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 ($M^+ - C_5H_{11}$).

Acknowledgment. The authors gratefully acknowledge the technical assistance of J. M. Baldwin, E. L. Cooper, and J. L. Thompson. We also thank P. A. Meulman, S. A. Mizsak, and R. J. Wnuk for the ir, nmr, and mass spectra. We especially acknowledge with gratitude Dr. H. A. Karnes and associates for the preparation of generous supplies of intermediates.

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

(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 Förlag AB, Stockholm, 1967.

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

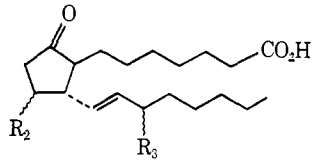
(3) (a) U. Axen, J. E. Pike, and W. P. Schneider in "Progress in the Total Synthesis of Natural Products," Vol. I, J. W. ApSimon, Ed., Wiley, New York, N. Y., 1973; (b) G. L. Bundy, *Annu. Rep. Med. Chem.*, 7, 157 (1972); (c) N. M. Weinshenker and N. H. Andersen in "The Prostaglandins," Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973.

(4) (a) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Amer. Chem. Soc.*, **96**, 5865 (1974); (b) G. L. Bundy, E. W. Yankee, J. R. Weeks, and W. L. Miller, *Advan. Biosci.*, **9**, 125 (1973); (c) E. W. Yankee and G. L. Bundy, *J. Amer. Chem. Soc.*, **94**, 3651 (1972); (d) J. R. Weeks, D. W. DuCharme, W. E. Magee, and W. L. Miller, *J. Pharmacol. Exp. Ther.*, **186**, 67 (1973); (e) K. T. Kirton and A. D. Forbes, *Prostaglandins*, **1**, 319 (1972); (f) S. M. M. Karim and S. D. Sharma, *J. Obstet. Gynaecol. Brit. Commonw.*, **79**, 737 (1972); (g) M. Bygdeman, F. Béguin, M. Toppazada, N. Wiqvist, and S. Bergström, *Lancet*, 1, 1336 (1972).

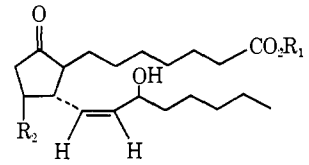
(5) (a) B. J. Magerlein, D. W. DuCharme, W. E. Magee, W. L. Miller, A. Robert, and J. R. Weeks, *Prostaglandins*, **4**, 143 (1973); (b) M. Hayashi, H. Miyake, T. Tanouchi, S. Iguchi, Y. Iguchi, and F. Tanouchi, *J. Org. Chem.*, **38**, 1250 (1973); (c) A. Robert and B. J. Magerlein, *Advan. Biosci.*, **9**, 247 (1973); (d) S. M. M. Karim, D. C. Carter, D. Bhana, and P. A. Ganeson, *ibid.*, 255 (1973); (e) *Brit. Med. J.*, **1**, 143 (1973); (f) A. Robert, B. Nylander, and S. Andersson, *Life Sciences*, **14**, 533 (1974).

the pharmacological activities of the natural prostaglandins, which contain a number of chiral centers and varying degrees of unsaturation, are dramatically influenced by configurational alterations,[1,2] the two early reports[6] of Ramwell, Corey, and coworkers describing some bioassay results of various *dl* and natural diastereomeric prostaglandins were of particular significance. These reports suggested that certain epimers of the *mirror image forms* of the naturally occurring prostaglandins of the PG_1 series would be biologically at least as active as (and in some cases more active than) their natural counterparts, would be dehydrogenated less rapidly by the enzyme 15-hydroxyprostaglandin dehydrogenase[7] than their natural counterparts, or would be inhibitors of the dehydrogenase enzyme.

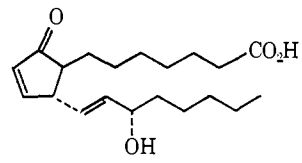
The first synthesis of an enantiomeric prostaglandin was achieved by Corey, *et al.*,[9] who prepared the enantiomer of prostaglandin E_1 (*ent*-PGE_1; *vide infra* for nomenclature), **1**, where *all* chiral centers are reversed. Since then, *ent*-PGE_1 has also been prepared by others.[10] Moreover, several enantiomeric prostaglandin analogs having reversed stereochemistry at all but one or two chiral centers have now been reported. These include compounds in the PG_1 series, formulas **2**,[11] **3**,[12] **4**,[11]



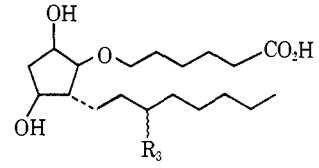
1,[9,10] $R_2 = \beta OH$; $R_3 = (15R)OH$
2,[11] $R_2 = \alpha OH$; $R_3 = (15S)OH$
3,[12] $R_2 = H$; $R_3 = (15S)OH$



5a,[13] $R_1 = H$; $R_2 = OH$
b,[13] $R_1 = CH_3$; $R_2 = OH$
6a,[13] $R_1 = H$; $R_2 = H$
b,[13] $R_1 = CH_3$; $R_2 = H$

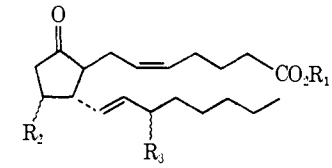


4[11]

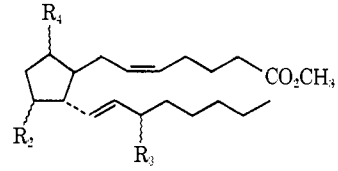


7,[14] $R_3 = (15S)OH$
8,[14] $R_3 = (15R)OH$

5,[13] **6**,[13] **7**,[14] and **8**,[14] as well as various PGE and PGF compounds in the PG_2 series, formulas **9**,[15] **10**,[15b] **11**,[16]

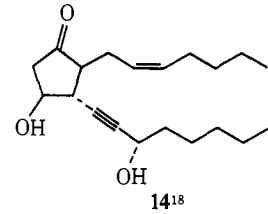


9,[15] $R_1 = H$; $R_2 = \alpha OH$; $R_3 = (15S)OH$
10,[15b] $R_1 = H$; $R_2 = \alpha OH$; $R_3 = (15R)OH$
11,[16] $R_1 = CH_3$; $R_2 = \beta OH$; $R_3 = (15S)OH$

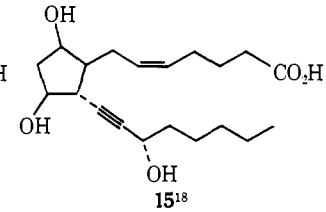


12,[16] $R_2 = \beta OH$; $R_3 = (15S)OH$; $R_4 = \beta OH$
13,[17] $R_2 = \beta OH$; $R_3 = (15R)OH$; $R_1 = \alpha OH$

12,[16] and **13**.[17] Several enantiomeric prostaglandins modified by replacement of Δ^{13} with an acetylenic group have been reported, formulas **14–16**.[18] More recently,

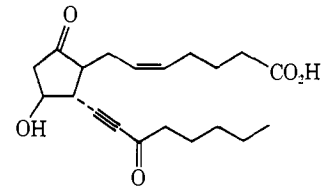


14[18]

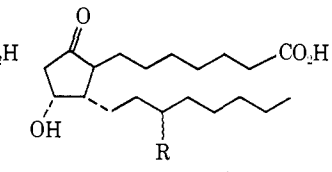


15[18]

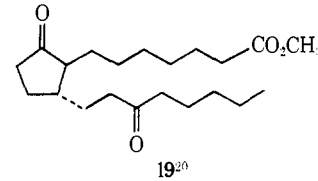
several saturated PGE enantiomeric compounds have also appeared, formulas **17**,[19] **18**,[19] and **19–21**.[20] In the



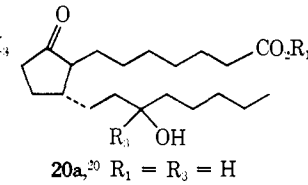
16[18]



17,[19] R = (15S)OH
18,[19] R = (15R)OH



19[20]



20a,[20] $R_1 = R_3 = H$
b,[20] $R_1 = CH_3$; $R_3 = H$
21a,[20] $R_1 = H$; $R_3 = CH_3$
b,[20] $R_1 = R_3 = CH_3$

case of structures **20** and **21**, they were each a mixture of C-15 epimers. No reports have appeared of any systematic attempts to prepare all possible diastereomers of enantiomeric prostaglandins within one structural family. Accordingly, we have prepared for biological evaluation all possible stereoisomers of 8β,12α-prostaglandins in the parent as well as the 15-methyl PG_2

(6) (a) P. W. Ramwell, J. E. Shaw, E. J. Corey, and N. Andersen, *Nature (London)*, 221, 1251 (1969); (b) H. Shio, P. W. Ramwell, N. H. Andersen, and E. J. Corey, *Experientia*, 26, 355 (1970).

(7) (a) E. Änggård and B. Samuelsson, *Ark. Kemi.*, 25, 293 (1966); (b) the enzyme 15-hydroxyprostaglandin dehydrogenase is responsible for the most rapid mode of prostaglandin metabolism.[8]

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

(9) E. J. Corey, I. Vlattas, and K. Harding, *J. Amer. Chem. Soc.*, 91, 535 (1969).

(10) H. L. Slates, Z. S. Zelawski, D. Taub, and N. L. Wendler, *J. Chem. Soc., Chem. Commun.*, 304 (1972).

(11) C. J. Sih, P. Price, R. Sood, R. G. Saloman, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, 94, 3643 (1972).

(12) C. J. Sih, R. G. Saloman, and G. Peruzzotti, *Tetrahedron Lett.*, 2435 (1972).

(13) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, 94, 9256 (1972).

(14) J. Fried, M. M. Mehra, and W. L. Kao, *J. Amer. Chem. Soc.*, 93, 5594 (1971).

(15) (a) E. J. Corey, S. Terashima, P. W. Ramwell, R. Jessup, N. M. Weinshenker, D. M. Floyd, and G. A. Crosby, *J. Org. Chem.*, 37, 3043 (1972); (b) C. Gandolfi, G. Doria, and P. Gaio, *Tetrahedron Lett.*, 4303 (1972).

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

(17) W. P. Schneider and H. C. Murray, *J. Org. Chem.*, 38, 397 (1973).

(18) J. Fried and C. H. Lin, *J. Med. Chem.*, 16, 429 (1973).

(19) M. Miyano and C. R. Dorn, *J. Amer. Chem. Soc.*, 95, 2664 (1973).

(20) J. F. Bagli, T. Bogri, and S. N. Sehga, *Tetrahedron Lett.*, 3329 (1973).

series. Certain compounds cited above, namely **9**,[15] **10**,[15b] **11**,[16] **12**,[16] and **13**,[17] which are either identical or structurally similar (free acid instead of methyl ester) to some of those described here, were reported subsequent to completion of this work.

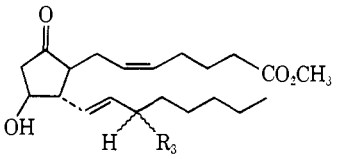
Nomenclature

Because literature precedents already exist,[6,10-20] and because this nomenclature is communicable, the term *ent* (formally *enantiomeric*) is used for those compounds possessing reversed stereochemistry at all chiral centers. The structures are drawn according to the convention already in use for the natural compound. The "*ent*" nomenclature can also be used for those prostaglandins in which the stereochemistry may be reversed only at C-8 and C-12 (*i.e.*, compounds which are 8β and 12α). Thus, compound **2** is *ent*-[11,15-di-epi-PGE_1], all chiral centers being enantiomeric to those in the structure named after "*ent*." The actual configurations in compound **2**, however, are 11α and (15*S*). For clarity and simplicity, therefore, we have adopted the practice in which all chiral centers differing from those in the pure enantiomeric compounds are defined preceding the ent designation. Thus, compound **2**, instead of being *ent*-[11,15-di-epi-PGE_1], becomes 11α-(15*S*)-*ent*-PGE_1; **10** is 11α-*ent*-PGE_1; **12** (with the 9β configuration as drawn) is (15*S*)-*ent*-$PGF_{2}\alpha$ methyl ester; and **13** (with the 9α configuration as drawn) is *ent*-$PGF_{2}\beta$ methyl ester.[21] This adopted practice is consistent with a recently described general convention for prostaglandin nomenclature.[21b]

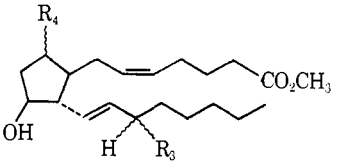
Synthesis

The parent *ent* prostaglandins having the 11β configuration are summarized in Table I (including the two PGA compounds). The chemistry used to prepare these is shown in Scheme I. Using a sequence analogous to that reported in several communications[15a,22] by Corey and coworkers, the previously reported[22] *l*-ephedrine salt **27** was converted to crystalline benzoate ketone **32**. The detailed procedures used to convert iodo lactone **28** to **31** were essentially identical with those used for the compounds having natural configurations described in the preceding manuscript.[4a] Thus, treatment of alcohol **28** with benzoyl chloride in pyridine at ambient temperature smoothly gave crystalline ester **29** which with tributyltin hydride was deiodinated to lactone benzoate **30**. Cleavage of the methyl ether of **30** with boron tribromide in methylene chloride gave crystalline benzoate alcohol **31** in 49% overall yield from ephedrine salt **27**. Oxidation of alcohol **31** with Collins reagent[23] gave a crude product which, without isolation or characterization, was treated with the ylide prepared from sodium hydride and dimethyl (2-oxoheptyl)phosphonate in tetrahydrofuran to give, after chromatography, ketone **32** in 44% yield after recrystallization.

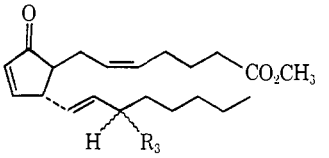
Table I



11,[16] R_3 = (15*S*)OH
22, R_3 = (15*R*)OH



23, R_3 = (15*S*)OH; R_4 = αOH
12,[16] R_3 = (15*S*)OH; R_4 = βOH
13,[17] R_3 = (15*R*)OH; R_4 = αOH
24, R_3 = (15*R*)OH; R_4 = βOH



25, R_3 = (15*S*)OH
26, R_3 = (15*R*)OH

Reduction of **32** with sodium borohydride in methanol at $-10°$ afforded in good yield the two separable epimeric alcohols **33** and **34** in about a 1:1 ratio. As has been noted previously (where *p*-phenylbenzoate rather than benzoate was used[15a]) the less polar epimer on silica gel corresponds to the (15*R*) isomer, compound **34**. This was established by comparison of one of the product prostaglandins with the natural product (*vide infra*). Using procedures outlined previously by Corey,[22] each C-15 epimer was taken separately and converted to the chromatographically pure enantiomeric compounds as shown in Scheme I. The PGA compounds, **25** and **26**, were obtained as by-products from the tetrahydropyranyl ether cleavage of the corresponding di-THP-PGE compounds **43** and **44**, respectively, using aqueous acetic acid at 40°. Reduction of the PGE compounds **11** or **22** directly with sodium borohydride in methanol at $-10°$ gave the PGF compounds **12** and **23** or **24** and **13**, respectively. For each C-15 epimer, the ratio of 9α:9β was nearly 1:1. The C-9 epimers were separated by silica gel chromatography. *Ent*-$PGF_{2}\alpha$ methyl ester, **24**, was identical spectrally and in chromatographic mobility to a standard of natural $PGF_{2}\alpha$ methyl ester.[24] This established the configuration at C-15 (and C-9) for all of the compounds in Table I and Scheme I.

The parent enantiomeric prostaglandins having the 11α configuration are summarized in Table II. The synthetic sequence used is outlined in Scheme II. Deiodination of **28**[22] directly with tributyltin hydride gave previously reported[25] **51** in 61% yield. The lower yield of this step compared to deiodination of the corresponding benzoate of **28** (96% for **29** → **30**) may be

(21) (a) The terms α and β are used to define configurations on the ring (for the conventional representation) while (*R*) and (*S*) are used to define chiral centers on the side chains; (b) N. A. Nelson, *J. Med. Chem.*, in press.

(22) (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. Koelliker, 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).

(23) (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).

(24) We are indebted to Mr. Frank H. Lincoln of The Upjohn Co. for prostaglandin reference standards.

(25) D. M. Floyd, G. A. Crosby, and N. M. Weinshenker, *Tetrahedron Lett.*, 3265 (1972).

