. The resulting mixture was transferred to a stoppered flask with the aid of ether and water, shaken, and filtered through a layer of Celite, washing well with ethyl acetate. The filtrate was separated and the aqueous phase extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 1.1 g (100%) of a light yellow oil. Tlc (50% EtOAc–SSB) showed one main spot, R_f ~0.2. Tlc using other solvents including 10% acetone–methylene chloride showed the main product to be one homogeneous spot. An analytical sample was prepared by chromatographing 200 mg on 20 g of silica gel (packed in 10% EtOAc–SSB). Taking 10-ml fractions, elution was with 25 ml of 10% and 250 ml of 50%. Fractions 8–12 contained good material, 0.16 g of colorless oil, $[\alpha]_D$ −80° (*c* 1.14, chloroform). The ir showed bands at 3500, 1770, 1715, 1600, 1580, 1490, 1450, 1315, 1270, 1175, 1110, 1070, 1045, 1025, 970, and 715 cm^{-1}. The nmr had absorptions at ($CDCl_3$) δ 0.6–3.0 (mult, 21), including singlets at 1.3 and 1.8, 4.8–5.4 (mult, 2), 5.5–5.7 (mult, 2). The mass spectrum showed ions at *m/e* 386 (weak), 384, 368, 315, 264, 249, 246, and 193.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.81; H, 7.65.

(−)-3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate [8(*RS*)] from Grignard. To a stirred solution of 0.20 g (0.54 mmol) of (−)-3α,5α-dihydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **6**, in 15 ml of tetrahydrofuran at −78° under nitrogen was added dropwise 3 ml of an ethereal solution 3 *M* in methylmagnesium bromide. The solution became heterogeneous. After 2 hr, a tlc (50% EtOAc–SSB) of an aliquot quenched with ether–ammonium chloride showed the reaction to be complete. To the mixture at −78° was added dropwise 10 ml of saturated aqueous ammonium chloride. The resulting mixture was allowed to warm with stirring to ambient temperature. The mixture was then diluted with ether and water, equilibrated, and separated. The aqueous phase was extracted three times more with ether. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 0.21 g (100%) of colorless oil. Tlc (50% EtOAc–SSB) showed one main spot, R_f ~0.2. This material appeared in every way identical with the main product formed upon treatment of **6** with trimethylaluminum, $[\alpha]_D$ −80° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 70.60; H, 7.95.

(−)-3α,5α-Dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone [9(*RS*)]. To a stirred solution of 0.50 g (1.8 mmol) of (−)-3α,5α-dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **8**(*RS*), in 10 ml of anhydrous methanol under nitrogen at ambient temperature was added 1.0 ml of a 25% solution of sodium methoxide in methanol. After 20 min, tlc (ethyl acetate) showed the reaction to be complete with only one vanillin-visible product. The reaction was quenched by the addition of 2 ml of acetic acid. The solution was rotary evaporated at 40° to give an oil. The product was dissolved in ethyl acetate and extracted twice with saturated aqueous sodium bicarbonate, the aqueous extracts being combined and backwashed with ethyl acetate. The organic solutions were combined, washed with brine, dried over sodium sulfate, and evaporated to give 0.41 g of a mobile yellow oil. Trituration twice with SSB left 0.34 g (85%) of viscous oil. Tlc (ethyl acetate) showed one main spot, R_f ~0.4.

An analytical sample was prepared by chromatographing a 0.2-g portion on 20 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 10-ml fractions, elution was with 50 ml of 75% ethyl acetate–hexane and 200 ml of ethyl acetate. Fractions 8–13 contained good material as analyzed by tlc (R_f 0.4 in ethyl acetate), 0.18 g (77%) of an oil, $[\alpha]_D$ −10° (*c* 1.21, chloroform). The mass spectrum exhibited *m/e* of 282 (very weak), 211, 193, and 133.

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.91; H, 9.35.

3α,5α-Dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol [10(*RS*)] from (−)-3α,5α-Dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone [9(*RS*)]. To a stirred solution of 0.50 g (1.8 mmol) of lactone diol, **9**(*RS*), in 15 ml of tetrahydrofuran at −78° under nitrogen was added carefully 12 ml of 10% diisobutylaluminum hydride in toluene. Gas evolution ceased before addition was complete. After addition, tlc (ethyl acetate) of an aliquot quenched in ether–aluminum chloride showed complete reaction. The reaction was quenched at −78° by dropwise addition of 15 ml of saturated aqueous ammonium chloride. The resulting mixture was allowed to warm to ambient temperature, transferred to a stoppered flask with the aid of ethyl acetate and water, shaken, and filtered through Celite, washing well with ethyl acetate. The filtrate was diluted with brine and ethyl acetate, equilibrated, and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated to give 0.51 g (100%) of oil. Tlc in EtOAc showed one main spot, R_f 0.3, with no starting material (R_f ~0.4), and a trace of a more polar product R_f <0.1. The material was used with no further purification or characterization.

3α,5α-Dihydroxy-2β-[3-(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol [10(*RS*)] from (−)-3α,5α-Dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate [8(*RS*)]. To a stirred solution of 0.50 g (1.3 mmol) of **8**(*RS*) in 15 ml of tetrahydrofuran at −78° under nitrogen was added 10 ml of 10% diisobutylaluminum hydride in toluene. After 30 min, tlc (ethyl acetate) of an aliquot quenched in ether–water showed one main product just behind the starting material. The solution was allowed to warm to −20°. After 20 min more, tlc showed complete reaction to **10**(*RS*) with some apparent overreduction (more polar material). The reaction at −20° was quenched by careful addition of 10 ml of water. The resulting mixture was stirred at ambient temperature then transferred to a stoppered flask with the aid of water and ethyl acetate, shaken, and filtered through Celite, washing well with ethyl acetate. The filtrate was diluted with ethyl acetate and brine, equilibrated, and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated to give 0.39 g (106%) of an oil. Tlc (ethyl acetate) showed the main product as **10**(*RS*) with some more polar products. The product was used without further purification or characterization.

3α,5α-Dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol 3-Benzoate [11(*RS*)]. To a stirred solution of 0.50 g (1.3 mmol) of (−)-3α,5α-dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic acid γ-lactone 3-benzoate, **8**(*RS*), in 15 ml of tetrahydrofuran at −78° under nitrogen was added dropwise 10 ml of 10% diisobutylaluminum hydride in toluene. Gas evolution occurred after a 15-sec delay. The rate of addition was controlled to avoid excess foaming. Before addition was complete, gas evolution had ceased. After 30 min, tlc (50% ethyl acetate–Skellysolve B and 100% ethyl acetate) of an aliquot quenched in ether–ammonium chloride showed the reaction to be complete with one major product running just behind the starting material. Traces of the more polar lactone diol **4**(*RS*) and lactol diol **10**(*RS*) were also present. The reaction was quenched at −78° by careful addition of 10 ml of saturated aqueous ammonium chloride. The resulting mixture was allowed to warm to ambient temperature with stirring, transferred to a stoppered flask with the aid of water and ethyl acetate, shaken, and finally filtered through Celite, washing well with ethyl acetate. The filtrate was diluted with ethyl acetate and brine, equilibrated, and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated to give 0.48 g (96%) of oil. Tlc showed the main product with R_f 0.18 and 0.49 in 50% EtOAc–SSB and 100% EtOAc, respectively. (Compare the starting material: R_f 0.20 and 0.56, respectively.) The product was used without further purification or characterization.