Scheme I

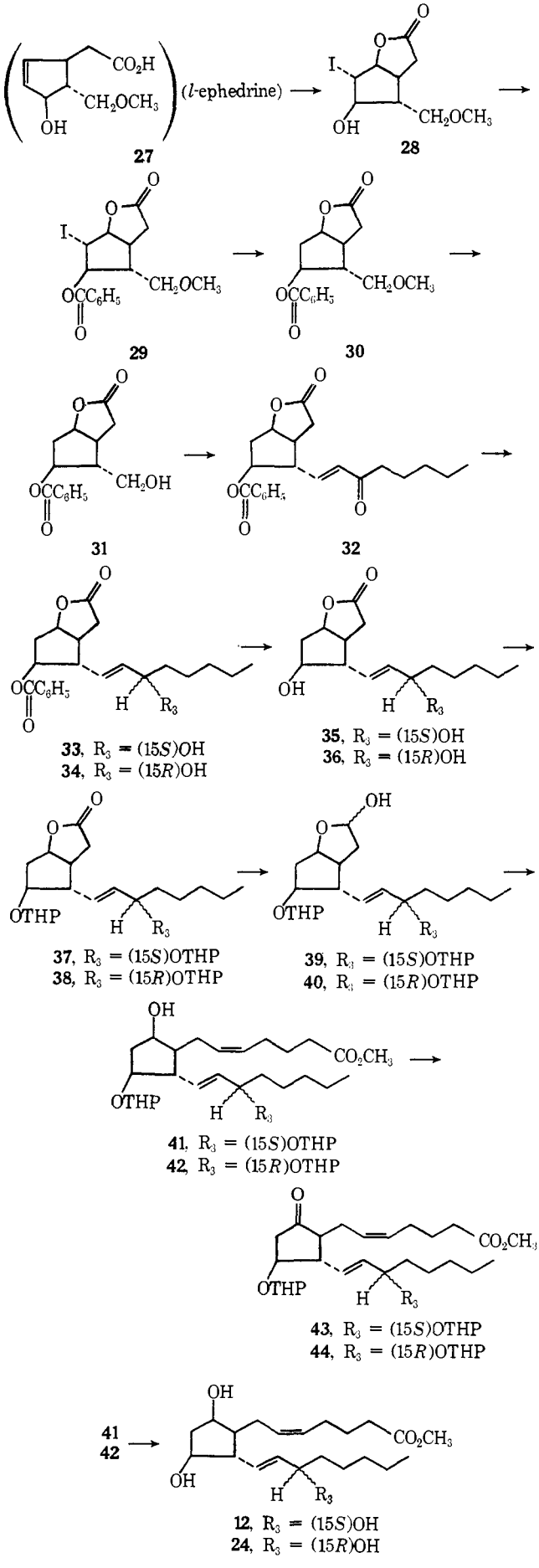
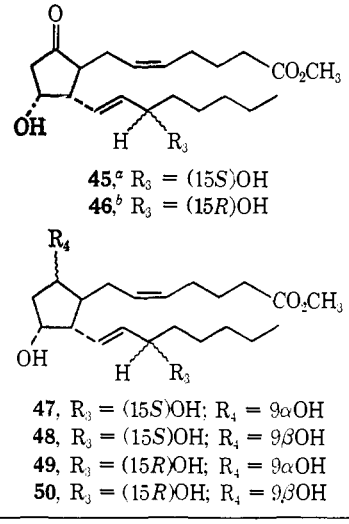


Table II

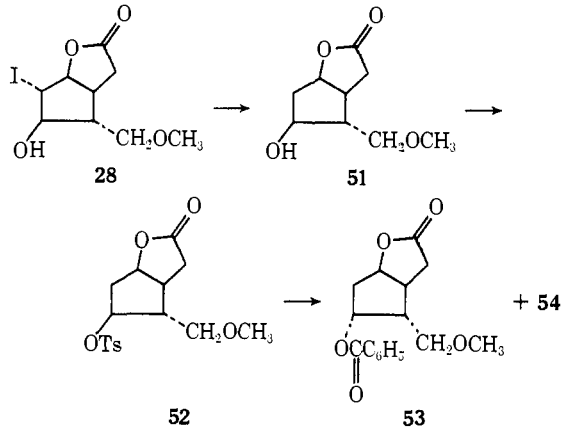


[a] The corresponding free acid was reported in ref 15. [b] The corresponding free acid was reported in ref 15b.

attributable to greater losses in isolation, possibly due to greater water solubility. This point was not pursued. Preparation of tosylate **52** by standard methods followed by treatment with sodium benzoate in dimethyl sulfoxide at 80–85° for 3.5 hr gave inverted benzoate **53** along with a compound of similar but slower tlc mobility, **54**. The by-product, amounting to 20–30% of the mixture as judged by tlc, was clearly not the 11β-benzoate (retained configuration) **30** by tlc. The identity of the by-product was at first tentatively assigned the structure shown. That this assignment had probably been correct is supported by results of studies[25,26] of this type of inversion where various nucleophiles, counterions, and leaving groups were re-

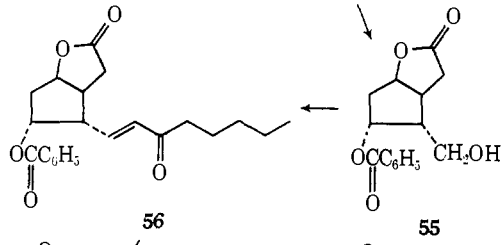
(26) E. J. Corey and S. Terashima, *Tetrahedron Lett.*, 111 (1972).

Scheme II

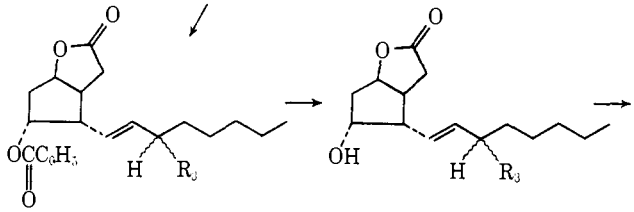


28 **51**

52 **53**

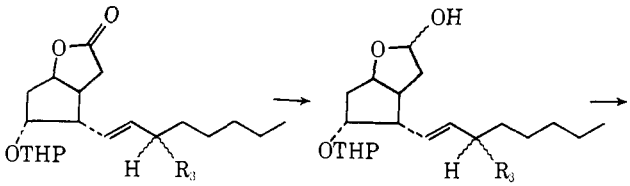


56 **55**



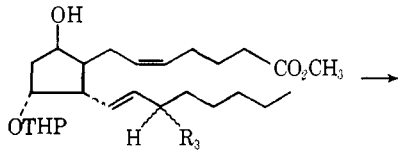
57, R_3 = (15*S*)OH
58, R_3 = (15*R*)OH

59, R_3 = (15*S*)OH
60, R_3 = (15*R*)OH

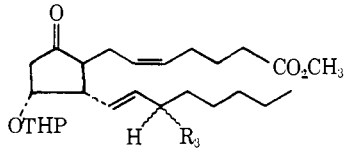


61, R_3 = (15*S*)OTHP
62, R_3 = (15*R*)OTHP

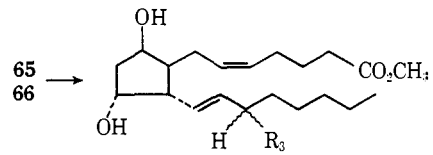
63, R_3 = (15*S*)OTHP
64, R_3 = (15*R*)OTHP



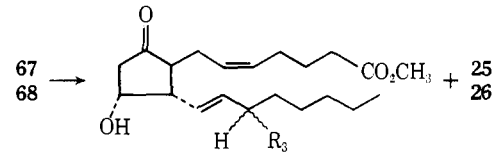
65, R_3 = (15*S*)OTHP
66, R_3 = (15*R*)CTHP



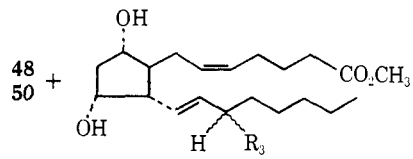
67, R_3 = (15*S*)OTHP
68, R_3 = (15*R*)OTHP



48, R_3 = (15*S*)OH
50, R_3 = (15*R*)OH

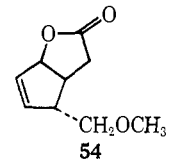


45, R_3 = (15*S*)OH
46, R_3 = (15*R*)OH



47, R_4 = (15*S*)OH
49, R_3 = (15*R*)OH

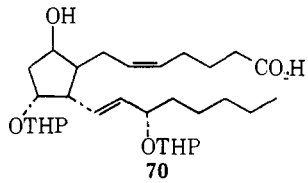
ported to give substantial amounts of elimination product **54**. Although this compound could be separated



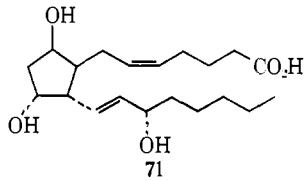
54

chromatographically from inverted benzoate **53**, a separation was much more easily accomplished after the subsequent step. Treatment of methyl ether **53** with boron tribromide *in ethyl acetate* gave alcohol **55** in 69% yield after chromatography. This cleavage could not be carried out in greater than 10% yield using methylene chloride as solvent (conditions used for conversion of **30** to **31**). The residual elimination product (from **54**) was conveniently separated at this point and probably accounts for most of the remaining 31% yield of the cleavage reaction. No attempts were made to isolate and characterize this by-product. Conversion of key intermediate **55** to the crystalline ketone **56** was accomplished in 45% yield by the same procedure as for ketone **32** (Scheme I). Reduction of ketone **56** with sodium borohydride in methanol at −15° gave two difficultly separable alcohols. The configurations at C-15 of each of these alcohols were originally assigned based on chromatographic behavior: the less polar epimer being assigned the (15*R*) and the more polar the (15*S*) configurations. That these assignments were indeed correct was established by comparisons of one of the end-product prostaglandins with standards of natural prostaglandins (*vide infra*). Each of the C-15 epimers was elaborated separately by the conventional reactions as shown in Scheme II. Preparations of compounds **61** and **62** and their elaboration to the free acids of **45** and **46** were reported by others[15] subsequent to our completion of this synthesis.

The crude Wittig products from **63** or **64** were usually treated with diazomethane prior to purification to give the methyl esters **65** or **66**. In one experiment, a small sample of the acidic crude product from **63** (compound **70**) was treated with aqueous acetic acid at 40°



70



71

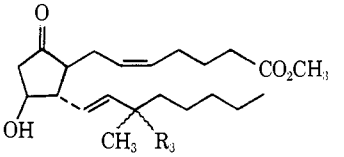
to give 11α-(15*S*)-*ent*-PGF$_{2\alpha}$, **71**. This material was identical in tlc mobility with 11,15-di-*epi*-PGF$_{2\alpha}$ and clearly different from 11-*epi*-PGF$_{2\alpha}$.[24,27] Thus, the configurations at C-15 in both **71** and alcohol **57** are established as being (*S*). This also establishes the configurations at C-15 in all compounds shown in Table II and Scheme II.

Removal of the protecting groups on **65** or **66** using aqueous acetic acid gave the 11α-*ent*-PGF$_{2\alpha}$ esters **48** or **50**, respectively. Oxidation of **65** or **66** with Collins reagent[23] followed by treatment with aqueous acetic acid gave the 11α-*ent*-PGE$_2$ esters **45** or **46**, respectively (along with small amounts of the PGA compounds **25** or **26**, Table I). Reduction of **45** or **46** with sodium borohydride in methanol at $-15°$ gave the corresponding PGF pairs **48** and **47** or **50** and **49**, respectively. For each C-15 epimer, the C-9 epimeric pairs could only be separated analytically using boric acid impregnated silica gel tlc,[28] or preparatively by column chromatography on boric acid impregnated, acid-washed silica gel.[29] The assignments of configuration at C-9 were made by comparisons of tlc mobilities of the mixtures (**47** and **48** or **49** and **50**) with the epimerically pure samples of **48** or **50** obtained directly from hydrolysis of the protecting groups on **65** or **66**. The chromatographic behavior of these diastereomers was consistent with that observed with other systems;[29] the cis diols were strikingly less polar than the trans diols on boric acid silica gel. Indeed, each trans isomer appeared to have the same R_f value by silica gel tlc with or without boric acid while the cis isomers were indistinguishable from the trans isomers in the absence of boric acid.

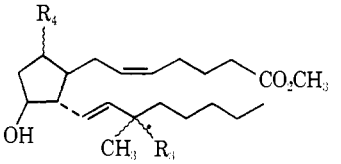
Because of the high interest in 15-methylprostaglandins[4] and because of the potential opportunity to compare in certain biological preparations the parent *ent* compounds with *ent*-prostaglandins substituted at C-15 (and thus inert[4d] to oxidation[8] by 15-hydroxyprostaglandin dehydrogenase[7]), the synthesis of all possible stereoisomers of 8β,12α-15-methyl-PG$_2$ structures was carried out. The *ent*-15-methyl compounds having the 11β configuration are summarized in Table III (including the PGA structures). The synthetic route to these compounds was essentially the same as that described for the natural 15-methylprostaglandins in the preceding manuscript.[4a] This is outlined in Scheme III. Treatment of ketone **32** with methylmagnesium bromide in tetrahydrofuran at $-78°$ gave alcohols **80**(*RS*). The two expected epimers were not separated. Cleavage of the benzoate with sodium methoxide in dry methanol, followed by reduction of the resulting lactone diols **81**(*RS*) with diisobutylaluminum hydride in tetrahydrofuran at $-78°$, gave oily lactols **82**(*RS*). Treatment of the latter with the Wittig reagent derived from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinylmethide in dimethyl sulfoxide gave, after isolation and treatment of the crude product with diazomethane, an approximately 1:1 mixture of **75** and **77** in 45% overall yield from ketone **32** (calculated on the amount of **75** and **77** recovered after chromatography). Chromatographic separation of the epimers gave pure materials which were physically identical in all respects with their respective enantiomers[4a] except for signs of optical rotations which were opposite. Conversion of each of these PGF compounds to the respective PGE prostaglandins, **72** or **73**, was accomplished by selective trimethylsilylation (using trimethylsilyldiethylamine) followed by oxidation and mild acid hydrolysis in 50 and 52% overall yields from the (15*S*) and (15*R*) epimers (**75** and **77**), respectively. Sodium borohydride reduction of the PGE compounds gave prostaglandins **74** and **75** or **76** and **77** as pairs of C-9 epimers for each C-15 epimer. Each 9β-PGF compound (**75** and **77**) was identical with its precursor PGF compound by tlc and nmr. The two PGA compounds **78** and **79** were prepared in 80 and 82% yields from the respective PGE prostaglandins **72** and **73** by first acetylation in pyridine followed by elimination of the unstable acetates in methanol containing sodium acetate. Although the acetates **87** and **88** were isolated, they were not purified or characterized. All of the prostaglandins in Table III were found to be identical spectrally and in chromatographic behavior with their natural counterparts[4a] except for optical rotations which were opposite in sign but equal in magnitude.

Table IV summarizes the 11α-*ent*-15-methylprostaglandins. Because in the synthesis of the 11β compounds (Scheme III) no easy preparative separation of C-15 epimers at any intermediate stage was available, the 11α compounds were prepared from the PGA compounds **78** and **79** as outlined in Scheme IV. Epoxidation of each PGA compound **78** or **79** using conditions previously described[30] for the conversion to PGE$_2$ of prostaglandins isolated from marine sources (*Plex-*

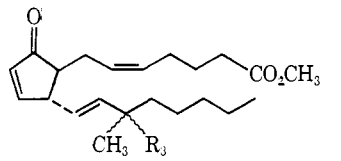
Table III



72, R_3 = (15*S*)OH
73, R_3 = (15*R*)OH



74, R_3 = (15*S*)OH; R_4 = 9αOH
75, R_3 = (15*S*)OH; R_4 = 9βOH
76, R_3 = (15*R*)OH; R_4 = 9αOH
77, R_3 = (15*R*)OH; R_4 = 9βOH



78, R_3 = (15*S*)OH
79, R_3 = (15*R*)OH

(27) A synthesis of 11-*epi*-PGF$_{2\alpha}$ has appeared: D. M. Floyd, G. A. Crosby, and N. M. Weinshenker, *Tetrahedron Lett.*, 3269 (1972).

(28) G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen, G. B. Spero, and J. E. Pike, *J. Amer. Chem. Soc.*, **91**, 5364 (1969).

(29) M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, 37, 1810 (1972).

(30) W. P. Schneider, G. L. Bundy, and F. H. Lincoln, *J. Chem. Soc., Chem. Commun.*, 254 (1973), and references cited therein.