3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Trimethylsilyl Ether [12(*RS*)]. To a stirred solution of 0.50 g (1.8 mmol) of (−)-3α,5α-dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic acid γ-lactone, **9**(*RS*), in 10 ml of acetone at 0° under nitrogen was added 1.0 ml (0.76 g, 5.2 mmol) of trimethylsilyldiethylamine. After 30 min, tlc (ethyl acetate) showed complete reaction. The excess reagent was quenched by dilution first with 15 ml of ether and then addition of the resulting solution to saturated aqueous sodium bicarbonate. After equilibration, the aqueous phase was extracted three times with ether (3 × 20 ml). The organic extracts were combined, washed with brine, dried

(sodium sulfate), and evaporated. The watery residue was azeotroped twice with benzene under reduced pressure at 40° to give 0.60 g (100%) of yellow oil. Tlc using ethyl acetate showed one main spot, R_f 0.8 (starting material, **9**(*RS*) has R_f 0.4). This material was used without further purification or characterization.

3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol 3-Trimethylsilyl Ether [13(*RS*)]. To a stirred solution of 0.60 g (1.7 mmol) of 3α,5α-dihydroxy-2β-[3(*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetic acid γ-lactone 3-trimethylsilyl ether, **12**(*RS*), in 10 ml of toluene at −78° under nitrogen was added 8 ml of 10% diisobutylaluminum hydride in toluene. Gas evolution ceased before complete addition. After addition, tlc (ethyl acetate) of an aliquot quenched in ether–ammonium chloride showed reaction to be complete. The reaction was quenched at −78° by the addition of 5 ml of water and 5 ml of tetrahydrofuran. The resulting mixture was allowed to warm to ambient temperature with stirring, transferred to a stoppered flask with the aid of ether and water, shaken, and filtered through Celite, washing well with ethyl acetate and water. The filtrate was equilibrated and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated to give, after azeotroping with benzene, 0.57 g (95%) of yellow oil. Tlc (ethyl acetate) showed one main spot, R_f 0.7 (compare starting material, R_f ~0.8, and lactol diol **10**(*RS*), R_f 0.3). The product was used without further purification or characterization.

(15*R*)- and (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Esters [15(*RS*)] from 3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol [10(*RS*)]. A mixture of 0.52 g (10.8 mmol theor) of 50% sodium hydride in mineral oil and 15 ml of dimethyl sulfoxide was stirred under nitrogen at 70–75° for 1.5 hr. The resulting dark solution was cooled to ambient temperature. To this was added 2.4 g (5.4 mmol) of 4-carboxybutyltriphenylphosphonium bromide with an additional 5 ml of dimethyl sulfoxide. The resulting dark solution was stirred 1 hr at ambient temperature. To this solution was added 0.51 g (1.8 mmol theor) of **10**(*RS*). The resulting mixture was allowed to stir overnight at ambient temperature. The reaction was quenched by addition to a mixture of 0.2 *M* sodium bisulfate in ice–water and ether. After equilibration, the aqueous phase (pH ≤1) was extracted well with ether. The organic extracts were combined and then washed once with 1 *N* sodium hydroxide and twice with water. The aqueous washings were combined and carefully acidified to pH <3 with 2 *M* sodium bisulfate in the presence of ether. After equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with water, dried (sodium sulfate), and evaporated to give 0.61 g of yellow oil. Tlc (A–IX) showed one main spot, R_f 0.4. The product **14**(*RS*) was dissolved in ether, methylene chloride, and methanol and treated with excess ethereal diazomethane to give, after evaporation, 0.68 g of dark oil. The crude product was chromatographed on 10 g of silica gel, packed in 50% ethyl acetate–Skellysolve B. Taking 20-ml fractions, elution was with 100 ml of 50%, 100 ml of 75%, and 100 ml of 100%. Fractions 7–12 contained good product **15**(*RS*) (as a mixture of C-15 epimers), 0.39 g (57%) of yellow oil, tlc R_f 0.4 in ethyl acetate. The mixture was purified further (see below). The nmr spectrum and tlc mobility of the crude product **15**(*RS*) were identical with **15**(*RS*) prepared by other methods.[6,7a] The nmr showed ($CDCl_3$) δ 0.70–2.60 (m, 29), including a singlet at 1.28, 3.70 (s, 3), 3.82–4.40 (m, 2), 5.27–5.68 (m, 4).

(15*R*)- and (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Esters [15(*RS*)] from 3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol 3-Benzoate [11(*RS*)]. A mixture of 0.23 g (4.8 mmol theoretical) of 50% sodium hydride dispersion in mineral oil and 10 ml of dimethyl sulfoxide was stirred under nitrogen at 70–75°. After 1 hr, gas evolution had ceased. The resulting solution was stirred an additional 0.5 hr and then cooled to ambient temperature. To this solution at ambient temperature was added 1.06 g (2.4 mmol) of 4-carboxybutyltriphenylphosphonium bromide and the resulting dark red solution stirred at ambient temperature for 0.5 hr. To this solution at ambient temperature was added a solution of 0.48 g (1.2 mmol theoretical) of **11**(*RS*) in a total of 15 ml of dimethyl sulfoxide. The resulting dark orange mixture was stirred at ambient temperature. After 1 hr, tlc (A–IX) of an aliquot quenched in ether–sodium bisulfate showed a complex mixture of which lactol diol **10**(*RS*) (or material with same R_f) was the major spot, along with some starting material and a product corresponding to free acid **14**(*RS*). After 2 hr, tlc showed little starting material with an apparent ratio of **10**(*RS*):product **14**(*RS*) of 2:1. After stirring 12 hr at ambient temperature, no further change was evident. Another 1.2 mmol of freshly prepared ylide in 3.6 ml of solution (prepared as above) was added. After 24 hr more, tlc showed 1:1 **10**(*RS*):product. After an additional 24 hr, tlc showed 1:2 **10**(*RS*):product with some very polar material. The reaction was quenched by addition to 15 ml of 2 *M* sodium bisulfate (diluted with ice–water) and 25 ml of ether. After equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined, washed once with 5 ml of 1 *N* sodium hydroxide, and twice with water. The aqueous washings were combined (pH ≤11) and carefully acidified with sodium bisulfate to pH ~1 in the presence of ether. After equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined, washed twice with water and once with brine, dried (sodium sulfate), and evaporated to give 0.45 g of dark oily solid. Tlc (A–IX) showed no change from before. The crude product was dissolved in a solution of methylene chloride, ether, and methanol and treated with excess ethereal diazomethane. Evaporation gave 0.40 g of dark oil. Tlc (ethyl acetate) showed **15**(*RS*) as major product (both epimers visible) with more polar impurities. The crude product was chromatographed on 10 g of silica gel, packed in 50% ethyl acetate–Skellysolve B. Taking 20-ml fractions elution was with 100 ml of 50%, 100 ml of 75%, and 140 ml of 100%. Fractions 9–12 contained good product **15**(*RS*) (as mixture of epimers), 160 mg (35%) of oil. The nmr spectrum and tlc mobility of the product **15**(*RS*) were identical with those for **15**(*RS*) prepared above and by other methods.[6,7a]

(15*R*)- and (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Esters [15(*RS*)] from 3α,5α-Dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-Lactol 3-Trimethylsilyl Ether [13(*RS*)]. A mixture of 0.40 g (8.4 mmol theoretical) of 50% sodium hydride dispersion in mineral oil and 10 ml of dimethyl sulfoxide was stirred under nitrogen at 70–75° for 1.5 hr. The resulting solution was allowed to cool to ambient temperature (~2 hr). To this solution was added 1.9 g (4.2 mmol) of 4-carboxybutyltriphenylphosphonium bromide. The resulting dark red solution was stirred at ambient temperature for 1 hr. To this solution was added a solution of 0.57 g (1.6 mmol) of 3α,5α-dihydroxy-2β-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-lactol, 3-trimethylsilyl ether [**13**(*RS*)] in 10 ml of dimethyl sulfoxide. The resulting solution was stirred overnight at ambient temperature. Tlc (A–IX) of an aliquot quenched in ether–sodium bisulfate showed the reaction to be complete with one main product corresponding to the free acid **14**(*RS*). The reaction was quenched by addition to a mixture of 0.2 *M* sodium bisulfate in ice–water and ether. After equilibration, the aqueous phase (pH ≤1) was extracted well with ether then discarded. The organic extracts were combined, washed once with dilute sodium hydroxide and twice with water, and then discarded. These aqueous washings were combined and then carefully acidified to pH <3 with 2 *M* sodium bisulfate in the presence of ether. After equilibration, the aqueous phase was extracted well with ether. These organic extracts were combined, washed with water and brine, dried (sodium sulfate), and evaporated to give 0.68 g of yellow oil. The product was dissolved in ether, methylene chloride, and methanol and the resulting solution treated with excess ethereal diazomethane to give, after evaporation, 0.72 g of dark yellow oil. This was chromatographed on 10 g of silica gel, packed in 50% ethyl acetate–Skellysolve B. Taking 20-ml fractions, elution was with 100 ml of 50%, 100 ml of 75%, and 100 ml of 100%. Fractions 7–13 contained good product **15**(*RS*) (as a mixture of epimers), 0.31 g (50%) of yellow oil. The nmr spectrum and tlc mobility of the product **15**(*RS*) were identical with those of **15**(*RS*) prepared above and by other methods.[6,7a]

Chromatographic Separation of (15*R*)- and (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Esters [15(*RS*)]. A 1.0-g sample of the mixture (15*R*)- and (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*RS*), was chromatographed on 100 g of silica gel, packed in 5% acetone–CH_2Cl_2 in a column having an effective height:diameter ratio of 37. Taking 11-ml fractions, elution was with 100 ml of 5%, and 2.5 l. of 30%. Fractions combined were: 81–110, ≥90% **15**(*R*), 0.22 g of oil; 111–130, ~1:1 mixture of (*R*):(*S*), 0.12 g; 131–140, ~1:3 mixture of (*R*):(*S*), 0.10 g; 141–200, ≥90% **15**(*S*), 0.21 g, crystalline. Recrystallization of the latter once from 25 ml of ether–hexane (1:1) gave 0.15 g, mp 52–54°. Recrystallization once more gave 0.12 g (24%), mp 55–56°, $[\alpha]_D$ +24° (*c* 0.81, ethanol). The ir spectrum of **15**(*S*) showed bands at 3300, 1735, 1315, 1260, 1195, 1170, 1130, 1040, 975, 965, 910, and 835 cm^{-1}. The mass spectrum of the tris(trimethylsilyl) ether derivative of **15**(*S*) showed *m/e* at 598 (M^+), 583 ($M^+ - CH_3$), 527 ($M^+ - C_5H_{11}$), 508, and 437. The nmr spectrum showed absorptions at ($CDCl_3$) δ 0.70–

2.60 (m, 29), including a singlet at 1.28, 3.70 (s, 3), 3.82–4.40 (m, 2), 5.27–5.68 (m, 4).

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.21; H, 10.11.

The **15**(*R*) obtained in fractions 81–110 above was rechromatographed on 25 g of silica gel packed in 50% ethyl acetate–hexane. Taking 25-ml fractions, elution was with 250 ml of 80% ethyl acetate–hexane. Fractions 8–12 contained good material, 0.17 g of oil, $[\alpha]D$ +26° (*c* 0.90, chloroform). The ir, nmr, and mass spectra were identical with **15**(*S*) above.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.47; H, 10.29.

(15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester 11-Trimethylsilyl Ether [16(*S*)]. To a stirred solution of 0.50 g (1.3 mmol) of (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*S*), and 20 ml of acetone at −45° under nitrogen was added 2.0 ml of *N*-trimethylsilyldiethylamine (ρ 0.763; 10 mmol). The temperature was maintained at −45 to −41° by periodic additions of Dry Ice to an acetone bath. The progress of the reaction was followed by tlc (50% ethyl acetate in Skellysolve B). After 1 hr, tlc showed no starting material with one major product (R_f 0.62) and a trace of a less polar product (bis-(TMS), R_f 0.83). The solution, while at −45°, was diluted with 80 ml of anhydrous ether, previously cooled to −78°. The resulting solution was transferred and partitioned over one-half saturated sodium bicarbonate. The aqueous phase was washed twice with ether. The ether solutions were combined, washed with brine, dried (sodium sulfate), and rotary evaporated at 40° to give 0.68 g of a light yellow oil. Further evaporation under high vacuum (20 μ) gave 0.61 g (103%) of oil which crystallized with cooling. Tlc showed no change from above. The bulk of the material was used without further purification. An analytical sample was prepared by recrystallization once from hexane (80% yield), mp 33–35°. The ir spectrum showed bands at 3400, 2900, 1730, 1430, 1360, 1240, 1140–1200, 970, and 830–900 cm^{-1}. The nmr spectrum showed absorption at ($CDCl_3$) δ 0.1 (s, 9), 0.7–2.8 (m, 28), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m, 2), and 5.2–5.7 (m, 4). The mass spectrum showed *m/e* at 454 (M^+), 439 ($M^+ - CH_3$), 436 ($M^+ - H_2O$), 418 ($M^+ - 2H_2O$), and 383 ($M^+ - C_5H_{11}$).

Anal. Calcd for $C_{25}H_{46}O_5Si$: C, 66.03; H, 10.20. Found: C, 66.05; H, 10.31.

(15*R*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester 11-Trimethylsilyl Ether [16(*R*)]. In exactly the same manner as described above for its C-15 epimer **15**(*S*), a sample of 0.50 g (1.3 mmol) of (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*R*), was converted to 0.57 g (100%) of crude (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester 11-trimethylsilyl ether, **16**(*R*), as an oil. The material was used without further purification. The ir spectrum showed bands at 3400, 2900, 1730, 1430, 1360, 1240, 1140–1200, 970, and 830–900 cm^{-1}. The nmr spectrum showed absorptions at ($CDCl_3$) δ 0.1 (s, 9), 0.7–2.8 (m, 28), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m, 2), and 5.2–5.7 (m, 4). The mass spectrum showed *m/e* at 454 (M^+), 439 ($M^+ - CH_3$), 436 ($M^+ - H_2O$), 418 ($M^+ - 2H_2O$), and 383 ($M^+ - C_5H_{11}$).