Scheme III

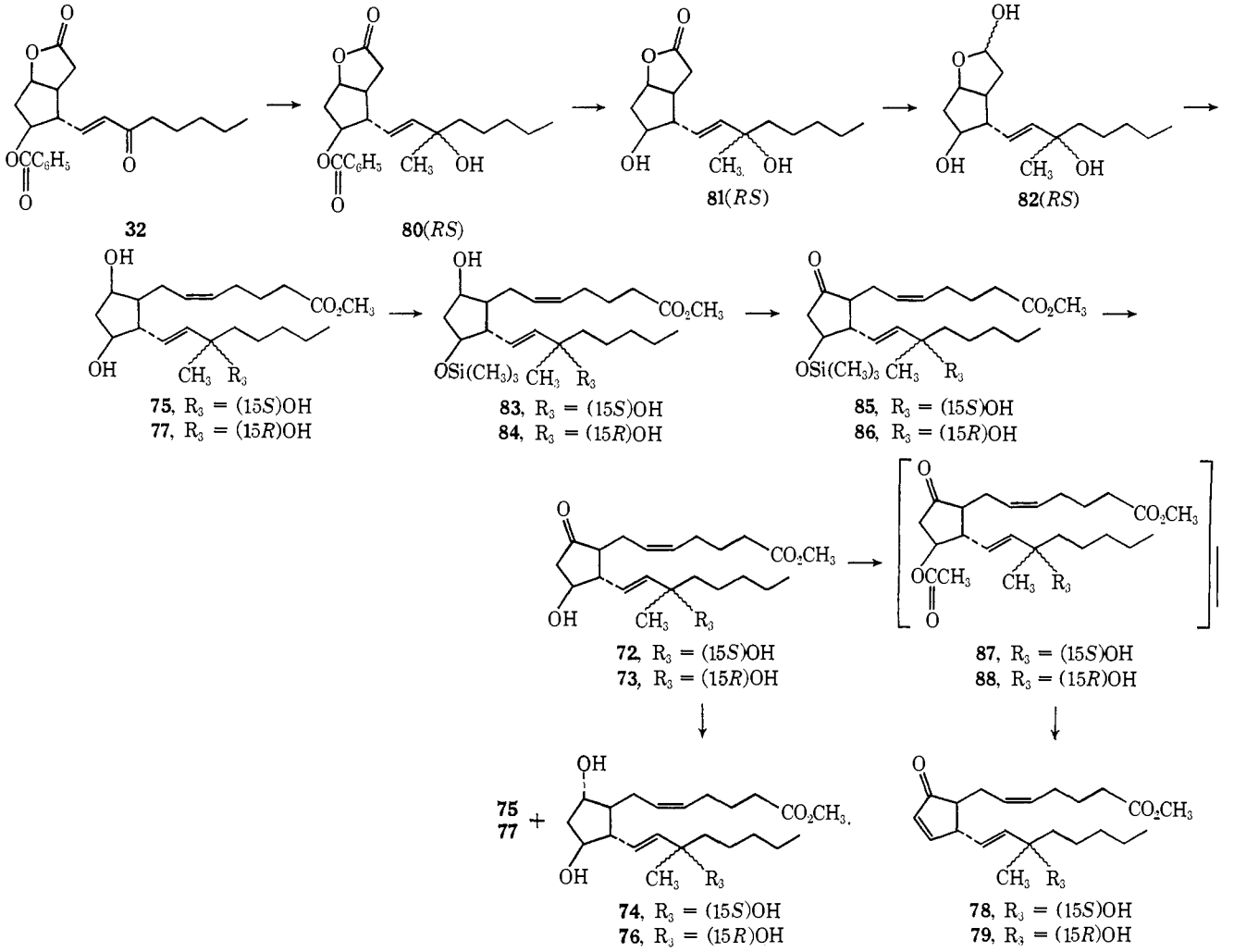
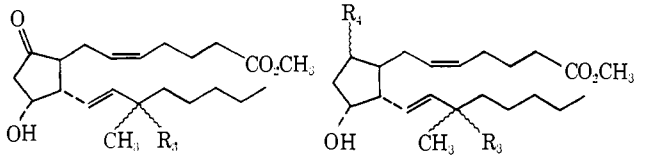


Table IV



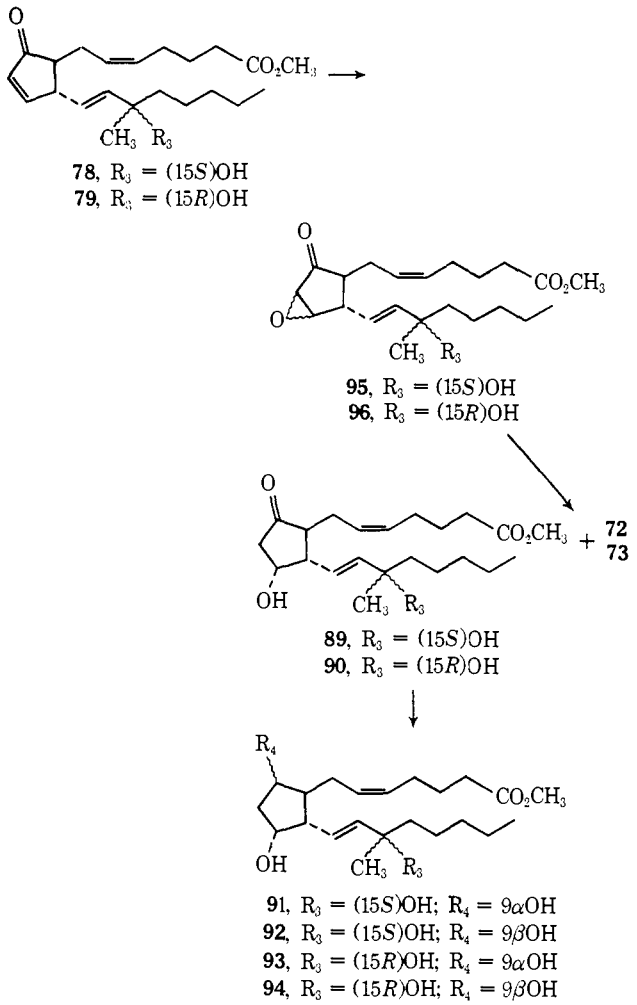
aura homomalla) gave compounds **95** or **96**. Without purification or characterization, the epoxides **95** or **96** were reduced with aluminum amalgam to give the PGE C-11 epimeric pairs **89** and **72** or **90** and **73** in overall yields of 50 and 64% from **78** and **79**, respectively (calculated on the amount of **89** and **72** or **90** and **73** recovered after chromatography). The components of each C-11 epimeric pair were separated chromatographically. The C-15 epimers **89** and **90** were indistinguishable from each other chromatographically and spectrally. The question of possible epimerization at the tertiary allylic C-15 position during the sequence of PGE → PGA → PGA epoxide → PGE (*i.e.*, **72** → **78** → **95** → **89** + **72** or **73** → **79** → **96** → **90** + **73**) was resolved when it was established that the recovered 11β-PGE compounds from each C-15 epimer (**72** or **73**) were epimerically pure by tlc (estimated limit of detection of C-15 epimer in each is ~2–5%).

Reduction of the PGE compounds **89** or **90** with sodium borohydride gave each C-15 epimer of the PGF compounds as a mixture of C-9 epimers (**91** and **92** or **93** and **94**). As with the parent *ent*-prostaglandins (*vide supra*) the C-9 epimers were separated only by using acidic silica gel impregnated with boric acid. By tlc, the ratio of 9α:9β for each C-15 epimer appeared to be ~4:1. Although, because of this, the 9β compounds were obtained in sufficient quantity for characterization only by tlc and high resolution mass spectrometry, the 9α epimers were characterized fully.

Epimerization at C-15 of 15-methylprostaglandins with acetic acid has been observed.[4a] That epimerization had not occurred during chromatography on boric acid silica gel was established since the tlc mobilities of **92** and **94** (C-15 epimers of the 9β-PGF compounds) clearly differed, with **92** being the less polar. Although **91** and **93** (C-15 epimers of the 9α-PGF compounds) were indistinguishable, clearly the chromatographic conditions were not sufficiently acidic to effect epimerization.

The biological evaluation of these structurally novel prostaglandins is in progress. The apparent potencies

Scheme IV



of, for example, 11α-(15*S*)-*ent*-PGE_2 methyl ester (**45**) and of 11α-(15*S*)-15-methyl-*ent*-PGE_2 methyl ester (**89**) are less than PGE_2 in stimulating gerbil colon *in vitro*.[31] However, the apparent potency of **45** is much greater than that of PGE_2 in certain assays. Biological properties of many of these compounds will be reported elsewhere.

Experimental Section

General. All melting points are uncorrected. All analytical data, except for nmr spectra, 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). The nmr spectra were obtained at 60 MHz 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 boric acid silica gel tlc were prepared by dipping the Analtech plates in a 10% solution of methanolic boric acid, followed by brief drying on a hot plate at 200°. Where mixed solvents are used for chromatography, 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[32] 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 tlc 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. Acid-washed silica gel was either Mallinkrodt CC-4 where indicated or was prepared by washing neutral Merck silica gel with dilute hydrochloric acid, washing well with water, and drying at 200° *in vacuo*. Boric acid impregnated silica gel was prepared by washing Merck neutral silica gel with a solution of 10% boric acid in methanol followed by vacuum oven drying at 50°. 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.

(+)-2α,4α-Dihydroxy-3β-iodo-5β-(methoxymethyl)cyclopentane-1α-acetic Acid γ-Lactone, 28. To a stirred slurry of 36 g of sodium hydroxide, 330 ml of water, and ~300 g of crushed ice was added 117 g (0.33 mol) of ephedrine salt, **27**[15a,22] [mp 134–135°; $[\alpha]_D$ −39° (*c* 0.92, methanol)], giving a precipitate. To the mixture was added 1 l. of methylene chloride giving two liquid phases. The aqueous phase was separated and the organic phase washed with 150 ml of water. The aqueous solutions were combined and the organic solution was discarded. The aqueous solution was acidified to pH ~7 by the addition of Dry Ice. This neutralized solution was added in portions to a stirred solution at 0° of 160 g of potassium iodide, 230 ml of water, and 230 g of iodine. The resulting mixture was stirred at 0° for 20 hr. The reaction was quenched by the cautious addition of a slurry of 125 g of sodium sulfite and 50 g of sodium carbonate in 370 ml of water. The resulting mixture was extracted with chloroform (4 × 350 ml). The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 97.5 g of a yellow solid. Recrystallization from 150 ml of hot methylene chloride gave 80.3 g, mp 101–104°. An analytical sample was prepared by recrystallization from ethanol: mp 102.5–103.5°, $[\alpha]_D$ +48° (*c* 1.11, chloroform). The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.3. The following spectral data were obtained: mass spectrum, ions at *m/e* 312, 184, and 152; nmr, δ 5.16–4.89 (m), 4.18–3.87 (m), 3.54 (d), 3.37 (s), 3.00–2.28 (m), and 2.03–1.67 (m); ir 3350, 1755, 1150, 1100, 1060, 1010, 950, 757, and 697 cm^{-1}.

Anal. Calcd for $C_9H_{13}IO_4$: C, 34.64; H, 4.20; I, 40.66. Found: C, 35.20; H, 4.36; I, 40.74.

(−)-2α,4α-Dihydroxy-3β-iodo-5β-(methoxymethyl)cyclopentane-1α-acetic Acid γ-Lactone 4-Benzoate, 29. To a stirred solution of 18 g (58 mmol) of iodo lactone **28** in 30 ml of dry pyridine maintained at ambient temperature under nitrogen was added dropwise 7.5 ml (9.1 g, 65 mmol) of benzoyl chloride. Toward the end of the addition the reaction became heterogeneous. After addition was complete the reaction was stirred an additional hour. The mixture was diluted with 60 ml of toluene and evaporated. This was repeated once to give an oily residue. The residue was partitioned between ethyl acetate and 10% sulfuric acid. After equilibration, the aqueous phase was extracted well with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. Evaporation gave 21.8 g of an oil which crystallized on standing. Recrystallization twice from ethanol gave a total of 17.2 g (72%), mp 85–89°, $[\alpha]_D$ −5° (*c* 0.80, chloroform). The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5. The mass spectrum showed ions at *m/e* 416, 294, 289, 262, 167, and 105.

Anal. Calcd for $C_{16}H_{17}IO_5$: C, 46.18; H, 4.12; I, 30.49. Found: C, 45.94; H, 4.08; I, 30.37.

(+)-3β,5β-Dihydroxy-2α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 30. To a stirred solution of 16.8 g (40 mmol) of iodo lactone benzoate **29** in 100 ml of benzene at ambient temperature under nitrogen was added 215 ml of a freshly prepared solution of 0.3 *M* tributyltin hydride in ether. After addition was complete the solution was stirred for 0.5 hr at ambient temperature. Tlc (50% ethyl acetate–Skellysolve B) showed reaction to be complete. The solution was evaporated to give a mobile cloudy oil. The oil was partitioned between 200 ml of water and 200 ml of Skellysolve B. After equilibration and standing overnight, the organic layer was removed and discarded. The aqueous mixture was extracted twice more with Skellysolve B (discarded). Finally, the aqueous mixture was extracted well with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, and evaporated to give 11.2 g (96%) of a cloudy mobile oil. The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.3. The nmr spectrum showed δ 8.04–7.80 (m), 7.54–7.14 (m), 5.44–4.84 (m), 3.35 (d, 6 Hz), 3.25 (s), 3.03–1.95 (m), and 1.38–0.86 (m).

(+)-3β,5β-Dihydroxy-2α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 31. To a well stirred solution of 101 g (0.38 mol) of lactone benzoate ether **30** in 800 ml of methylene chloride at 0° under nitrogen was added slowly a solution of 175 g

(31) Private communication from J. R. Weeks, The Upjohn Co.
(32) M. Hamburg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

(0.60 mol) of boron tribromide in 400 ml of methylene chloride. After 20 hr, tlc (ethyl acetate) of an aliquot quenched in ether–sodium bicarbonate showed complete reaction. The reaction while at 0° was quenched by careful addition of a solution of 405 g (3.8 mol) of sodium carbonate in 1050 ml of water. The mixture was allowed to warm to ambient temperature then saturated with sodium chloride and extracted well with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, and evaporated to give a solid. Recrystallization from methylene chloride and carbon tetrachloride gave a total of 85 g (89%), mp 115–116°, $[\alpha]_D$ +81° (*c* 0.91, chloroform). The material was homogeneous by tlc in ethyl acetate with R_f 0.4. The mass spectrum showed ions at *m/e* 276, 154, and 136. The nmr spectrum showed δ 8.01–7.82 (m), 7.54–7.14 (m), 5.54–4.89 (m), and 3.80–2.03 (m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.69; H, 5.90.

(+)-3β,5β-Dihydroxy-2α-(3-oxo-*trans*-1-octenyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 32. To a stirred mixture of 10.6 g (0.22 mol) of 50% sodium hydride dispersion in 1500 ml of tetrahydrofuran under nitrogen at 0° was added a solution of 48.8 g (0.22 mol) of dimethyl (2-oxoheptyl)phosphonate in 120 ml of tetrahydrofuran. After stirring at 0° for 5 min, the resulting ylide solution was stirred at ambient temperature for 1.25 hr and then cooled again to 0°.

To a stirred solution of 107 g (1.36 mol) of dry pyridine in 1500 ml of methylene chloride at 0° under nitrogen was added 84 g (0.84 mol) of anhydrous chromium trioxide. The resulting Collins[23] oxidant was stirred 5 min more at 0° then at ambient temperature for 45 min and then cooled again to 0°. To the stirred Collins oxidant was added a solution of 30.5 g (0.11 mol) of lactone benzoate alcohol **31** in 300 ml of methylene chloride. The resulting aldehyde mixture was stirred at 0° for 5 min then at ambient temperature for 5 min.

Into the cold ylide solution prepared previously was decanted the aldehyde mixture above. The resulting mixture was then stirred at ambient temperature for 4 hr. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–sodium bisulfate showed reaction complete. The reaction was quenched by addition to a mixture of 2000 ml of 2 *M* sodium bisulfate and ice. The aqueous mixture was extracted well with chloroform. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give a dark mobile oil. The oil was dissolved in ether and filtered through ~5 in. of silica gel washing with 4 l. of 10% ethyl acetate–Skellysolve B and then 4 l. of 50% ethyl acetate–Skellysolve B. The latter filtrate was evaporated to give 26.2 g of a light green oil which slowly crystallized. Recrystallization from hexane–ethyl acetate gave 17.6 g, mp 62–64°, $[\alpha]_D$ +113° (*c* 0.92, chloroform). The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B. The uv (ethanol) showed λ_{max} at 229 (ε 25,800), 269 sh (ε 919), 274 (ε 1050), 282 (ε 852), and 316 (ε 74). The nmr showed δ 8.11–7.84 (m), 7.62–7.20 (m), 6.95–6.50 (d of d, 16 Hz), 6.17 (d, 16 Hz), 5.46–4.92 (m), 3.52 (d, 6 Hz), and 3.10–0.62 (m).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.42; H, 7.34.

(+)-3β,5β-Dihydroxy-2α-[(3*RS*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 33 and 34. To a stirred mixture of 5.30 g (0.14 mol) of sodium borohydride in 500 ml of methanol at −20° under nitrogen was added 33.6 g (0.09 mol) of lactone benzoate ketone **32** in 250 ml of methanol. After 2 hr, tlc (20% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed reaction to be complete. The reaction while at −20° was quenched by slow addition of 250 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature then evaporated. The residue was partitioned between ethyl acetate and 0.2 *M* sulfuric acid. After equilibration the acidic aqueous layer was extracted well with ethyl acetate. The organic extracts were combined, washed with saturated bicarbonate and brine, dried over sodium sulfate, and evaporated to give 41.6 g of oil. Of this crude product, 20 g was chromatographed on 2 kg of silica gel, packed in 20% ethyl acetate–Skellysolve B. Taking 350-ml fractions, elution was with 50% ethyl acetate–Skellysolve B. The following were combined: fractions 27–37, pure less polar (15*R*), 4.4 g; fraction 38–54, mixture, 6.6 g; fraction 55–70, pure more polar (15*S*), 1.9 g. Both the (15*R*) and the (15*S*) compounds crystallized.

Recrystallization of the less polar 15*R*-**34** from hexane–ethyl acetate gave an analytical sample, mp 69–70°, $[\alpha]_D$ +77° (*c* 1.04, chloroform). The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5. The mass spectrum showed ions at *m/e* 314, 301, and 250. The nmr spectrum showed δ 8.17–7.82 (m), 7.65–7.23 (m), 5.78–4.78 (m), 4.28–3.82 (m), 3.08–1.90 (m), and 1.73–0.45 (m).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.18; H, 7.68.

Recrystallization of the more polar 15*S*-**33** from hexane–ethyl acetate gave an analytical sample, mp 76–77°, $[\alpha]_D$ +98° (*c* 0.78, chloroform). The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.4. The mass spectrum showed ions at *m/e* 345, 301, and 250. The nmr showed δ 8.17–7.82 (m), 7.72–7.17 (m), 5.81–4.82 (m), 4.25–3.82 (m), and 3.15–0.52 (m).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.18; H, 7.62.

3β,5β-Dihydroxy-2α-[(3*S*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 35. A mixture of 10.2 g (31 mmol) of lactone benzoate alcohol **33** and 5.6 g (40 mmol) of potassium carbonate in 100 ml of methanol was stirred at ambient temperature under nitrogen. After 2 hr, tlc (ethyl acetate) showed complete reaction. The dark mixture was filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated to give a mobile oil. The oil was partitioned between brine and ethyl acetate. After equilibration the organic extract was dried over sodium sulfate and evaporated to give a mobile oil. Trituration of this oil with Skellysolve B left a viscous residue. The brine extract was acidified with 2 *M* sodium bisulfate and extracted well with ethyl acetate. The organic extracts were combined and washed with brine, dried over sodium sulfate, and evaporated to give an oil. Tlc (ethyl acetate and A-IX) showed some opened lactone. This oil and the residue from the Skellysolve B trituration were combined and dissolved in 250 ml of ethyl acetate containing 100 mg of pyridine hydrochloride. This solution was refluxed for 1 hr and then filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 6.9 g (83%) of oil. The material was homogeneous by tlc in ethyl acetate with R_f 0.33. The nmr spectrum showed δ 5.68–5.50 (m), 5.13–4.76 (m), 4.25–3.80 (m), 3.70–3.08 (m), and 2.97–0.67 (m).

(+)-3β,5β-Dihydroxy-2α-[(3*R*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone, 36. A mixture of 4.4 g (12 mmol) of lactone benzoate alcohol **34** and 2.1 g (15 mmol) of anhydrous potassium carbonate in 40 ml of methanol was stirred at ambient temperature under nitrogen for 4.5 hr. The resulting dark mixture was filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated to give a mobile oil. The oil was partitioned between brine and ethyl acetate. After equilibration the organic extract was dried over sodium sulfate and evaporated to give a mobile oil. Trituration of this oil with Skellysolve B left a viscous residue. The brine extract was acidified with 2 *M* sodium bisulfate and extracted well with ethyl acetate. The organic extracts were combined and washed with brine, dried over sodium sulfate, and evaporated to give an oil. Tlc (ethyl acetate and A-IX) showed much opened lactone. This oil and the residue from the Skellysolve B triturates were combined and dissolved in 100 ml of ethyl acetate containing 40 mg of pyridine hydrochloride. This solution was refluxed for 1 hr and then filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 2.3 g (73%) of oil containing traces of less and more polar impurities but no opened lactone. This material was chromatographed on 50 g of silica gel packed in ethyl acetate. Taking 30-ml fractions, elution was with ethyl acetate. Fractions 4–9 contained pure material, 2.0 g of oil, $[\alpha]_D$ +10° (*c* 2.51, chloroform). In addition, fractions 3 and 10 contained less pure material, 0.1 g of oil. The material was homogeneous by tlc in ethyl acetate with R_f 0.35. The nmr spectrum showed δ 5.65–5.43 (m), 5.07–4.74 (m), 4.35–3.76 (m), 3.54–3.28 (m), and 2.92–0.50 (m).

3β,5β-Dihydroxy-2α-[(3*S*)-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 3-Tetrahydropyranyl Ether, 37. A solution of 0.66 g (2.5 mmol) of lactone diol **35**, 2.5 g (30 mmol) of dihydropyran, and 75 mg of pyridine hydrochloride in 20 ml of methylene chloride was stirred at ambient temperature for 24 hr. Tlc (50% ethyl acetate–Skellysolve B) showed complete reaction. The solution was filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 1.2 g of mobile oil. The crude product was chromatographed on 120 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 30-ml fractions, elution was with 500 ml of 20%, 500 ml of 30%, 500 ml of 40%, and 1500 ml of 50% ethyl acetate–Skellysolve B. Fractions 44–66 were combined to give good product, 0.67 g (62%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5.

3β,5β-Dihydroxy-2α-[(3*R*)-tetrahydropyranyloxy-*trans*-1-octenyl]-cyclopentane-1β-acetic Acid γ-Lactone 3-Tetrahydropyranyl Ether, 38. A solution of 0.56 g (2.1 mmol) of lactone diol **36**, 2.1 g (25 mmol) of dihydropyran, and 60 mg of pyridine hydrochloride in 15 ml of methylene chloride was stirred at ambient temperature for 18 hr. Tlc (50% ethyl acetate–Skellysolve B) showed complete reaction. The solution was filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 0.90 g of mobile oil. The crude product was chromatographed on 90 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 25-ml fractions, elution was with 1500 ml of 30% and 2000 ml of 50%. Fractions 32–50 were combined to give good product, 0.70 g (77%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5.

3β,5β-Dihydroxy-2α-[(3*S*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-carboxaldehyde γ-Lactol 3-Tetrahydropyranyl Ether, 39. To a stirred solution of 0.67 g (1.5 mmol) of lactone di-THP **37** in 20 ml of toluene at −78° under nitrogen was added 5 ml (3.1 mmol) of a solution of 10% diisobutylaluminum hydride in toluene. After 2 hr, tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–water showed complete reaction. The reaction while at −78° was quenched by addition of 24 ml of a solution of tetrahydrofuran and water (2:1). The resulting mixture was allowed to warm to ambient temperature with stirring, then filtered through Celite, washing well with ether. The filtrate was diluted with water, equilibrated, and separated. The aqueous layer was extracted well with ether. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 0.67 g (100%) of oil, homogeneous by tlc in A-IX (R_f 0.7) and 50% ethyl acetate–Skellysolve B (R_f 0.3).

3β,5β-Dihydroxy-2α-[(3*R*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-carboxaldehyde γ-Lactol 3-Tetrahydropyranyl Ether, 40. To a stirred solution of 18.1 g (41 mmol) of lactone di-THP **38** in 450 ml of toluene at −78° under nitrogen was added 136 ml (83 mmol) of 10% diisobutylaluminum hydride in toluene. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–water after 1 hr showed complete reaction. The reaction while at −78° was quenched by addition of 540 ml of a solution of tetrahydrofuran and water (2:1). The resulting mixture was allowed to warm to ambient temperature, then filtered through Celite, washing well with ether. The filtrate was diluted with water, equilibrated, and separated. The aqueous layer was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 18.2 g (100%) of oil, homogeneous by tlc in A-IX (R_f 0.7) and 50% ethyl acetate–Skellysolve B (R_f 0.3).

(15*S*)-*ent*-PGF$_{2\alpha}$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 41. A slurry of 3.54 g (147 mmol) of 50% sodium hydride dispersion and 580 ml of dimethyl sulfoxide was stirred at 65–70° for 1 hr under N_2. The resulting solution was cooled to 15–20°. To this was added 31.6 g (74 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting dark solution was stirred at ambient temperature for 30 min then cooled to 15–20°. To this was added a solution of 10.7 g (24 mmol) of lactone di-THP **39** in 250 ml of dimethyl sulfoxide. The resulting dark mixture was allowed to stir at ambient temperature. After 18 hr, tlc (A-IX, product R_f ~0.8) of an aliquot quenched in ether sodium bisulfate showed complete reaction. The reaction was quenched by addition to a mixture of 660 ml of 2 *M* sodium bisulfate, 190 ml of water, and ice. The resulting mixture was extracted well with ether. The organic extracts were combined and extracted three times with 1 *N* sodium hydroxide. The basic aqueous extracts were combined and carefully acidified to pH ≤ 3 with 2 *M* sodium bisulfate in the presence of ice and ether. After equilibration and separation, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give a dark oil.

The crude product was esterified immediately by dissolving first in 100 ml of a 1:1 solution of ether and methanol. This solution was treated with excess diazomethane in ether. The resulting solution was first evaporated on a steam bath to ~0.5 volume then rotary evaporated under vacuum to give 7.0 g of oil. The crude product was chromatographed on 700 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 250-ml fractons, elution was with 1 l. of 30%, 1 l. of 40%, 4 l. of 50%, and 2 l. of 100%. Fractions 15–17 contained good quality product **41** [(15*S*)-*ent*-PGF$_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) methyl ester], 6.2 g (49%) oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.6.

***ent*-PGF$_{2\alpha}$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 42.** A slurry of 6.1 g (254 mmol) of 50% sodium hydride dispersion and 1000 ml of dimethyl sulfoxide was stirred at 65–70° for 1 hr under nitrogen. The resulting solution was cooled to 15–20°. To this was added 54.5 g (127 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting dark solution was stirred at ambient temperature for 20 min then cooled to 15–20°. To this was added a solution of 18.2 g (41 mmol) of lactol-di-THP **40** in 450 ml of dimethyl sulfoxide. The resulting dark mixture was stirred at ambient temperature for 18 hr. Tlc (A-IX, product R_f ~0.8) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction was quenched by addition to a mixture of 660 ml of 2 *M* sodium bisulfate, 190 ml of water, and ice. The resulting mixture was extracted well with ether. The organic extracts were combined and extracted three times with 1 *N* sodium hydroxide. The basic aqueous extracts were combined and carefully acidified to pH ≤3 with 2 *M* sodium bisulfate in the presence of ether and ice. After equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give a dark oil.

The crude product was esterified immediately by dissolving first in 100 ml of a 1:1 solution of ether and methanol. This solution was treated with excess diazomethane in ether. The resulting solution was first evaporated on a steam bath to ~0.5 volume then rotary evaporated under vacuum to give 17.1 g of oil. The crude product was chromatographed on 2 kg of silica gel, packed with 10% ethyl acetate–Skellysolve B. Taking 350-ml fractions, elution was with 3 l. of 30% and 2 l. of 50%. Fractions 17–24 contained good product, 12.5 g (56%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5.

(15*S*)-*ent*-PGE$_2$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 43. To a stirred solution of 1.5 g (18 mmol) of dry pyridine in 60 ml of methylene chloride at 0° under nitrogen was added 0.92 g (9.2 mmol) of anhydrous chromium trioxide. The resulting mixture was stirred at ambient temperature for 1 hr then cooled again to 0°. To this was added a solution of 0.55 g (1.0 mmol) of (15*S*)-*ent*-PGF$_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **41**, in 15 ml of methylene chloride. The resulting mixture was stirred for 10 min at ambient temperature then filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated to give a mobile oil containing pyridine. The residue was dissolved in ether and washed once with 0.2 *M* sodium bisulfate. The aqueous phase was extracted well with ether. The combined organic extracts were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 0.52 g of oil. The crude product was chromatographed on 50 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 50-ml fractions, elution was with 250 ml of 50% ethyl acetate–Skellysolve B. Fractions 1 and 2 contained good material, 0.50 g (100%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.60.

***ent*-PGE$_2$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 44.** To a stirred solution of 32.8 g (0.41 mmol) of dry pyridine in 1.2 l. of methylene chloride at 0° under nitrogen was added 20.7 g (0.21 mmol) of anhydrous chromium trioxide. The resulting mixture was stirred at ambient temperature for 1 hr then cooled to 0°. To this was added a solution of 12.5 g (23 mmol) of *ent*-PGF$_{2\alpha}$ 11,15-bis-(tetrahydropyranyl ether) methyl ester, **42**, in 250 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 15 min then filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated to give a dark oil containing pyridine. The residue was dissolved in ether and washed once with 0.2 *M* sodium bisulfate. The aqueous phase was extracted well with ether. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 12.2 g (98%) of light colored oil. The crude product was used directly without further purification. Tlc in 50% ethyl acetate–Skellysolve B showed the major product to have R_f 0.6.

(15*S*)-*ent*-PGF$_{2\alpha}$ Methyl Ester, 12. A solution of 0.11 g (0.20 mmol) of (15*S*)-*ent*-PGF$_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **41**, in 4 ml of acetic acid, water, and tetrahydrofuran (20:10:3) was heated at 40° for 4 hr. The solution was cooled to ambient temperature, diluted with 4 ml of water, and freeze dried to give 0.1 g of oil. The crude product was chromatographed on 10 g of silica gel, packed in 10% acetone–methylene chloride. Taking 11-ml fractions, elution was with 500 ml of 30%. Fractions 7–19 contained good material, 66 mg (87%) of oil, $[\alpha]_D$ −9° (*c* 0.33, tetrahydrofuran). The material was homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.4. The following spectral

data were obtained: nmr δ 6.10–5.32 (m), 4.32–3.81 (m), 3.67 (s), 2.60–0.76 (m); ir 3400, 1750, 1185, and 972 cm^{-1}; high resolution mass spectrum, parent ion of tris-TMS derivative at *m/e* 584.3695 (calcd for $C_{30}H_{60}Si_3O_5$: 584.3746), with other ions at 569, 553, 541, 521, 513, 494, 479, and 423.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.59; H, 9.70.

***ent*-PGF$_2\alpha$ Methyl Ester, 24.** A solution of 60 mg (0.11 mmol) of *ent*-PGF$_2\alpha$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **42**, in 2 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 4 hr. The solution was cooled to ambient temperature, diluted with 2 ml of water, and freeze dried to give 100 mg of oil. The crude product was chromatographed on 5 g of silica gel, packed in 10% acetone–methylene chloride. Taking 5-ml fractions, elution was with 200 ml of 30% and 100 ml of 50%. Fractions 12–35 contained good material, 36 mg (87%) of oil, $[\alpha]_D$ −24° (*c* 0.58, ethanol), homogeneous by tlc in 50% acetone–methylene chloride with R_f 0.4. (This material was identical by tlc with PGF$_2\alpha$ methyl ester.) The following spectral data were obtained: nmr δ 5.64–5.26 (m), 4.27–3.77 (m), 3.67 (s), 3.34–2.86 (m), and 2.53–0.67 (m); ir, 3350, 3000, 2940, 2920, 2850, 1735, 1720, 1665, 1450, 1435, 1365, 1245, 1170, 1080, 970, and 735 cm^{-1}; high resolution mass spectrum, parent ion of tris-TMS derivative at 584.3741 (calcd for $C_{30}H_{60}Si_3O_5$: 584.3747), with other ions at 569, 553, 541, 513, 423, and 404.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.19; H, 10.35.