(15*S*)-15-Methyl-PGE$_2$ Methyl Ester 11-Trimethylsilyl Ether [17(*S*)]. A solution of Collins reagent[16] was prepared *in situ* by adding 1.0 g (10 mmol) of anhydrous chromium trioxide to a mechanically stirred solution of 1.6 g (20 mmol) of dry pyridine and 50 ml of methylene chloride cooled in an ice–water bath, under nitrogen. The mixture was allowed to stir at room temperature for at least 45 min and then cooled again to 0°. To the cold vigorously stirred Collins solution was added in one portion a solution of 0.58 g (1.3 mmol theoretical) of (15*S*)-15-methyl PGF$_{2\alpha}$ methyl ester 11-trimethylsilyl ether, **16**(*S*), in 15 ml of methylene chloride. The resulting dark mixture was stirred at ambient temperature for 10 min and then decanted and filtered under vacuum through 3 in. of neutral silica gel into a suction flask, washing well with ethyl acetate. The yellow filtrate was rotary evaporated to give, after further drying under a stream of nitrogen, 0.57 g (100%) of a dark yellow oil. Tlc (50% ethyl acetate in Skellysolve B) showed one major product (R_f 0.67) with a trace of starting material (R_f 0.63) and traces of other less and more polar by-products. The crude product was used without further purification. The ir spectrum of **17**(*S*) showed bands at 3400, 2900, 1730, 1720, 1430, 1360, 1240, 1140–1200, 970, and 830–900 cm^{-1}. The nmr showed absorptions at ($CDCl_3$) δ 0.1 (s, 9), 0.7–2.8 (m, 27), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m 1), and 5.2–5.7 (m, 4). The mass spectrum showed *m/e* at 452 (M^+), 437 ($M^+ - CH_3$), 434 ($M^+ - H_2O$), and 381 ($M^+ - C_5H_{11}$).

(15*R*)-15-Methyl-PGE$_2$ Methyl Ester 11-Trimethylsilyl Ether [17(*R*)]. In exactly the same manner as described for its C-15 epimer **16**(*S*) above, a sample of 0.57 g (1.3 mmol theoretical) of (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester 11-trimethylsilyl ether, **16**(*R*), was oxidized to give 0.58 g (100%) of (15*R*)-15-methyl-PGE$_2$ methyl ester 11-trimethylsilyl ether, **17**(*R*), as a dark yellow oil. Tlc (50% ethyl acetate in Skellysolve B) showed one major product (R_f 0.67) with a trace of starting material (R_f 0.63) and traces of other less and more polar by-products. The crude product was used without further purification. The ir spectrum of **17**(*R*) showed bands at 3400, 2900, 1730, 1720, 1430, 1360, 1240, 1140–1200, 970, and 830–900 cm^{-1}. The nmr showed absorptions at ($CDCl_3$) δ 0.1 (s, 9), 0.7–2.8 (m, 27), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m, 1), and 5.2–5.7 (m, 4). The mass spectrum showed *m/e* at 452 (M^+), 437 ($M^+ - CH_3$), 434 ($M^+ - H_2O$), and 381 ($M^+ - C_5H_{11}$).

(15*S*)-15-Methyl-PGE$_2$ Methyl Ester [18(*S*)]. To a solution of 0.57 g (1.3 mmol theoretical) of crude (15*S*)-15-methyl-PGE$_2$ methyl ester 11-trimethylsilyl ether, **17**(*S*), in 30 ml of methanol at room temperature in a water bath was added with stirring a solution of 15 ml of water and 1.5 ml of acetic acid (exothermic). The reaction was stirred 15 min or until homogeneous. The solution was transferred and partitioned between ether and 0.2 *M* sodium bisulfate. The aqueous phase was washed once with ether. The ether solutions were combined, washed with saturated sodium bicarbonate and brine, dried (sodium sulfate), and rotary evaporated at 40° to give 0.43 g of light yellow oil. Tlc (100% ethyl acetate) showed one main component (R_f 0.4) with small amounts of less and more polar by-products and with a trace of (15*S*)-15-methyl PGF$_{2\alpha}$ methyl ester, **15**(*S*) (R_f 0.3).

The crude product was chromatographed on 50 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 25-ml fractions, elution was with 700 ml of 80% ethyl acetate–hexane. Fractions 9–15 were combined to give 0.24 g (49%) of product **18**(*S*) as a colorless oil, $[\alpha]D$ −79° (*c* 1.3, chloroform). The ir of **18**(*S*) showed bands at 3400, 2960, 2860, 1735, 1455, 1435, 1370, 1335, 1315, 1245, 1220, 1160, 1080, and 975 cm^{-1}. The nmr spectrum showed absorptions at ($CDCl_3$) δ 0.7–2.8 (m, 28), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m, 1), and 5.2–5.7 (m, 4). The mass spectrum showed no molecular ion with *m/e* at 362 ($M^+ - H_2O$), 344 ($M^+ - 2H_2O$), 309 ($M^+ - C_5H_{11}$), and 291. The uv in neutral ethanol showed end absorption only but in basic ethanol showed λ_{max} 278 (25,250) and 350 sh (780). Careful tlc showed one spot having R_f values of 0.44 and 0.14 in ethyl acetate and 20% acetone–methylene chloride, respectively (compare **18**(*R*): R_f 0.47 and 0.17, respectively).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.03; H, 9.54.

(15*R*)-15-Methyl-PGE$_2$ Methyl Ester [18(*R*)]. To a solution of 0.58 g (1.3 mmol theoretical) of crude (15*R*)-15-methyl-PGE$_2$ methyl ester 11-trimethylsilyl ether, **17**(*R*), in 30 ml of methanol at room temperature in a water bath was added with stirring a solution of 15 ml of water and 1.5 ml of acetic acid (exothermic). The reaction was stirred 15 min or until homogeneous. The solution was transferred and partitioned between ether and 0.2 *M* sodium bisulfate. The aqueous phase was washed once with ether. The ether solutions were combined, washed with saturated sodium bicarbonate and brine, dried (sodium sulfate), and rotary evaporated at 40° to give 0.45 g of light yellow oil. Tlc (100% ethyl acetate) showed one main component (R_f 0.4) with small amounts of less and more polar by-products and with a trace of (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **17**(*R*) (R_f 0.3).

The crude product was chromatographed on 45 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 20-ml fractions, elution was with 80% ethyl acetate–hexane. Fractions 12–17 were combined to give 0.18 g (38%) of (15*R*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*), as a colorless oil, $[\alpha]D$ −74° (*c* 1.0, chloroform). The ir of **18**(*R*) showed bands at 3430, 2950, 2930, 2860, 1740, 1460, 1440, 1335, 1315, 1255, 1225, 1160, 1075, and 975 cm^{-1}. The nmr spectrum showed absorptions at ($CDCl_3$) δ 0.7–2.8 (m, 28), including a singlet at 1.28, 3.70 (s, 3), 3.8–4.3 (m, 1), and 5.2–5.7 (m, 4). The mass spectrum showed no molecular ion wih *m/e* at 362 ($M^+ - H_2O$), 344 ($M^+ - 2H_2O$), 309 ($M^+ - C_5H_{11}$), and 291. The uv in neutral ethanol showed end absorption only but in basic ethanol showed λ_{max} 278 (25,200) and 343 sh (699). Careful tlc showed one spot having R_f values of 0.47 and 0.17 in ethyl acetate and 20% acetone–methylene chloride, respectively (compare **18**(*S*): R_f 0.44 and 0.14, respectively).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.08; H, 9.24.