(15*S*)-*ent*-PGE$_2$ Methyl Ester, 11, and (15*S*)-*ent*-PGA$_2$ Methyl Ester, 25. A solution of 0.55 g (1.0 mmol) of (15*S*)-*ent*-PGE$_2$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **43**, in 18 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 3 hr. The resulting solution was cooled to ambient temperature, diluted with 40 ml of water, and freeze dried to give 0.36 g of oil. The crude product was chromatographed on 40 g of silica gel, packed in 2% acetone–methylene chloride. Taking 35-ml fractions, elution was with 250 ml of 10%. Fractions 5–9 contained 30 mg of impure PGA compound **25** which was purified further (see below). Fractions 15 and 16 contained 170 mg of good PGE compound, **11** (while fractions 14 and 18–24 contained 80 mg of impure material), as an oil, $[\alpha]_D$ +67° (*c* 0.68, tetrahydrofuran), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.45. The following spectral data were obtained: uv neutral ethanol, end absorption, and basic ethanol, λ_{max} 278 nm (ε 21,050); nmr δ 5.77–5.60 (m), 5.50–5.26 (m), 4.32–3.87 (m), 3.67 (s), 3.05–0.61 (m); ir, 3420, 3000, 2950, 2920, 2850, 1735, 1625, 1450, 1435, 1245, 1160, 1085, 1025, and 970 cm^{-1}; high resolution mass spectrum, parent ion of the bis-TMS derivative at *m/e* 510.3195 (calcd for $C_{27}H_{50}Si_2O_5$: 510.3195) with other ions at 495, 479, 439, 420, and 349.

The 30 mg of impure PGA compound **25** (combined with 20 mg of material obtained in a similar fashion) was purified further by preparative silica gel tlc using 10% acetone–methylene chloride to give 18 mg of material with a polar impurity. This material was filtered through a short column of silica gel eluting with 50% ethyl acetate–hexane, to give 15.3 mg of **25** as an oil $[\alpha]_D$ −76° (*c* 0.15, chloroform), homogeneous by tlc in 10% acetone–methylene chloride with R_f 0.38. The ir spectrum showed 3440, 3000, 2920, 2850, 1735, 1705, 1625, 1585, 1540, 1450, 1370, 1335, 1240, 1200, 1170, 1075, 1020, and 975 cm^{-1}; the high resolution mass spectrum of the mono-TMS derivative showed the parent ion at *m/e* 420.2727 (calcd for $C_{24}H_{40}SiO_4$: 420.2695), with other ions at 405, 389, 349, and 330. The nmr spectrum showed δ 7.62–7.40 (m), 6.28–6.10 (m), 5.73–5.30 (m), 4.30–3.87 (m), 3.67 (s), 3.42–3.10 (m), and 2.63–0.60 (m).

***ent*-PGE$_2$ Methyl Ester, 22, and *ent*-PGA$_2$ Methyl Ester, 26.** A solution of 12.2 g (23 mmol) of *ent*-PGE$_2$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **44**, in 545 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 3.5 hr. The resulting solution was cooled to ambient temperature, diluted with 500 ml of water, and freeze dried to give 11.6 g of oil. The crude product was chromatographed on 1.2 kg of silica gel, packed in 2% acetone–methylene chloride. Taking 300-ml fractions, elution was with 1 l. of 10%, 4 l. of 20%, and 8 l. of 30%. Fraction 6 contained 0.41 g of impure PGA compound **26** which was purified further (see below). Fractions 20–28 contained 4.2 g (50%) of good quality PGE compound, **22**, $[\alpha]_D$ +55° (*c* 0.86, tetrahydrofuran), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.3. The following spectral data were obtained: uv, neutral ethanol, end absorption, and basic ethanol, λ_{max} 278 nm (ε 21,900); nmr, δ 5.72–5.37 (m), 4.32–3.82 (m), 3.68 (s), and 2.75–0.69 (m); ir, 3380, 3000, 1740, 1455, 1365, 1245, 1215, 1160, 1075, 1015, and 970 cm^{-1}; high resolution mass spectrum, parent ion of the bis-TMS derivative at *m/e* 510.3198 (calcd for $C_{27}H_{50}Si_2O_5$: 510.3195) with other ions at 495, 492, 379, 467, 439, 420, and 349.

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.92; H, 9.64.

The impure PGA compound **26** was purified further by chromatography on 50 g of silica gel, packed in 1% acetone–methylene chloride. Taking 40-ml fractions, elution was with 60 ml of 1%, 200 ml of 5%, and 500 ml of 10%. Fractions 11–13 contained good PGA compound **26**, 0.23 g of oil, $[\alpha]_D$ −148° (*c* 0.67, chloroform), homogeneous by tlc in 10% acetone–methylene chloride with R_f 0.34. The following spectral data were obtained: uv, neutral ethanol, λ_{max} 217 nm (ε 10,600), and basic ethanol λ_{max} 278 nm (23,400); nmr, δ 7.62–7.45 (d of d), 6.29–6.10 (d of d), 5.73–5.30 (m), 4.30–3.95 (m), 3.67 (s), 3.33–3.11 (m), and 2.63–0.67 (m); ir, 3440, 3000, 1735, 1705, 1585, 1540, 1435, 1365, 1315, 1245, 1175, 1055, 1020, and 970 cm^{-1}; high resolution mass spectrum, parent ion of the mono-TMS derivative at *m/e* 420.2658 (calcd for $C_{24}H_{40}SiO_4$: 420.2695), with other ions at 405, 389, 340, and 330.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.93; H, 9.23.

(15*S*)-*ent*-PGF$_2\beta$ Methyl Ester, 23. To a stirred mixture of 18 mg (0.5 mmol) of sodium borohydride in 6 ml of methanol at −20° under nitrogen was added 0.12 g (0.34 mmol) of (15*S*)-*ent*-PGE$_2$ methyl ester, **11**. After 30 min, the reaction while at −20° was quenched by careful addition of 6 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and evaporated. The residue was dissolved in ethyl acetate and washed with 0.2 *M* sulfuric acid. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 0.10 g of oil. Tlc (30% acetone–methylene chloride) showed two products in nearly equal concentration. The crude product was chromatographed on 20 g of silica gel, packed in 10% acetone–methylene chloride. Taking 20-ml fractions, elution was with 30% acetone–methylene chloride. The following fractions were combined: 12–20, good less polar product (50 mg), oil; 21–25, mixture (25 mg), oil; 26–31, good more polar product (21 mg), oil. The less polar material was identical with (15*S*)-*ent*-PGF$_2\alpha$ methyl ester **12** by tlc. The more polar material was assigned (15*S*)-*ent*-PGF$_2\beta$ methyl ester, **23**, homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.2. The ir showed 3350, 3000, 1735, 1720, 1665, 1440, 1330, 1250, 1225, 1165, 1090, 1040, and 975 cm^{-1}. The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at *m/e* 584.3753 (calcd for $C_{30}H_{60}Si_3O_5$: 584.3746) with other ions at 569, 553, 541, 513, and 494.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.11; H, 10.37.

***ent*-PGF$_2\beta$ Methyl Ester, 13.** To a stirred mixture of 0.15 g (3.9 mmol) of sodium borohydride in 50 ml of methanol at −20° under N_2 was added a solution of 1.0 g (2.7 mmol) of *ent*-PGE$_2$ methyl ester, **22**, in 50 ml of methanol. After 15 min, the reaction while at −20° was quenched by careful addition of 50 ml of acetic acid. The resulting solution was warmed to ambient temperature and evaporated. The residue was dissolved in ethyl acetate and washed once with 0.2 *M* sulfuric acid. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 0.74 g of crystalline product. Tlc (30% acetone–methylene chloride and ethyl acetate) showed two products in nearly equal concentration. The crude product was combined with 0.10 g of material obtained in a similar fashion and chromatographed on 85 g of silica gel, packed in 10% acetone–methylene chloride. Taking 40-ml fractions, elution was with 50% acetone–methylene chloride. The following fractions were combined: 15–20, good less polar product, 0.36 g; 21–24, mixture, 60 mg of oil; 25–49, good more polar product, 0.40 g, crystalline. The less polar product was identical by tlc with PGF$_2\alpha$ methyl ester[3] and with *ent*-PGF$_2\alpha$ methyl ester, **24**. The more polar material was identical by tlc with *ent*-PGF$_2\beta$ methyl ester, **13**, prepared by an alternate method.[17] An analytical sample was prepared by recrystallization from ethyl acetate–Skellysolve B to give 0.36 g (36%), mp 90–91°, $[\alpha]_D$ +7° (*c* 0.85, ethanol). The material was homogeneous by tlc in 50% acetone–methylene chloride with R_f 0.3. The following spectral data were obtained: nmr δ 5.64–5.34 (m), 4.17–3.78 (m), 3.67 (m), and 3.00–0.45 (m); ir, 3280, 3200, 3000, 1735, 1670, 1315, 1215, 1170, 1045, 1020, and 970 cm^{-1}; high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 584.3770 (calcd for $C_{30}H_{60}O_5Si_3$: 584.3746), with other ions at 569, 553, 541, 503, 494, 479, 463, and 457.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.66; H, 10.30.

3β,5β-Dihydroxy-2α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone, 51. To a stirred solution of 20.5 g (66 mmol) of lactone iodo alcohol methyl ether **28** in 125 ml of benzene at ambient temperature under nitrogen was added 250 ml of an ethereal solution 0.3 *M* in tributyltin hydride (total 75 mmol). After 1 hr, tlc (50% ethyl acetate–Skellysolve B) showed the reaction complete. The cloudy solution was rotary evaporated at 40° to give 48 g of a cloudy mobile liquid. To this was added 300 ml of Skellysolve B and 300 ml of water. The resulting mixture was stirred overnight at ambient temperature. The mixture was transferred to a separatory funnel (leaving a residue of product), shaken, and separated. The organic layer was washed twice with water. The aqueous washings were combined with the residue from above and the organic layer was discarded. The aqueous mixture was saturated with salt and extracted well with ethyl acetate. The organic extracts were combined, dried over sodium sulfate, and evaporated to give 7.5 g (61%) of an oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.1. The ir spectrum showed bands at 3300, 1755, 1170, 1037, 959, and 890 cm^{-1}.

(+)-3β,5β-Dihydroxy-2α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 3-*p*-Toluenesulfonate, 52. A solution of 1.0 g (5.4 mmol) of lactone hydroxy methyl ether **51**, 1.9 g (10 mmol) of tosyl chloride, and 20 ml of dry pyridine was stirred at ambient temperature under nitrogen. After 2 days, tlc (ethyl acetate) of an aliquot quenched in ether–sodium bisulfate showed the reaction to be complete. The solution was diluted with ice and excess 10% sulfuric acid. The resulting mixture was extracted well with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 1.8 g (100%) of a solid, mp 85–95°. Recrystallization once from benzene–Skellysolve B gave an analytical sample, mp 97–98°, $[\alpha]D$ +55° (*c* 1.09, chloroform), homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.3. The nmr spectrum showed δ 7.90–7.20 (m), 5.10–4.70 (m), 3.31 (d, 6 Hz), 3.23 (s), and 2.98–2.12 (m), including a singlet at 2.4. The mass spectrum showed ions at *m/e* 340, 186, 168, 155, and 91.

Anal. Calcd for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92. Found: C, 56.59; H, 6.09.

3α,5β-Dihydroxy-2α-(methoxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 53. A mixture of 1.8 g (5.3 mmol) of tosylate **52**, 5.0 g of sodium benzoate (34 mmol), and 100 ml of dimethyl sulfoxide was stirred under nitrogen at 80–85°. After 3.5 hr the reaction was homogeneous. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–water showed no starting material and two products of unequal intensities. The solution was diluted with 500 ml of ice–water. The cloudy solution was extracted well with ether. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 1.5 g (100%) of oil. Tlc (50% ethyl acetate–Skellysolve B) showed two spots, R_f 0.4 and 0.5. The product could be used without further purification. The product was chromatographed on 150 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 150-ml fractions, elution was with 500 ml of 10%, 1 l. of 20%, 1 l. of 30%, and 1 l. of 40%. Fraction 15 contained pure less polar product **53** (0.13 g); fractions 16–18 contained a mixture (0.8 g); and fractions 19–23 contained fairly pure more polar product (0.1 g). The more polar product (R_f ~0.4 in 50% ethyl acetate–Skellysolve B) appeared to be elimination product **54**[25,26] from its mass and ir spectra. The less polar product **53** was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.5 (*cf.* 11β epimer R_f 0.3). The nmr spectrum of **53** showed δ 8.30–7.91 (m), 7.73–7.31 (m), 5.80–5.55 (m), 5.34–4.89 (m), 3.74–3.43 (m), 3.28 (s), and 3.11–2.00 (m).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.09; H, 7.20.

(−)-3α,5β-Dihydroxy-2α-(hydroxymethyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 55. To a stirred solution of 0.5 g (1.7 mmol) of lactone benzoate methyl ether **53** in 20 ml of ethyl acetate under nitrogen at 0° was added 0.7 ml of boron tribromide. The solution was allowed to stir 0.5 hr at 0° and then 2 hr at ambient temperature. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–sodium bicarbonate showed complete reaction. The reaction was quenched by addition of 75 ml of saturated sodium bicarbonate. The resulting mixture was equilibrated and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 0.47 g of colorless oil. The crude product was chromatographed on 30 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 100-ml fractions, elution was with: 100 ml of 50%, 100 ml of 75%, 200 ml of 100%. Fractions 2 and 3 contained fairly good product, 0.33 g (69%) of oil, $[\alpha]D$ −8° (*c* 1.17, chloroform), homogeneous by tlc in 50% ethyl acetate–Skellysolve B (R_f 0.25) and in ethyl acetate (R_f 0.5). The ir spectrum of **55** showed 3300, 1590, 1570, 1530, 1250, 1150, 1095, 1055, 1030, 1010, 900, 804, and 710 cm^{-1}. The nmr spectrum showed δ 8.17–7.83 (m), 7.67–7.29 (m), 5.76–5.57 (m), 5.35–4.93 (m), 3.27 (d, 6 Hz), and 3.13–1.95 (m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.65; H, 5.72.

(−)-3α,5β-Dihydroxy-2α-(3-oxo-*trans*-1-octenyl)cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 56. To a stirred mixture of 0.12 g (2.5 mmol) of 50% sodium hydride dispersion in 20 ml of tetrahydrofuran under nitrogen at 0° was added a solution of 0.64 g (2.9 mmol) of dimethyl(2-oxoheptyl)phosphonate in 2 ml of tetrahydrofuran. After stirring at 0° for 5 min, the resulting ylide solution was stirred at ambient temperature for 1.5 hr then cooled again to 0°.

To a stirred solution of 1.2 g (15 mmol) of dry pyridine in 25 ml of methylene chloride at 0° under nitrogen was added 1.0 g (10 mmol) of anhydrous chromium trioxide. The resulting Collins[23] oxidant was stirred 5 min more at 0° then at ambient temperature for 45 min and then cooled again to 0°. To the stirred Collins[23] oxidant was added a solution of 0.33 g (1.2 mmol) of lactone benzoate alcohol **55** in 2 ml of methylene chloride. The resulting aldehyde mixture was stirred at 0° for 5 min then at ambient temperature for 5 min.

Into the cold ylide solution prepared previously was decanted the aldehyde mixture above. The resulting mixture was then stirred at ambient temperature for 4 hr. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction was quenched by addition to a mixture of 150 ml of 2 *M* sodium bisulfate, ice, and 100 ml of ether. After equilibration and separation, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 0.77 g of a dark liquid. Tlc (50% ethyl acetate–Skellysolve B) showed one product, R_f ~0.6. The crude product was chromatographed on 55 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 30-ml fractions, elution was with: 100 ml of 10% and 500 ml of 50% (begin count). Fractions 5–7 contained good product (0.28 g of colorless oil which slowly crystallized). Recrystallization from hexane–ethyl acetate gave 0.20 g, mp 65.5–66°, $[\alpha]D$ −149° (*c* 0.71, chloroform), homogeneous by tlc in 20% acetone–methylene chloride with R_f 0.5. The mass spectrum showed ions at *m/e* 370, 248, and 192. The nmr spectrum showed δ 8.13–7.82 (m), 7.60–7.22 (m), 7.10–6.64 (d of d), 6.20 (d, 16 Hz), 5.75–5.50 (m), 5.33–4.98 (m), 4.29–3.91 (d of d), and 3.45–0.57 (m). The ir showed 1765, 1715, 1690, 1625, 1600, 1585, 1495, 1320, 1275, 1165, 1115, 1075, 1030, 985, 975, and 715 cm^{-1}. The uv (ethanol) showed λ_{max} 228 (ε 26,150), 258 sh (ε 899), 273 (ε 1000), and 281 nm (ε 829).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.99; H, 7.19.