Epimerization of (15*R*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester [15(*R*)]. A solution of 1.0 g (26 mmol) of (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*R*), in 60 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 2.5 hr. The solution was cooled to ambient

temperature, diluted with 80 ml of water, and freeze dried to give 0.96 g of oil. Tlc (30% acetone–methylene chloride) showed **15**-(*RS*) to be the main product (epimer ratio ~1:1 *S*:*R*) with several less polar spots. The crude product was chromatographed on 100 g of silica gel, packed in 5% acetone–methylene chloride. Taking 30-ml fractions after the first 500 ml, elution was with 1 l. of 30% acetone–methylene chloride. Fractions combined were: 3, impure **15**(*R*), 40 mg of oil; 4 and 5, 3:1 (*R*):(*S*), 0.13 g of oil; 6–11, 1:1 (*R*):(*S*), 0.23 g of oil; 12–29, 1:3 (*R*):(*S*), 0.19 g of oil. Total recovery of **15**(*RS*) was 0.59 g (59%).

Epimerization of (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester [15(*S*)]. A solution of 0.10 g (2.5 mmol) of (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*S*), in 6 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 2.5 hr. The solution was cooled to ambient temperature, diluted with 8 ml of water, and carefully acidified by addition of saturated sodium bisulfate. The resulting mixture was extracted well with ether. The organic extracts were combined, washed once each with saturated sodium bicarbonate and brine, dried (sodium sulfate), and evaporated to give 0.1 g of oil. Tlc (30% acetone–methylene chloride) showed a product distribution identical with that from epimerization of **15**(*R*): ratio of 1:1 of **15**(*R*) and **15**(*S*) with some less polar materials.

Epimerization of (15*R*)-15-Methyl-PGE$_2$ Methyl Ester [18(*R*)]. A solution of 50 mg of (15*R*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*), in 3 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 2.5 hr. The solution was cooled to ambient temperature, diluted with 4 ml of water, and freeze dried. Tlc (20% acetone–methylene chloride) showed clearly the presence in a 1:1 ratio of both (15*R*)- and (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*) and **18**(*S*). In addition, small amounts of materials having higher R_f values were also present.

Epimerization of (15*S*)-15-Methyl-PGE$_2$ Methyl Ester [18(*S*)]. A solution of 9 mg of (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*S*), in 0.3 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 2.5 hr. The solution was cooled to ambient temperature, diluted with 1 ml of water, and freeze dried. Tlc (20% acetone–methylene chloride) of the residue showed clearly the presence in a 1:1 ratio of both (15*R*)- and (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*) and **18**(*S*). In addition, small amounts of materials having higher R_f values were also present.

Chromatographic Separation of (15*R*)- and (15*S*)-15-Methyl-PGE$_2$ Methyl Ester [18(*R*)] and [18(*S*)]. A sample of 1.1 g of crude product consisting of a 1:1 ratio of **18**(*R*) and **18**(*S*) (along with less polar material) was chromatographed in a column having an effective height-to-diameter ratio of 34 on 150 g of silica gel, packed in 5% acetone–methylene chloride. Taking 25-ml fractions, the column was eluted with 1000 ml of 10% (acetone in methylene chloride), 1000 ml of 15%, 2500 ml of 20%, and 3000 ml of 30%. The main product came during the 20% elution. Fractions were analyzed using tlc by running the plates up twice in 20% acetone–methylene chloride. Fractions combined were: 103–117, 0.14 g of pure **18**(*R*); 118–142, 0.27 g of a mixture of **18**(*R*) and **18**(*S*); 143–155, 50 mg of pure **18**(*S*); and 157–165, 20 mg of a mixture of **18**(*S*) and more polar materials.

Epimeric Stability of (15*R*)- or (15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester [15(*R*) or 15(*S*)] to Conditions for Trimethylsilyl Ether Hydrolysis. A solution of 10 mg of either (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*R*), or (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*S*), in 0.8 ml of a solution of methanol–water–acetic acid (20:10:1) was allowed to stand at ambient temperature for 30 min. The solution was then partitioned between ether and 0.2 *M* sodium bisulfate. After equilibration, the aqueous layer was extracted twice with ether. The organic extracts were combined, washed once each with saturated sodium bicarbonate and brine, and then dried (sodium sulfate) and evaporated at 40° to give 10 mg each of oil (the product from the **15***S* crystallized). Tlc (30% acetone–methylene chloride) showed no change from starting materials (the presence of 5% of each C-15 epimer could have been seen as an impurity in the other).

Epimeric Stability of (15*R*)- or (15*S*)-15-Methyl-PGE$_2$ Methyl Ester [18(*R*) or 18(*S*)] to Conditions for Trimethylsilyl Ether Hydrolysis. A solution of 25 mg of either (15*R*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*), or (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*S*), in 2 ml of a solution of methanol–water–acetic acid (20:10:1) was allowed to stand at ambient temperature for 30 min. The solution was partitioned between ether and 0.2 *M* sodium bisulfate. After equilibration, the aqueous layer was extracted twice with ether. The organic extracts were combined, washed once each with saturated sodium bicarbonate and brine, and dried (sodium sulfate) and evaporated at 40° to give 25 mg of oil. Tlc (20% acetone–methylene chloride, developed twice) showed no change from starting material (the presence of 5% of each C-15 epimer could have been seen as an impurity in the other).

(15*S*)-15-Methyl-PGF$_2\beta$ Methyl Ester [19(*S*)]. To a stirred solution of 0.40 g (1.1 mmol) of (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*S*), in 20 ml of methanol at −20° was added 60 mg (1.6 mmol) of sodium borohydride. After 30 min, the excess borohydride was quenched by dropwise addition of 4 ml of 1:1 water–acetic acid. The resulting solution was allowed to warm to ambient temperature and then diluted with ethyl acetate. This solution was washed sequentially with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine and then dried (sodium sulfate) and evaporated to give 0.3 g of residue. Tlc using 30% acetone in methylene chloride showed the presence of two products, the less polar of which appeared identical with (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*S*). The crude product was chromatographed on 30 g of silica gel, packed in 25% ethyl acetate–hexane. Taking 10-ml fractions, elution was with 100 ml of 75% and 600 ml of 100%. Fractions 7–15 were combined to give 103 mg of crystalline material identical with **15**(*S*) (optical rotation, ir, nmr, mp, tlc). Fractions 16–24 contained 20 mg of a mixture of the two products. Fractions 25–55 contained 150 mg of crystalline material assigned to be (15*S*)-15-methyl-PGF$_2\beta$ methyl ester, **19**(*S*). Recrystallization once from ethyl acetate–hexane gave 70 mg, mp 101–102°, $[\alpha]_D$ −7° (*c* 0.87, ethanol). The nmr spectrum showed δ 0.6–2.5 (m, 26), including a singlet at 1.27, 2.9 (broad s, 3), 3.70 (s, 3), 3.8–4.2 (m, 2), and 5.3–5.7 (m, 4). The ir spectrum showed bands at 3250, 3020, 1740, 1345, 1310, 1235, 1215, 1190, 1170, 1085, 1040, 970, 920, and 875 cm^{-1}. The mass spectrum of the tris(trimethylsilyl) derivative gave peaks at *m/e* 598 (M^+), 583 ($M^+ - CH_3$), 567 ($M^+ - OCH_3$), 527 ($M^+ - C_5H_{11}$), 508, 493, 477, 437, and 418.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.80; H, 10.20.

(15*R*)-15-Methyl-PGF$_2\beta$ Methyl Ester [19(*R*)]. To a stirred solution of 0.40 g (1.1 mmol) of (15*R*)-15-methyl-PGE$_2$ methyl ester, **18**(*R*), in 20 ml of methanol at −20° was added 60 mg (1.6 mmol) of sodium borohydride. After 30 min, the excess borohydride was quenched by dropwise addition of 4 ml of 1:1 water–acetic acid. The resulting solution was allowed to warm to ambient temperature and then diluted with ethyl acetate. This solution was washed sequentially with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine and then dried (sodium sulfate) and evaporated to give 0.4 g of oil. Tlc using 30% acetone in methylene chloride showed the presence of two products, the less polar of which appeared identical with (15*R*)-15-methyl-PGF$_{2\alpha}$ methyl ester, **15**(*R*). The crude product was chromatographed on 40 g of silica gel, packed in 50% ethyl acetate–hexane. Taking 10-ml fractions, elution was with 1000 ml of 75% and 1000 ml of 100%. Fractions 21–43 were combined to give 144 mg of oily material identical with **15**(*R*) (optical rotation, ir, nmr, tlc). Fractions 44–49 contained 15 mg of a mixture. Fractions 50–71 contained 160 mg of crystalline material assigned to be (15*R*)-15-methyl-PGF$_2\beta$ methyl ester, **19**(*R*). Recrystallization once from ethyl acetate–hexane gave 110 mg, mp 94.3–95.5°, $[\alpha]_D$ −1° (*c* 1.10, ethanol). The nmr showed absorptions at δ 0.6–2.5 (m, 26), including a singlet at 1.27, 2.9 (broad s, 3), 3.70 (s, 3), 3.8–4.2 (m, 2), and 5.3–5.7 (m, 4). The ir showed bands at 3320, 3020, 1740, 1660, 1410, 1345, 1245, 1210, 1195, 1085, and 980 cm^{-1}. The mass spectrum of the tris(trimethylsilyl) derivative showed peaks at *m/e* 598 (M^+), 583 ($M^+ - CH_3$), 567 ($M^+ - OCH_3$), 527 ($M^+ - C_5H_{11}$), 508, and 437.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.11; H, 10.11.

(15*S*)-15-Methyl-PGA$_2$ Methyl Ester [21(*S*)]. To a stirred solution of 0.40 g (1.0 mmol) of (15*S*)-15-methyl-PGE$_2$ methyl ester, **18**(*S*), in 10 ml of dry pyridine under nitrogen and at ambient temperature was added 4.0 ml (4.3 g, 42 mmol) of acetic anhydride. After 6 hr, tlc (5 and 30% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed complete reaction with one major product, R_f 0.1 (in 5% acetone–methylene chloride), and a trace of a slightly faster moving compound (the PGA compound, see below). The solution was cooled in an ice–water bath and diluted with 20 ml of methanol. The resulting solution was stirred 16 hr at ambient temperature at which time a tlc (5% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed no starting material (acetate) with the major product having an R_f of 0.15. The solution was added to an equilibrated mixture of ether, ice, sodium bisulfate (2 *M*), and water. After equilibration, the aqueous phase (pH ≤1) was extracted well with ether. The organic extracts were combined, washed with water (three times), saturated sodium bicarbonate, and brine, and then dried

(sodium bisulfate) and evaporated to give 0.37 g of light yellow oil. The material appeared homogeneous by tlc in the following: 30% acetone–Skellysolve B (R_f 0.36); 5% acetone–methylene chloride (0.15); and 25% ethyl acetate–Skellysolve B (R_f 0.05).

The crude product was chromatographed on 50 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 22-ml fractions, elution was with 200 ml of 50% (ethyl acetate–hexane) and 100 ml of 75%. Fractions 7–9 were combined to give 0.34 g (89%) of colorless oil, $[\alpha]D$ +152° (*c* 0.68, chloroform). The uv spectrum in neutral ethanol showed λ_{max} 217 (ϵ 10,700) and 328 nm (ϵ 268) and in basic ethanol λ_{max} 278 (ϵ 25,450) and 350 nm (ϵ 699). The nmr spectrum showed absorptions at δ 0.6–2.6 (m, 24), including a singlet at 1.28, 3.0–3.4 (m, 1), 3.67 (s, 3), 5.3–5.7 (m, 4), 6.1–6.25 (m, 1), and 7.45–7.6 (m, 1). The ir showed bands at 3480, 3010, 2950, 2930, 2860, 1740, 1710, 1585, 1315, 1245, and 975 cm^{-1}. The mass spectrum showed the parent ion at *m/e* 362.2452 (theoretical for $C_{22}H_{34}O_4$: 362.2457) with fragments at 347 ($M^+ - CH_3$), 344 ($M^+ - H_2O$), 331 ($M^+ - OCH_3$), 291 ($M^+ - C_5H_{11}$), 259, and 204.

(15*R*)-15-Methyl-PGA$_2$ Methyl Ester [21(*R*)]. To a solution of 3.0 g (7.9 mmol) of (15*R*)-15-methyl PGE_2 methyl ester, **18**(*R*), in 100 ml of dry pyridine under nitrogen and at ambient temperature was added 30 ml (32 g, 0.32 mol) of acetic anhydride. After 4 hr, tlc (50% ethyl acetate–Skellysolve B and ethyl acetate) showed complete reaction. The solution was cooled in an ice–water bath and then diluted with 100 ml of methanol. The resulting solution was stirred at ambient temperature for 16 hr at which time tlc (25 and 50% ethyl acetate–Skellysolve B) showed no starting material (acetate). The solution was added to an equilibrated mixture of ice, ether, sodium bisulfate (2 *M*), and water. After equilibration again, the aqueous layer was extracted well with ether. The organic extracts were combined and washed with water (three times), saturated sodium bicarbonate, and brine, and then dried (sodium sulfate) and evaporated to give 2.5 g of yellow oil.

The crude product was chromatographed on 250 g of silica gel, packed in 5% ethyl acetate–hexane. Taking 125-ml fractions, elution was with 1000 ml of 50% ethyl acetate–hexane. Fractions 5 and 6 were combined to give 2.4 g (84%) of colorless oil, $[\alpha]D$ +146° (*c* 0.78, chloroform). The uv spectrum in neutral ethanol showed λ_{max} 217 (ϵ 10,400) and 328 nm (ϵ 300) and in basic ethanol λ_{max} 278 (ϵ 24,600) and 350 nm sh (ϵ 872). The nmr spectrum showed absorptions at δ 0.6–2.6 (m, 24) including a singlet at 1.27, 3.1–3.35 (m, 1), 3.67 (s, 3), 5.3–5.7 (m, 4), 6.1–6.25 (m, 1), and 7.45–7.6 (m, 1). The ir spectrum showed bands at 3470, 3010, 2950, 2930, 2860, 1735, 1705, 1585, 1455, 1315, 1245, and 975 cm^{-1}. The mass spectrum showed the parent ion at *m/e* 362.2448 (theoretical for $C_{22}H_{34}O_4$: 362.2457) with fragments at 347 ($M^+ - CH_3$), 344 ($M^+ - H_2O$), 331 ($M^+ - OCH_3$), 291 ($M^+ - C_5H_{11}$), 259, and 204.