3α,5β-Dihydroxy-2α-[(3*RS*)-3-hydroxy-*trans*-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 58 and 57. To a stirred mixture of 90 mg (2.4 mmol) of sodium borohydride in 40 ml of methanol at −15 to −20° under nitrogen was added 0.61 g (1.6 mmol) of lactone benzoate ketone **56** in 40 ml of methanol. After 1.5 hr, tlc (20% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed reaction complete. The reaction mixture was quenched by the addition of 5 ml of acetic acid while at −15°. The solution was then allowed to warm to ambient temperature and then diluted with 5 ml of water and rotary evaporated at 40° to give a cloudy oil. The oil was dissolved in ethyl acetate and 0.2 *M* sodium bisulfate. After equilibration and separation, the aqueous layer was extracted well with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated to give 0.59 g (98%) of oil. Tlc in 50% ethyl acetate–Skellysolve B showed two touching spots, R_f ~0.3. The product was chromatographed on 90 g of acid-washed silica gel, packed in 20% ethyl acetate–Skellysolve B. Taking 7-ml fractions, elution was with 700 ml of 50%. Fractions 48–56, pure less polar, 0.16 g of oil; fractions 57–62, mixture, 0.22 g of oil; fractions 63–95, pure more polar, 0.12 g of oil. The less polar was assigned (15*R*) (**58**) and the more polar (15*S*) (**57**). The compounds were each homogeneous by tlc in 50% ethyl acetate–Skellysolve B with the (15*R*) (**58**) having R_f 0.35 and the (15*S*) (**57**) having R_f 0.30.

(−)-3α,5β-Dihydroxy-2α-[(3*S*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone, 59. A mixture of 2.8 g (7.6 mmol) of lactone benzoate alcohol, **57**, 1.4 g (9.8 mmol) of potassium carbonate, and 250 ml of methanol was stirred under nitrogen at ambient temperature. After stirring for 24 hr, tlc (50% ethyl acetate–Skellysolve B) showed complete reaction. The mixture was filtered through silica gel and the filtrate evaporated. The residue was dissolved in ethyl acetate and brine, equilibrated, and separated. The aqueous phase was extracted once more with ethyl acetate and saved. The aqueous phase was acidified with 2 *M* sodium bisulfate and extracted well with ethyl acetate. The total organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 1.9 g of oil. The oil slowly crystallized. Recrystallization once from hexane–ethyl acetate gave 0.73 g (1st crop), mp 79–81°, $[\alpha]_D$ −39° (*c* 0.83, chloroform), homogeneous by tlc in ethyl acetate with R_f 0.33. The mass spectrum showed ions at *m/e* 250, 193, and 179.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.78; H, 8.97.

(−)-3α,5β-Dihydroxy-2α-[(3*R*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone, 60. A mixture of 3.1 g (8.2 mmol) of lactone benzoate alcohol **58** and 1.5 g (11 mmol) of anhydrous potassium carbonate in 300 ml of methanol was stirred at ambient temperature under nitrogen. After stirring for 18 hr, tlc (75% ethyl acetate–Skellysolve B) showed complete reaction. The dark mixture was filtered through silica gel, washing well with ethyl acetate, and the filtrate was evaporated. The residue was partitioned between ethyl acetate and brine, equilibrated, and separated. The aqueous layer was extracted once more with ethyl acetate and saved. The organic extracts were combined, dried over sodium sulfate, and evaporated to give a mobile oil. Trituration with Skellysolve B left a viscous oil. The aqueous phase from above was acidified with 2 *M* sodium bisulfate and extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give an oil. This was combined with the triturated residue to give a total of 2.1 g of oil, $[\alpha]_D$ −54° (*c* 0.68, chloroform). Tlc (A-IX and 75% ethyl acetate–Skellysolve B) showed no opened lactone. The material was homogeneous by tlc in ethyl acetate with R_f 0.34.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.04; H, 9.37.

3α,5β-Dihydroxy-2α-[(3*S*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 3-Tetrahydropyranyl Ether, 61. A solution of 1.6 g (6.0 mmol) of lactone diol **59**, 6.2 g (75 mmol) of dihydropyran, 0.16 g of pyridine hydrochloride, and 37 ml of methylene chloride was stirred at room temperature under nitrogen. After 4 hr, tlc (50% ethyl acetate–Skellysolve B) showed complete reaction. The solution was filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 2.8 g of mobile oil. The product was chromatographed on 400 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 40-ml fractions, elution was with 500 ml of 20%, 1000 ml of 30%, and 1000 ml of 45%. Fractions 29–42 were combined to give 1.7 g (63%) of oil. (Additional less pure material was in fractions 27, 28, 43, and 46 (0.5 g)). The product was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.63.

3α-5β-Dihydroxy-2α-[(3*R*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-acetic Acid γ-Lactone 3-Tetrahydropyranyl Ether, 62. A solution of 2.1 g (7.8 mmol) of lactone diol **60**, 8.2 g (97 mmol) of dihydropyran, 0.21 g of pyridine hydrochloride, and 40 ml of methylene chloride was stirred at ambient temperature under nitrogen. Tlc (50% ethyl acetate–Skellysolve B) showed complete reaction after 16 hr. The solution was filtered through silica gel, washing well with ethyl acetate. Evaporation of the filtrate gave 3.5 g of mobile oil. The crude product was chromatographed on 350 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 40-ml fractions, elution was with 500 ml of 30%, 1000 ml of 40%, and 1000 ml of 50%. Fractions 28–40 contained good material, 2.4 g (71%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.63.

3α,5β-Dihydroxy-2α-[(3*S*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-carboxaldehyde γ-Lactol 3-Tetrahydropyranyl Ether, 63. To a stirred solution of 1.7 g (3.8 mmol) of lactone di-THP **61** in 18 ml of toluene at −78° under nitrogen was added 12.4 ml (7.6 mmol) of 10% diisobutylaluminum hydride in toluene. After 1 hr, tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–water showed reaction complete. The reaction was quenched at −78° by the dropwise addition of 24 ml of a 2:1 tetrahydrofuran–water solution. The resulting mixture was allowed to warm to ambient temperature and then filtered through Celite, washing well with ether. The filtrate was washed twice with brine, dried over sodium sulfate, and evaporated to give 1.7 g (100%) of oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.4.

3α,5β-Dihydroxy-2α-[(3*R*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1β-carboxaldehyde γ-Lactol 3-Tetrahydropyranyl Ether, 64. To a stirred solution of 2.4 g (5.5 mmol) of lactone di-THP **62** in 25 ml of toluene at −78° under nitrogen was added 18 ml of a 10% solution of diisobutylaluminum hydride in toluene. After 1 hr, tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction was quenched at −78° by addition of 25 ml of a 2:1 solution of tetrahydrofuran–water. The resulting mixture was allowed to warm to ambient temperature and filtered through Celite, washing well with ether. The filtrate was diluted with brine, equilibrated, and separated. The aqueous layer was extracted well with ether. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 2.4 g (100%) of viscous oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.4.

11α-(15*S*)-*ent*-PGF$_2\alpha$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 65. A mixture of 1.1 g (23 mmol theoretical) of 50% sodium hydride dispersion in mineral oil and 125 ml of dimethyl sulfoxide was stirred under nitrogen at 75° for 1 hr. The resulting solution was cooled to ambient temperature. To this was added 5.0 g (12 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting dark solution was stirred 1.5 hr at ambient temperature. To this solution was added 1.7 g (3.8 mmol) of lactol di-THP **63** in 50 ml of dimethyl sulfoxide. The resulting mixture was allowed to stir at ambient temperature. After 16 hr, tlc (A-IX) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction was quenched by addition to a mixture of 0.2 *M* sodium bisulfate and ether. After equilibration, the aqueous phase (pH ≤3) was extracted well with ether. The organic extracts were combined and then washed once with 1 *N* sodium hydroxide and twice with water. The basic aqueous washings were combined, equilibrated with ether, and carefully acidified with 2 *M* sodium bisulfate. After final equilibration, the aqueous solution was extracted well with ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give 1.9 g of oil, R_f ~0.7 (A-IX). The crude product was dissolved in 40 ml of 50% ether–methanol, cooled to 0°, and treated with excess diazomethane. The resulting solution was evaporated to give 1.8 g of oil, R_f ~0.7 (A-IX) and ~0.4 (50% ethyl acetate–Skellysolve B). The crude product was chromatographed on 200 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 40-ml fractions, elution was with 400 ml of 20%, 500 ml of 40%, 500 ml of 50%. Fractions 18–23 were combined to give 1.0 g (49% yield from lactone di-THP **61**) of good material as an oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.45.

11α-*ent*-PGF$_2\alpha$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 66. A mixture of 1.6 g (34 mmol theoretical) of 50% sodium hydride dispersion in mineral oil and 150 ml of dimethyl sulfoxide was stirred under nitrogen at 65–70° for 1 hr. The resulting solution was cooled to 15–20°. To this was added 7.4 g (17 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting dark solution was stirred 1 hr at ambient temperature. To this solution was added 2.4 g (5.5 mmol) of lactol di-THP **64** in 60 ml of dimethyl sulfoxide. The resulting mixture was allowed to stir at ambient temperature. After 18 hr, tlc (A-IX and 50% ethyl acetate–Skellysolve B) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction was quenched by addition to a mixture of 120 ml of 2 *M* sodium bisulfate, 40 ml of water, and ice. The resulting mixture was extracted well with ether. The organic extracts were combined and then washed once with 1 *N* sodium hydroxide and twice with water. The basic aqueous washings were combined, equilibrated with ether, and carefully acidified with 2 *M* sodium bisulfate. After final equilibration, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give an oil (R_f ~0.7 in A-IX). The crude product was dissolved in 40 ml of a 1:1 solution of ether–methanol and treated with excess diazomethane. The solution was evaporated to 0.5 vol at atmospheric pressure on a steam bath, then rotary evaporated *in vacuo* to give 1.15 g of oil. The crude product was chromatographed on 185 g of silica gel, packed in 10% ethyl acetate–Skellysolve B. Taking 25-ml fractions, elution was with 250 ml of 25%, 250 ml of 35%, 2000 ml of 50%, and 1000 ml of 80%. Fractions 49–59 contained 1.2 g (48%) of **66** as an oil homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.45

11α-(15*S*)-*ent*-PGE$_2$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester 67. To a stirred solution of 2.6 g (33 mmol) of dry pyridine in 80 ml of methylene chloride at 0° under nitrogen was added 1.7 g (17 mmol) of anhydrous chromium trioxide.[23] The resulting mixture was stirred at ambient temperature for 1 hr, then cooled to 0° again. To this was added a solution of 1.0 g (1.9 mmol) of 11α-(15*S*)-*ent*-PGF$_2\alpha$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **65**, in 30 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 10 min then decanted and filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated (40°) to give a dark oil. The residue was dissolved in ether and the ethereal solution washed with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, dried over sodium sulfate, and evaporated to give 0.84 g of oil. Tlc (50% ethyl acetate–Skellysolve B) showed one main spot, R_f ~0.5. The material was used without further purification.

11α-*ent*-PGE$_2$ 11,15-Bis(tetrahydropyranyl ether) Methyl Ester, 68. To a solution of 0.69 g (8.7 mmol) of dry pyridine in 25 ml of methylene chloride at 0° under nitrogen was added 0.44 g (4.4 mmol) of anhydrous chromium trioxide.[23] The resulting mixture was stirred at ambient temperature for 1 hr, then cooled to 0° again. To this was added a solution of 0.26 g (0.48 mmol) of 11α-*ent*-PGF$_2\alpha$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **66**, in 7 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 10 min, then decanted and filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated to give a dark oil. The residue was dissolved in ether and the ethereal solution washed with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, dried over sodium sulfate, and evaporated to give 0.24 g of oil. Tlc (50% ethyl acetate–Skellysolve B) showed one main spot, R_f ~0.5. The material was used without further purification.

11α-(15*S*)-*ent*-PGF$_2\alpha$ Methyl Ester, 48. A solution of 0.46 g (0.86 mmol) of 11α-(15*S*)-*ent*-PGF$_2\alpha$ methyl ester 11,15-bis(tetrahydropyranyl ether), **65**, in 28 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 3 hr. The resulting solution was diluted with 25 ml of water and freeze dried to give 0.34 g of oil. Tlc in ethyl acetate (R_f ~0.2) showed one spot. Tlc on boric acid impregnated silica gel using either ethyl acetate (R_f ~0.2) or 90:10:1 chloroform–methanol–acetic acid (R_f 0.5) showed one spot, identical with the more polar spot and different from the less polar spot from borohydride reduction of the PGE (see below). The product was chromatographed on 35 g of silica gel, packed in 20% acetone–methylene chloride. Taking 20-ml fractions, elution was with 250 ml of 50% acetone–methylene chloride. Fractions 4–6 gave good material, 0.21 g of 11α-(15*S*)-*ent*-PGF$_2\alpha$ methyl ester, **48**, as an oil, $[\alpha]_D$ −73° (*c* 0.96, chloroform), homogeneous by tlc in 50% acetone–methylene chloride with R_f 0.5. The following spectral data were obtained: nmr, δ 5.75–5.30 (m), 4.47–3.95 (m), 3.67 (s), and 2.70–0.73 (m); ir 3380, 3000, 2920, 2850, 1720, 1455, 1440, 1315, 1245, 1220, 1170, 1150, 1055, 1025, and 980 cm^{-1}; high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 584.3753 (calcd for $C_{30}H_{60}O_5Si_3$: 584.3746), with other ions at 569, 553, 541, 513, 494, and 479.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.72; H, 9.42.

11α-*ent*-PGF$_2\alpha$ Methyl Ester, 50. A solution of 0.24 g of 11α-*ent*-PGF$_2\alpha$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **66**, in 14 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 3.5 hr. The resulting solution was cooled to ambient temperature, diluted with 20 ml of water, and freeze dried to give 0.23 g of crystalline material. This material was combined with 0.47 g of material obtained similarly to give 0.70 g of crystals. Recrystallization from ethyl acetate–hexane gave 0.31 g, mp 106.8–109°, $[\alpha]_D$ −76° (*c* 0.62, chloroform), homogenous by tlc in 50% acetone–methylene chloride with R_f 0.4. The following spectral data were obtained: nmr, δ 5.75–5.30 (m), 4.49–3.97 (m), 3.68 (s), and 2.53–0.72 (m); ir, 3270, 3010, 2710, 2180, 1735, 1665, 1435, 1340, 1315, 1280, 1245, 1195, 1175, 1100, 1040, 975, and 850 cm^{-1}; high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 584.3729 (calcd for $C_{30}H_{60}O_5Si_3$: 584.3746), with other ions at 569, 553, 541, 513, 494, and 479.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.05; H, 9.58.

11α-(15*S*)-*ent*-PGE$_2$ Methyl Ester, 45. The 0.84 g of crude 11α-(15*S*)-*ent*-PGE$_2$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **67**, was dissolved in 50 ml of a solution of acetic acid–water–tetrahydrofuran (20:10:3) and heated at 40° for 3 hr. The solution was cooled to ambient temperature, diluted with 70 ml of water, and freeze dried to give 0.74 g of viscous oil. Tlc (30% acetone–methylene chloride) showed one main spot, R_f ~0.5. The crude product was chromatographed on 75 g of silica gel, packed in 10% acetone–methylene chloride. Taking 25-ml fractions, elution was with 500 ml of 20% and 1000 ml of 30%. Fractions 8–10 were combined to give 60 mg of (15*S*)-*ent*-PGA$_2$ methyl ester **25**. Fractions 21–26 gave 0.5 g (74%) of 11α-(15*S*)-*ent*-PGE$_2$ methyl ester, **45**, as a viscous oil, $[\alpha]_D$ +51° (*c* 0.82, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.50. The following spectra data were obtained: uv, neutral ethanol, end absorption and basic ethanol, λ_{max} 278 nm (ε 23,650); ir, 3420, 1740, 1455, 1435, 1375, 1315, 1275, 1245, 1220, 1160, 1045, 1020, and 975 cm^{-1}; nmr δ 5.83–5.60 (m), 5.50–5.20 (m), 4.49–3.95 (m), 3.67 (s), and 2.98–0.67 (m); high resolution mass spectrum, parent ion of the bis-TMS derivative at *m/e* 510.3197 (calcd for $C_{27}H_{50}Si_2O_5$: 510.3195), with other ions at 495, 492, 479, 420, and 349.