15(*S*)-15-Methyl-PGF$_{1\alpha}$ Methyl Ester [22(*S*)]. A mixture of 0.50 g (1.3 mmol) of (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester, **15**(*S*), and 100 mg of 5% palladium on carbon in 150 ml of ethyl acetate was stirred at −15° (methanol–ice) under 1 atm of hydrogen. Progress of the reaction was monitored by tlc (ethyl acetate) of aliquots using silver nitrate silica gel (R_f 0.2 and 0.3 for starting material and product **22**(*S*), respectively). After 95 min, the reaction was judged complete. The mixture was filtered through Celite, washing well with ethyl acetate. Rotary evaporation of the filtrate gave 0.50 g of an oil which readily crystallized at room temperature. Recrystallization once from hexane–ethyl acetate gave 0.42 g (84%), mp 71–74°. Silver nitrate treated (ethyl acetate or 30% acetone–methylene chloride as eluant) or regular (ethyl acetate as eluant) silica gel tlc of the recrystallized product showed one main spot, identical with (15*S*)-15-methyl-$PGF_{1\alpha}$ methyl ester, **22**(*S*), prepared by a different route,[6,7a] and a less polar spot amounting to 10–20% of the total.

A portion (220 mg) of the recrystallized product was chromatographed on 28 g of silica gel, packed in 5% acetone–methylene chloride. Taking 11-ml fractions, the column was eluted with 100 ml of 5% (acetone–methylene chloride), 100 ml of 10%, 100 ml of 20%, 100 ml of 20%, and 1000 ml of 30%. The product was obtained during the first one-third of the 30% as follows: fractions 34–36, less polar by-product, 20 mg (9%), crystalline; fractions 37–43, mixture, 133 mg (60%), crystalline; fractions 44–65, main product, 74 mg (34%), crystalline. The latter material was recrystallized once from hexane–ethyl acetate to give 50 mg (68%) of (15*S*)-15-methyl-$PGF_{1\alpha}$ methyl ester, **22**(*S*), mp 84–85°. Overall yield of **22**(*S*) from **15**(*S*) (including estimated material in mixed fractions) was 75%. The mass spectrum of the tris(trimethylsilyl) derivative of the product showed the parent ion at 600.4026 (calcd for $C_{31}H_{14}O_5Si_3$: 600.4060). Other ions present were at *m/e* 585 ($M^+ - CH_3$), 569 ($M^+ - OCH_3$), 529 ($M^+ - C_5H_{11}$), and 520.

Anal. Calcd for $C_{22}H_{40}O_5$: C, 68.71; H, 10.49. Found: C, 68.75; H, 10.60.

13,14-Dihydro-(15*S*)-15-methyl-PGF$_{1\alpha}$ Methyl Ester [23(*S*)]. A mixture of 0.50 g (1.3 mmol) of (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester, **15**(*S*), and 100 mg of 5% palladium on carbon in 150 ml of ethyl acetate was stirred at 0° under 1 atm of hydrogen. Progress of the reaction was monitored by tlc (ethyl acetate) of aliquots using regular and silver nitrate silica gel. After 2.5 hr, the reaction appeared complete. The mixture was filtered through Celite, washing well with ethyl acetate. The filtrate was evaporated to give 0.54 g of oil which crystallized on standing. The product was recrystallized from hexane–ethyl acetate to give a total of 0.45 g (90%) of crystalline product, mp 58–59°, $[\alpha]D$ +40° (*c* 1.07, chloroform). The mass spectrum of the tris(trimethylsilyl) derivative showed *m/e* at 612 (M^+), 597 ($M^+ - CH_3$), 571 ($M^+ - OCH_3$), 531.3366 ($M^+ - C_5H_{11}$; calcd for $C_{26}H_{55}O_5Si_3$: 531.3355), 512, 497, and 422. The nmr spectrum showed ($CDCl_3$) δ 0.7–2.9 (mult, 35), including a singlet at 1.16, 3.2–3.5 (mult, 2), 3.67 (s, 3), and 3.8–4.3 (mult, 2).

(15*S*)-15-Methyl-PGF$_{1\alpha}$ 11-Trimethylsilyl Ether Methyl Ester [24(*S*)]. To a stirred solution of 110 mg (0.28 mmol) of (15*S*)-15-methyl-$PGF_{1\alpha}$ methyl ester, **23**(*S*) (containing 10–20% of a less polar impurity by tlc), in 4 ml of acetone at −45° (Dry Ice–acetone bath) was added 1.5 ml of trimethylsilyldiethylamine. The resulting solution was stirred at −45° for 1 hr or until tlc using 50% ethyl acetate in Skellysolve B showed disappearance of **23**(*S*) (R_f **23**(*S*) ~0.1; R_f **24**(*S*) ~0.6). To the solution while at −45° was added 20 ml of ether, previously cooled to −78°. This solution was added to 20 ml of cold aqueous one-half saturated sodium bicarbonate. After equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined and washed with brine. The organic solution was dried (sodium sulfate) and rotary evaporated to give a wet oil. This oil was dried further by azeotroping twice with benzene to give 130 mg (100%) of viscous oil which partially crystallized at 0°. This was used without further purification.

(15*S*)-15-Methyl-PGE$_1$ 11-Trimethylsilyl Ether Methyl Ester [25(*S*)]. To a stirred solution of 0.41 g (5.2 mmol) of dry pyridine in 10 ml of methylene chloride (Burdick and Jackson) at room temperature under nitrogen was added 0.26 g (2.6 mmol) of anhydrous chromium trioxide. The resulting mixture was stirred for 1.5 hr and then cooled to 0°. To the dark red mixture at 0° was added, with vigorous stirring, a solution of 0.13 g (0.29 mmol) of (15*S*)-15-methyl-$PGF_{1\alpha}$ 11-trimethylsilyl ether methyl ester, **24**(*S*), in 1 ml of methylene chloride. The resulting mixture was stirred at 0° for 15 min then decanted and filtered through ~3 in. of silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 140 mg of a dark oil. Tlc using 50% ethyl acetate–Skellysolve B showed one main spot (R_f 0.7). The material was used without further purification.

(15*S*)-15-Methyl-PGE$_1$ Methyl Ester [26(*S*)]. To a stirred solution of 140 mg (0.29 mmol theoretical) of crude (15*S*)-15-methyl-PGE_1 11-trimethylsilyl ether methyl ester, **25**(*S*), in 6 ml of methanol at 0° was added a solution of 6 drops of acetic acid in 3 ml of water. The resulting mixture was stirred for 30 min at room temperature and then diluted with 50 ml of 0.2 *M* aqueous sodium bisulfate. The resulting mixture was extracted well with ether. The organic extracts were combined and washed in turn with saturated aqueous sodium bicarbonate and brine. The organic solution was dried (sodium sulfate) and rotary evaporated to give 110 mg of a light yellow oil. Tlc using 30% acetone in methylene chloride showed one main spot, R_f 0.4, with a minor slightly less polar spot and small amounts of less and more polar spots.