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.58; H, 9.67.

11α-*ent*-PGE$_2$ Methyl Ester, 46. The 0.24 g of crude 11α-*ent*-PGE$_2$ 11,15-bis(tetrahydropyranyl ether) methyl ester, **68**, was dissolved in 14 ml of a solution of acetic acid–water–tetrahydrofuran (20:10:3) and heated at 40° for 4 hr. The resulting solution was cooled to ambient temperature, diluted with 20 ml of water, and freeze dried to give 0.18 g of oil. The crude product was chromatographed on 20 g of silica gel, packed in 2% acetone–methylene chloride taking 25-ml fractions; elution was with 150 ml of 15% and 200 ml of 25%. Fractions 4–6 contained 24 mg of semipure *ent*-PGA$_2$ methyl ester **26** by tlc comparison. Fractions 13–16 contained 60 mg (34%) of pure 11α-*ent*-PGE$_2$ methyl ester, **68**, as an oil, $[\alpha]_D$ +34° (*c* 0.88, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.43. (Fractions 17–21 contained an additional 50 mg of less pure **68**.) The following spectral data were obtained: uv, neutral ethanol, end absorption and basic ethanol, λ_{max} 278 nm (ε 23,300); ir, 3420, 3000, 2950, 2920, 2850, 1735, 1455, 1435, 1375, 1315, 1245, 1220, 1160, 1075, and 975 cm^{-1}; nmr, δ 5.82–5.69 (m), 5.52–5.24 (m), 4.49–4.00 (m), 3.68 (s), and 2.75–0.73 (m); high resolution mass spectrum, parent ion of bis-TMS derivative at *m/e* 510.3207 (calcd for $C_{27}H_{50}O_5Si_2$: 510.3195), with other ions at 495, 492, 439, 420, and 349.

11α-(15*S*)-*ent*-PGF$_2\beta$ Methyl Ester, 47. To a stirred slurry of 30 mg (0.8 mmol) of sodium borohydride in 12 ml of methanol at −15° under nitrogen was added a solution of 0.20 g (0.55 mmol) of 11α-(15*S*)-*ent*-PGE$_2$ methyl ester, **45**, in 12 ml of methanol. After 1 hr the reaction while at −15° was quenched by dropwise addition of 10 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and then evaporated to give 0.9 g of solid residue. The residue was triturated with ethyl acetate. Evaporation of the organic solution gave 0.24 g of oil. Tlc in 100% ethyl acetate (R_f 0.4), 50% acetone–methylene chloride (R_f ~0.4), or 90:10:1 chloroform–methanol–acetic acid (R_f ~0.5) showed only one spot. Using boric acid impregnated silica gel plates, tlc in 90:10:1 showed two main spots with a ratio of less polar–more polar of ~3:1. The crude product was chromatographed on 25 g of acid-washed, boric acid impregnated silica gel packed in chloroform. A solution (200 ml) of 90% chloroform and 10% methanol (saturated with boric acid) was used for elution, taking 10-ml fractions. Fractions 8–11 gave less polar material of low purity, 0.11 g. Fractions 12–15 gave 50 mg of mixed fractions. The more polar material was identical by tlc with 11α-(15*S*)-*ent*-PGF$_2\alpha$ methyl ester, **48**. On the basis of the relative tlc mobility on boric acid plates,[28] the less polar was assigned the structure 11α-(15*S*)-*ent*-PGF$_2\beta$ methyl ester. This material was purified further by chromatography on 10 g of neutral silica gel, packed in 15% acetone–methylene chloride. Taking 7-ml fractions, elution was with 30 ml of 15%, 30 ml of 25%, 100 ml of 35%, and 50 ml of 50%. The compound came off during the last of the 35% and the first of the 50%. Fractions 14–17 contained impure material, 20 mg; fractions 18–23 contained good material, 60 mg of oil, homogeneous by tlc in 50% acetone–methylene chloride (R_f 0.45) and 90:10:1 chloroform–methanol–acetic acid (R_f 0.45). The following spectral data were obtained: nmr, δ 5.84–5.37 (m), 4.27–3.87 (m), 3.67 (s), and 2.70–0.73 (m); high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 584.3747 (calcd for $C_{30}H_{60}O_5Si_3$: 584.3746), with other ions at 569, 553, 541, 494, and 404.

11α-*ent*-PGF$_2\beta$ Methyl Ester, 49. To a stirred mixture of 8 mg (0.2 mmol) of sodium borohydride and 3 ml of methanol at −20° under nitrogen was added a solution of 50 mg (0.1 mmol) of 11α-*ent*-PGE$_2$ methyl ester, **46**, in 3 ml of methanol. After 1 hr, tlc (30% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed complete reaction. The reaction while at −20° was quenched by careful addition of 2.5 ml of acetic

acid. The resulting solution was allowed to warm to ambient temperature and then evaporated to give 50 mg of oil. Tlc (90:10:1; chloroform–methanol–acetic acid) using boric acid impregnated plates showed two products with ~3:1 in favor of less polar. The crude product was chromatographed on 5 g of acid-washed, boric acid impregnated silica gel, packed in 10% methanol–chloroform (saturated with boric acid). Taking 1-ml fractions, elution was with 10% methanol in chloroform (saturated with boric acid). Fractions 10–13 contained 17 mg of impure less polar product. Fractions 14–20 contained 30 mg of a mixture of both epimers. The more polar product was identical by tlc with 11α-*ent*-$PGF_{2\alpha}$ methyl ester, **50**. The impure 17 mg was chromatographed again on 5 g of silica gel, packed in 5% acetone–methylene chloride. Taking 1-ml fractions, elution was with 30% acetone in methylene chloride. Fractions 9–15 contained good material, 17 mg of oil, homogeneous by tlc in 30% acetone–methylene chloride (R_f 0.2) and in 90:10:1 chloroform–methanol–acetic acid (R_f 0.37). The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at *m/e* 584.3753 (calcd for $C_{30}H_{60}O_5Si_3$: 584.3746), with other ions at 569, 553, 541, 513, 494, and 404.

11α-(15*S*)-*ent*-$PGF_{2\alpha}$, 71. A solution of 5 mg of 11α-(15*S*)-*ent* $PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether), **70**, in 3 ml of acetic acid–water–tetrahydrofuran (20:10:3) was heated at 40° for 4 hr. The resulting solution was cooled to room temperature, diluted with 5 ml of water, and freeze dried to give 2.5 mg of oil. Tlc in 90:10:1 (chloroform–methanol–acetic acid) showed one main spot R_f 0.21 identical with 11β-(15*R*)-$PGF_{2\alpha}$ and less polar than 11β-$PGF_{2\alpha}$.[24,27]

3β,5β-Dihydroxy-2α-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]-cyclopentane-1β-acetic Acid γ-Lactone 3-Benzoate, 80(*RS*). To a well-stirred solution of 19.9 g (53.8 mmol) of *ent*-lactone benzoate ketone **32** in 1200 ml of dry tetrahydrofuran at −78° under nitrogen was added 107 ml (320 mmol) of 3 *M* methylmagnesium bromide in ether dropwise. The solution became cloudy but no heavy precipitate formed. Tlc (50% ethyl acetate–Skellysolve B) of an aliquot quenched in saturated ammonium chloride–ether showed the reaction was completed in 2 hr. The reaction was quenched while still at −78° by dropwise addition of 350 ml of saturated ammonium chloride which gave a finely granular precipitate. After addition, the mixture was allowed to come to ambient temperature with stirring.

With the aid of 600 ml of ethyl acetate and 300 ml of water, the mixture was transferred to a separatory funnel, equilibrated, and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 23.4 g (110%) of a yellow oil, homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.2. The nmr showed δ 8.13–7.36 (m), 5.72–5.58 (m), 5.44–4.90 (m), and 3.37–0.57 (m), including a singlet at 1.3. This material was identical by nmr and tlc with its enantiomer.[4a]

3β,5β-Dihydroxy-2α-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]-cyclopentane-1β-acetic Acid γ-Lactone, 81(*RS*). To a stirred solution of 22.7 g (52 mmol theory) of *ent*-lactone benzoate alcohol **80(*RS*)** in 430 ml of dry methanol at ambient temperature under nitrogen was added 43 ml (~190 mmol) of 25% sodium methoxide in methanol. The solution turned orange after addition and gradually got darker. Tlc (ethyl acetate) showed the reaction complete in 45 min. The reaction was quenched by addition of 25 ml of acetic acid. Reaction color lightened upon addition. The solution was then evaporated cautiously under reduced pressure at 40°.

The residue was cautiously dissolved in 350 ml of saturated sodium bicarbonate and ethyl acetate. After equilibrium the aqueous phase (pH ~7–8) was separated and extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give 21.3 g of oil.

The crude product was chromatographed on 213 g of silica gel packed in 20% ethyl acetate–Skellysolve B. Taking 200-ml fractions, elution was with 400 ml of 20%, 800 ml of 50%, 500 ml of 75%, and 1600 ml of 100% ethyl acetate. Fractions 8–13 contained 12.0 g (82%) of good material, an oil homogeneous by tlc in ethyl acetate with R_f 0.4. This material was identical by tlc with its enantiomer.[4a]

3β,5β-Dihydroxy-2α-[(3*RS*)-3-hydroxy-3-methyl-*trans*-1-octenyl]-cyclopentane-1β-carboxaldehyde γ-Lactol, 82(*RS*). To a well-stirred solution of 12.0 g (42.5 mmol) of *ent*-lactone diol **81(*RS*)** in 350 ml of dry tetrahydrofuran at −78° under nitrogen was added 304 ml (~186 mmol) of 10% diisobutylaluminum hydride in toluene dropwise. Tlc (ethyl acetate) of an aliquot quenched in saturated ammonium chloride–ether showed reaction was completed in 4 hr. The reaction while maintained at −78° was quenched by slow dropwise addition of 350 ml of saturated ammonium chloride, which gave a granular precipitate. The mixture was allowed to return to ambient temperature with stirring. A heavy gel-like precipitate was present after warming.

With the aid of 150 ml of water and 250 ml of ethyl acetate, the mixture was transferred to a stoppered flask, shaken, then filtered through a thin layer of Celite. The residue was washed with water and then well with ethyl acetate. The filtrate was equilibrated and separated. The aqueous phase was extracted well with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated. The residue was azeotroped twice with benzene to give 12.0 g (99%) of oil, homogeneous by tlc in ethyl acetate with R_f 0.3.

(15*RS*)-15-Methyl-*ent*-$PGF_{2\alpha}$ Methyl Ester, 77 and 75. A slurry of 11.9 g (248 mmol) of 50% sodium hydride dispersion and 400 ml of dimethyl sulfoxide was stirred at 75° under nitrogen. The reaction was stirred until H_2 evolution stopped (~1 hr) and the dark solution was cooled to 15°. To this was added 53.5 g (124 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in small portions. The resulting dark solution was stirred at ambient temperature for 1 hr then cooled to 15°. To this was added a solution of 11.4 g (40.6 mmol) of *ent*-lactol diol **82(*RS*)** in 100 ml of dimethyl sulfoxide. The resulting dark rust-colored mixture was allowed to stir at ambient temperature. After 18 hr, tlc (A-IX) of an aliquot quenched in ether–sodium bisulfate showed the reaction to be completed. The reaction was quenched by addition to an equilibrated mixture of 470 ml of 2 *M* sodium bisulfate, 500 ml of ether, 1000 ml of water, and ice. After equilibration the aqueous phase (pH ~3) was extracted well with ether. The organic extracts were combined and extracted with 200 ml of 1 *N* sodium hydroxide and three times with water (3 × 200 ml). The basic aqueous solution (pH 11) was cooled to 0° by the addition of excess ice and equilibrated with 500 ml of ether. To this mixture was added carefully, in portions, with frequent equilibration 125 ml of 2 *M* sodium bisulfate. After the final equilibration, the aqueous phase (pH ~3) was extracted well with ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give 11.4 g of a dark orange oil. The tlc showed R_f ~0.4 in A-IX.

The crude product was esterified immediately by dissolving first in 100 ml of a 1:1 solution of ether–methanol. This solution was treated with excess diazomethane in ether. The resulting solution was first evaporated on a steam bath to 0.5 volume then rotary evaporated (40°) under reduced pressure to give 10.4 g of a dark oil, R_f ~0.1 in 30% acetone–methylene chloride.

The crude product was chromatographed on 1500 g of silica gel packed in 5% acetone–methylene chloride. Taking 200-ml fractions, elution was with 1 l. of 30%, 10 l. of 40%, and 10 l. of 50% acetone–methylene chloride. The following fractions were combined: 34–38, good (15*S*) epimer, 0.84 g of oil; 39–44, ~3:1 (*S*:*R*) mixture, 2.0 g of oil; 45–56, 1:1 (*S*:*R*) mixture, 2.4 g of oil; 57–71, 1:3 (*S*:*R*) mixture, 2.6 g of oil; 72–83, good (15*R*) epimer, 0.84 g of oil.

Upon running nine more similar chromatograms on the mixtures obtained, 2.3 g more of good (15*S*) epimer **75** and 2.4 g more of good (15*R*) epimer 77 were obtained. The products obtained from these chromatograms were further purified by column chromatography using an ethyl acetate–hexane mixture (see below).

A 4.13-g sample of semipure (15*R*)-15-methyl-*ent*-$PGF_{2\alpha}$ methyl ester, 77, was chromatographed on 500 g of silica gel packed in 50% ethyl acetate–hexane. Taking 25-ml fractions, elution was with 5 l. of ethyl acetate. The following fractions were combined: 39–110, pure (15*R*) epimer, 3.55 g (20%), crystalline; 111–115, impure (15*R*) epimer, 0.2 g of oil. The pure (15*R*) epimer, 77, exhibited mp 49–53°, $[\alpha]D$ −25° (*c* 0.92, ethanol), and was homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.10. The following spectral data were obtained: nmr, δ 5.68–5.31 (m), 4.40–3.85 (m), 3.70 (s). and 2.60–0.70 (m), including a singlet at 1.28; ir, 3310, 3010, 1740, 1440, 1375, 1315, 1240, 1195, 1170, 1130, 1105, 1040, 975, and 965 cm^{-1}; high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 598.3907 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3903), with other ions at 583, 527, 508, 493, 437, and 418.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 69.01; H, 10.03.

A 4.57-g sample of semipure (15*S*)-15-methyl-*ent*-$PGF_{2\alpha}$ methyl ester, **75**, was similarly chromatographed to give 3.68 g (23%) of pure (15*S*) epimer, **75**, as an oil, $[\alpha]D$ −29° (*c* 0.93, ethanol), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.15. The following spectral data were obtained: nmr, δ 5.68–5.27 (m), 4.34–3.82 (m), 3.68 (s), and 2.58–0.70 (m), including a singlet at 1.28; ir, 3380, 3000, 2920, 2860, 1740, 1725, 1660, 1455, 1435,

1370, 1315, 1245, 1220, 1170, 1080, 1050, and 975 cm^{-1}; high resolution mass spectrum, parent ion of the tris-TMS derivative at *m/e* 598.3931 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3903), with other ions at 583, 527, 508, 493, 437, and 418.

(15*S*)-15-Methyl-*ent*-PGF$_{2\alpha}$ 11-Trimethylsilyl Ether Methyl Ester, 83. To a stirred solution of 3.68 g (9.6 mmol) of (15*S*)-15-methyl-*ent*-PGF$_{2\alpha}$ methyl ester, **75**, in 120 ml of acetone at −45° under nitrogen was added 14.6 ml (11.5 g, 79 mmol) of trimethylsilyldiethylamine. Tlc (50% ethyl acetate–Skellysolve B) showed the reaction was completed in 3 hr. To this solution at −45° was added 400 ml of anhydrous ether, previously cooled to −78°. The resulting solution while still cold was equilibrated with 800 ml of half-saturated sodium bicarbonate with excess ice. After separation, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated. The residue was azeotroped with benzene to give 4.3 g (98%) of a yellow oil. Tlc in 50% ethyl acetate–Skellysolve B showed the major product at R_f 0.61 with a small amount of a less polar material (bis-TMS) at R_f 0.8.