The crude product was chromatographed on 15 g of silica gel, packed in 5% acetone–methylene chloride. Taking 3-ml fractions, the column was eluted with 50 ml of 5% (acetone in methylene chloride), 100 ml of 10%, and 350 ml of 30%. The product was obtained during the first part of the 30% in fractions 65–75, 50 mg (45%), crystalline. The material was recrystallized once from hexane–ether to give 33 mg (66%) of off-white small needles, mp 45–47°. Overall yield of recrystallized **26**(*S*) from **23**(*S*) was 30%. The mass spectrum of the bis(trimethylsilyl) derivative of **26**(*S*) showed the parent ion at 526.3478 (calcd for $C_{28}H_{54}O_5Si_2$: 526.3508). Other ions present were *m/e* 511 ($M^+ - CH_3$), 495 ($M^+ - OCH_3$), 455 ($M^+ - C_5H_{11}$), and 436. The uv showed end absorption only in neutral ethanol but in basic ethanol exhibited λ_{max} 278 (27,250).

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.07; H, 10.06.

(15*R*)-15-Methyl-PGE$_1$ Methyl Ester [25(*R*)]. A mixture of 50 mg (0.13 mmol) of (15*R*)-15-methyl-PGE_2 methyl ester, **18**(*R*), and

10 mg of 5% palladium on carbon in 15 ml of ethyl acetate was stirred at −5° under 1 atm of hydrogen. The progress of the reaction was monitored by tlc (ethyl acetate) of aliquots using both regular and silver nitrate silica gel. After 2 hr the reaction was complete. The mixture was filtered through Celite, washing well with ethyl acetate. The filtrate was rotary evaporated at 40° to give 45 mg of oil. The crude product was chromatographed on 5 g of silica gel, packed in 50% ethyl acetate–hexane. Taking 5-ml fractions, elution was with 50 ml of ethyl acetate. Fraction 2 contained 15 mg of an impurity (probably the dihydro-PG_1 compound) and fractions 3–5 contained 30 mg (60%) of (15*R*)-15-methyl-PGE_1 methyl ester, **26**(*R*). The uv spectrum of **26**(*R*) in neutral ethanol showed end absorption only but in basic ethanol showed λ_{max} 278 (ϵ 23,550) and 350 sh (ϵ 677). The mass spectrum of the bis(trimethylsilyl) ether derivative of **26**(*R*) showed the parent ion at *m/e* 526.3498 (calcd for $C_{28}H_{54}Si_2O_5$: 526.3508) with other peaks at *m/e* 511 ($M^+ - CH_3$), 495 ($M^+ - OCH_3$), 455 ($M^+ - C_5H_{11}$), 365, and 311.

13,14-Dihydro-(15*S*)-15-methyl-PGE_1 Methyl Ester [27(*S*)]. A mixture of 350 mg (0.92 mmol) of (15*S*)-15-methyl-PGE_2 methyl ester, **18**(*S*), and 70 mg of 5% palladium on carbon in 100 ml of ethyl acetate was stirred at 10° under 1 atm of hydrogen. The progress of the reaction was followed by tlc (ethyl acetate) of aliquots on regular and silver nitrate silica gel. After 3 hr, the reaction was complete. The mixture was filtered through Celite, washing well with ethyl acetate. The filtrate was rotary evaporated at 40° to give 0.36 g of oil. The crude product was chromatographed on 30 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 10-ml fractions, elution was with 200 ml of 75% ethyl acetate–hexane and 100 ml of ethyl acetate. Fractions 7–14 contained 0.20 g (57%) of pure 13,14-dihydro-(15*S*)-15-methyl-PGE_1 methyl ester, **27**(*S*), as an oil. The nmr spectrum showed ($CDCl_3$) δ 0.7–2.0 (mult, 33), 2.1–2.9 (mult, 3), including a singlet at 1.18, 3.67 (s, 3), and 3.8–4.3 (mult, 1).

(15*S*)-15-Methyl-PGA_1 Methyl Ester [28(*S*)]. To a stirred solution of 0.20 g (0.50 mmol) of (15*S*)-15-methyl-PGE_1 methyl ester, **26**(*S*), in 5 ml of dry pyridine under nitrogen and at ambient temperature was added 2.0 ml (2.1 g, 21 mmol) of acetic anhydride. After 6 hr, tlc (5 and 30% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed complete reaction with one major product, R_f 0.4 in 5% acetone–methylene chloride and a trace of a slightly faster moving compound (the PGA compound, see below). The solution was cooled in an ice–water bath and diluted with 10 ml of methanol. The resulting solution was stirred 16 hr at ambient temperature at which time a tlc (5% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed no starting material (acetate) with the major product being uv-visible and having an R_f of 0.15. The solution was added to an equilibrated mixture of ether, ice, sodium bisulfate (2 *M*), and water. After equilibration, the aqueous layer (pH <1) was extracted well with ether. The organic extracts were combined, washed with water (three times), saturated sodium bicarbonate, and brine, and then dried (sodium sulfate) and evaporated to give 0.21 g of oil. The crude product was chromatographed on 25 g of silica gel, packed in 20% ethyl acetate–hexane. Taking 12 ml fractions, elution was with 100 ml of 50% (ethyl acetate–hexane) and 100 ml of 75%. Fractions 9–12 were combined to give 0.18 g (95%) of (15*S*)-15-methyl-PGA_1 methyl ester, **28**(*S*), as a colorless oil. The uv of **28**(*S*) in neutral ethanol showed λ_{max} 217 (ϵ 9750) and in basic ethanol showed λ_{max} 278 (ϵ 24,750). The mass spectrum showed the parent ion at *m/e* 364.2637 (calcd for $C_{22}H_{36}O_4$: 364.2613) with other ions at 349 ($M^+ - CH_3$), 346 ($M^+ - H_2O$), 333 ($M^+ - OCH_3$), and 293 ($M^+ - C_5H_{11}$).

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Enantiomeric Prostaglandins

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Abstract: A total synthesis of all possible diastereomers of enantiomeric 8β,12α-prostaglandins A, E, and F in the parent (unsubstituted) and 15-methyl substituted "two" series is described. The synthesis originates from the previously described *l*-ephedrine salt of 3β-carboxy-4α-(methoxymethyl)-5β-hydroxycyclopentene. For those parent prostaglandins containing the 11α stereochemistry, the C-11 position was inverted at an early stage in the synthesis by displacement of a tosylate with benzoate. For those 15-methyl substituted prostaglandins containing the 11α stereochemistry, the C-11 position was inverted at the final prostaglandin stage by mild dehydration of the 11β-PGE compounds to the PGA structures, followed by epoxidation and reduction of the resultant epoxy ketones with aluminum amalgam. All prostaglandins were epimerically pure at all chiral centers. Unambiguous configurational assignments for all 28 prostaglandins were based on comparisons with key prostaglandins in the natural (parent or 15-methyl) series.

The general biology[1,2] and chemistry[3] of the natural prostaglandins have been recently reviewed. Because of potential therapeutic advantages, increasing attention is being focused on prostaglandin analogs. Particularly interesting, both pharmacologically and clinically, are analogs incorporating methyl groups into the prostaglandin skeleton at C-15[4] and C-16.[5] Because

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