(15*R*)-15-Methyl-*ent*-PGF$_{2\alpha}$ 11-Trimethylsilyl Ether Methyl Ester, 84. To a stirred solution of 3.55 g (9.3 mmol) of (15*R*)-15-methyl-*ent*-PGF$_{2\alpha}$ methyl ester, 77, in 120 ml of acetone at −45° under nitrogen was added 14.1 ml (11.1 g, 76.5 mmol) of trimethylsilyldiethylamine. Tlc (50% ethyl acetate–Skellysolve B) showed the reaction completed in 90 min. To this solution at −45° was added 400 ml of anhydrous ether, previously cooled to −78°. This resulting solution while still cold was equilibrated with 800 ml of half-saturated sodium bicarbonate with excess ice. After separation, the aqueous phase was extracted well with ether. The organic extracts were combined, washed with brine, dried (sodium sulfate), and evaporated. The residue was azeotroped with benzene to give 4.07 g of a light yellow oil which crystallized at 0°.

The product was recrystallized from 50 ml of hexane by dissolving at ambient temperature, cooling to −25°, and then seeding to give 3.41 g (81%) of yellow crystals, mp 32–34°. The material was homogeneous by tlc in 50% ethyl acetate–Skellysolve B with R_f 0.61.

(15*S*)-15-Methyl-*ent*-PGE$_2$ 11-Trimethylsilyl Ether Methyl Ester, 85. To a stirred solution of 10.6 g (134 mmol) of dry pyridine in 300 ml of methylene chloride at 0° under nitrogen was added 6.7 g (67 mmol) of anhydrous chromium trioxide.[23] The resulting mixture was stirred at ambient temperature for 60 min, then cooled to 0° again. To this was added a solution of 3.04 g (6.7 mmol) of (15*S*)-15-methyl-*ent*-PGF$_{2\alpha}$ 11-trimethylsilyl ether methyl ester, **83**, in 30 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 10 min then decanted and filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated (40°) to give 2.74 g (91%) of a dark oil which without purification was used immediately in the next step. Tlc in 50% ethyl acetate–Skellysolve B showed the major product at R_f 0.67.

(15*R*)-15-Methyl-*ent*-PGE$_2$ 11-Trimethylsilyl Ether Methyl Ester, 86. To a stirred solution of 14.0 g (176.6 mmol) of dry pyridine in 400 ml of methylene chloride at 0° under nitrogen was added 8.8 g (88.3 mmol) of anhydrous chromium trioxide.[23] The resulting mixture was stirred at ambient temperature for 60 min, then cooled to 0° again. To this was added a solution of 4.00 g (8.83 mmol) of (15*R*)-15-methyl-*ent*-PGF$_{2\alpha}$ 11-trimethylsilyl ether methyl ester, **84**, in 35 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 10 min then decanted and filtered through silica gel, washing well with ethyl acetate. The filtrate was evaporated (40°) to give 3.73 g (95%) of a dark oil which without purification was used immediately in the next step. Tlc in 50% ethyl acetate–Skellysolve B showed the major product at R_f 0.66.

(15*S*)-15-Methyl-*ent*-PGE$_2$ Methyl Ester, 72. To a stirred solution of 2.74 g (6.7 mmol theory) of (15*S*)-15-methyl-*ent*-PGE$_2$ 11-trimethylsilyl ether methyl ester, **85**, in 150 ml of methanol at 0° under nitrogen was added a solution of 7.6 ml of acetic acid in 76 ml of water, which gave a cloudy mixture. This mixture was stirred at 0° for 5 min and then at ambient temperature for 15 min. The reaction was quenched by addition to an equilibrated mixture of 600 ml of 0.2 *M* sodium bisulfate, 250 ml of ether, and excess ice. The resulting mixture was equilibrated. The aqueous phase (pH <2) was extracted well with ether. The organic extracts were combined and washed with saturated sodium bicarbonate and brine, dried (sodium sulfate), and evaporated to give 2.26 g of a light brown oil.

The crude product was chromatographed on 226 g of silica gel, packed in 30% ethyl acetate–hexane. Taking 20-ml fractions, elution was with 200 ml of 50% ethyl acetate–hexane, 200 ml of 60%, 200 ml of 70%, 400 ml of 80%, and 500 ml of 100%. Fractions 22–53 gave 1.42 g (56%) of good product: (15*S*)-15-methyl-*ent*-PGE$_2$ methyl ester, **72**, as an oil, $[\alpha]_D$ +78° (*c* 0.84, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.5. The following spectral data were obtained: nmr, δ 5.77–5.26 (m), 4.33–3.84 (m), 3.52 (s), and 3.00–0.67 (m), including a singlet at 1.28; ir, 3440, 3010, 2930, 2840, 1740, 1455, 1435, 1370, 1335, 1315, 1245, 1220, 1160, 1075, and 975 cm^{-1}; uv, neutral ethanol, end absorption and basic ethanol, λ_{max} 278 nm (ε 24,950); high resolution mass spectrum, parent ion of the bis-TMS derivative at *m/e* 524.3358 (calcd for $C_{28}H_{52}O_5Si_2$: 524.3351), with other ions at 579, 576, 493, 467, 453, 434, 363, 344, and 309.

(15*R*)-15-Methyl-*ent*-PGE$_2$ Methyl Ester, 73. To a stirred solution of 3.73 g (8.83 mmol theory) of (15*R*)-15-methyl-*ent*-PGE$_2$ 11-trimethylsilyl ether methyl ester, **86**, in 200 ml of methanol at 0° under nitrogen was added a solution of 10 ml of acetic acid in 100 ml of water, which gave a cloudy mixture. This mixture was stirred at 0° for 5 min and then at ambient temperature for 15 min. The reaction was quenched by addition to an equilibrated mixture of 800 ml of 0.2 *M* sodium bisulfate, 250 ml of ether, and excess ice. The resulting mixture was equilibrated. The aqueous phase (pH <2) was extracted well with ether. The organic extracts were combined and washed with saturated sodium bicarbonate and brine, dried (sodium sulfate), and evaporated to give 3.28 g oil.

The crude product was chromatographed on 300 g of silica gel, packed in 5% acetone–methylene chloride. Taking 100-ml fractions, elution was with 1 l. of 10%, 5 l. of 20%, and 3 l. of 30% acetone–methylene chloride. Fractions 11–16 were combined to give 340 mg of what was assigned as (15*R*)-15-methyl-*ent*-PGA$_2$ methyl ester, 79 (see below). Fractions 32–70 gave 2.23 g (67%) of good product: (15*R*)-15-methyl-*ent*-PGE$_2$ methyl ester, **73**, as an oil, $[\alpha]_D$ +77° (*c* 0.75, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.5. The following spectral data were obtained: nmr, 5.75–5.30 (m), 4.34–3.80 (m), 3.52 (s), and 3.67–0.67 (m), including a singlet at 1.28; ir, 3430, 3010, 2960, 2930, 2860, 1740, 1455, 1435, 1370, 1330, 1315, 1245, 1220, 1160, 1080, 975, and 735 cm^{-1}; uv, neutral ethanol, end absorption, and basic ethanol, λ_{max} 278 nm (ε 24,600); high resolution mass spectrum, parent ion of the bis-TMS derivative at *m/e* 524.3326 (calcd for $C_{28}H_{52}O_5Si_2$: 524.3351), with other ions at 579, 576, 493, 467, 453, 434, 363, 344, and 309.

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.12; H, 9.89.

(15*S*)-15-Methyl-*ent*-PGF$_{2\beta}$ Methyl Ester, 74. To a stirred slurry of 18 mg (0.48 mmol) of sodium borohydride in 6 ml of methanol at −20° under nitrogen was added a solution of 0.12 g (0.32 mmol) of (15*S*)-15-methyl-*ent*-PGE$_2$ methyl ester, **72**, in 6 ml of methanol. After 45 min, the reaction while still at −20° was quenched by dropwise addition of 6 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and then ethyl acetate added. This solution was washed with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, dried (sodium sulfate), then evaporated to give 0.11 g of oil. Tlc (30% acetone–methylene chloride) showed two products in nearly equal concentration.

The crude product was chromatographed on 11 g of silica gel, packed in 5% acetone–methylene chloride. Taking 3-ml fractions, elution was with 300 ml of 30% acetone–methylene chloride and 100 ml of 50%. The following fractions were combined: 41–75, good less polar product, 0.05 g (41%); 76–105, mixture, 5 mg; 106–180, good more polar product, 60 mg. crystalline. The less polar product was identical by tlc with (15*S*)-15-methyl-*ent*-PGF$_{2\alpha}$ methyl ester, **75**. The more polar material was assigned (15*S*)-15-methyl-*ent*-PGF$_{2\beta}$ methyl ester, **74**.

This crystalline material was chromatographed on 7 g of silica gel packed in 10% acetone–methylene chloride. Taking 5-ml fractions, elution was with 100 ml of 30% and 100 ml of 50% acetone–methylene chloride. Fractions 28–38 contained 52 mg (43%) of good material: (15*S*)-15-methyl-*ent*-PGF$_{2\beta}$ methyl ester, **74**, mp 39.5–40.5°, $[\alpha]_D$ −20° (*c* 1.03, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.13. The ir showed 3540, 3490, 3320, 3020, 1735, 1660, 1440, 1345, 1315, 1285, 1245, 1210, 1195, 1180, 1150, 1085, 1035, and 990 cm^{-1}. The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at *m/e* 598.3941 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3905), with other ions at 583, 567, 527, 508, 493, 486, and 217.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.79; H, 10.35.

(15*R*)-15-Methyl-*ent*-PGF$_{2\beta}$ Methyl Ester, 76. To a stirred mixture of 30 mg (0.80 mmol) of sodium borohydride in 10 ml methanol at −20° under nitrogen was added a solution of 0.20 g (0.53

mmol) of (15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **73**, in 10 ml of methanol. After 45 min the reaction while still at −20° was quenched by dropwise addition of 10 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and ethyl acetate added. This solution was washed sequentially with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, then dried (sodium sulfate), and evaporated to give 0.20 g of oil. Tlc (30% acetone–methylene chloride) showed two spots in nearly equal concentration.

The crude product was chromatographed on 20 g of silica gel, packed in 5% acetone–methylene chloride. Taking 5-ml fractions, elution was with 300 ml of 30% and 500 ml of 50% acetone–methylene chloride. The following fractions were combined: 46–62, good less polar product, 90 mg (45%); 63–134, good more polar product, 100 mg, crystalline. The less polar product was identical by tlc with (15*R*)-15-methyl-*ent*-$PGF_{2\alpha}$ methyl ester, **77**. The more polar material was assigned (15*R*)-15-methyl-*ent*-$PGF_{2\beta}$ methyl ester, **76**. This crystalline material was recrystallized from ethyl acetate–hexane to give 0.07 g (35%), mp 99–100.5°, $[\alpha]_D$ −4° (*c* 1.12, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.1. The ir spectrum showed 3260, 3180, 3020, 2740, 1740, 1660, 1440, 1365, 1330, 1235, 1190, 1080, 970, 915, and 870 cm^{-1}. The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at *m/e* 598.3912 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3905), with other ions at 583, 567, 527, 508, 493, 437, and 418.

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.72; H, 10.14.

(15*S*)-15-Methyl-*ent*-PGE_2 11-Acetate Methyl Ester, 87. To a stirred solution of 0.52 g (1.4 mmol) of (15*S*)-15-methyl-*ent*-PGE_2 methyl ester, **72**, in 52 ml of dry pyridine at ambient temperature under nitrogen was added 5.4 ml (58 mmol) of acetic anhydride. After 5 hr, tlc (5% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed the reaction to be complete. The reaction was quenched by addition to an equilibrated mixture of 500 ml of 2 *M* sodium bisulfate, ice, and 80 ml of ethyl acetate. After equilibration, the aqueous phase (pH <3) was separated and extracted well with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, then dried (sodium sulfate) and evaporated (40°) to give 0.68 g (110%) of oil. Tlc in 5% acetone–methylene chloride showed the major component at R_f 0.34 with a minor slightly less polar compound (PGA, see below).

(15*R*)-15-Methyl-*ent*-PGE_2 11-Acetate Methyl Ester, 88. To a stirred solution of 2.23 g (5.88 mmol) of (15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **73**, in 223 ml of dry pyridine at ambient temperature under nitrogen was added 23 ml (248 mmol) of acetic anhydride. After 5 hr, tlc (5% acetone–methylene chloride) of an aliquot quenched in ether–sodium bisulfate showed the reaction to be complete. The reaction was quenched by addition to an equilibrated mixture of 1500 ml of 2 *M* sodium bisulfate, ice, and 250 ml of ethyl acetate. After equilibration, the aqueous phase (pH <3) was separated and extracted well with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, then dried (sodium sulfate) and evaporated (40°) to give 3.07 g (123%) of a mobile oil. Tlc in 5% acetone–methylene chloride showed the major component at R_f 0.34 with a minor, slightly less polar compound (PGA, see below).

(15*S*)-15-Methyl-*ent*-PGA_2 Methyl Ester, 78. A solution of 0.68 g (1.4 mmol theory) of (15*S*)-15-methyl-*ent*-PGE_2 11-acetate methyl ester, **87**, and 1.2 g (12.2 mmol) of potassium acetate in 45 ml of methanol was stirred at ambient temperature under nitrogen. After 18 hr, tlc (5% acetone–methylene chloride) showed the reaction to be complete. The reaction was quenched by addition to a mixture of saturated sodium bicarbonate and ethyl acetate. After equilibration, the aqueous phase was extracted three times more with ethyl acetate. The organic extracts were combined and washed with brine and then dried (sodium sulfate) and evaporated to give 0.51 g of oil.

The oil was combined with additional material prepared in a similar manner to give 0.69 g and chromatographed on 70 g of silica gel, packed in 25% ethyl acetate–hexane. Taking 20-ml fractions, elution was with 200 ml of 25% and 300 ml of 50% ethyl acetate–hexane. Fractions 7–13 contained 0.55 g (80%) of good product: (15*S*)-15-methyl-*ent*-PGA_2 methyl ester, **78**, as an oil, $[\alpha]_D$ −140° (*c* 0.88, chloroform), homogeneous by tlc in 5% acetone–methylene chloride with R_f 0.42. The following spectral data were obtained: uv, neutral ethanol, λ_{max} 217 nm (ϵ 10,350), and basic ethanol, λ_{max} 278 nm (ϵ 28,150); nmr, δ 7.6–7.3 (m), 6.25–6.05 (m), 5.74–5.32 (m), 3.68 (s), 3.39–3.12 (m), and 2.63–0.67 (m), including a singlet at 1.28; ir, 3460, 3000, 2950, 2920, 2860, 1735, 1705, 1585, 1435, 1365, 1315, 1245, 1215, 1200, 1170, 1035, and 975 cm^{-1}; high resolution mass spectrum, parent ion of the mono-TMS derivative *m/e* 419.2591 (calcd for $C_{24}H_{35}O_4Si$ 419.2619), with other ions at 403, 391, 363, 362, 347, 344, and 291.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.38; H, 9.59.

(15*R*)-15-Methyl-*ent*-PGA_2 Methyl Ester, 79. A solution of 3.07 g (5.88 mmol theory) of (15*R*)-15-methyl-*ent*-PGE_2 11-acetate methyl ester, **88**, in 250 ml of methanol was stirred at ambient temperature under nitrogen. After 18 hr, tlc (5% acetone–methylene chloride) showed the reaction to be complete. The reaction was quenched by addition to a mixture of saturated sodium bicarbonate and ethyl acetate. After equilibration, the aqueous phase was separated and extracted well with ethyl acetate. The organic extracts were combined and washed with brine and then dried (sodium sulfate) and evaporated to give 2.33 g of oil.

The crude product was chromatographed on 233 g of silica gel, packed in 5% acetone–methylene chloride. Taking 40-ml fractions elution was with 2000 ml of 5% acetone–methylene chloride. Fractions 29–45 contained 1.74 g (82%) of good product: (15*R*)-15-methyl-*ent*-PGA_2 methyl ester, **79**, as an oil, $[\alpha]_D$ −128° (*c* 0.79, chloroform), homogeneous by tlc in 5% acetone–methylene chloride with R_f 0.42. The following spectral data were obtained: uv, neutral ethanol, λ_{max} 217 nm (ϵ 10,700), and basic ethanol, λ_{max} 278 nm (ϵ 25,750); nmr, δ 7.6–7.3 (m), 6.25–6.05 (m), 5.74–5.32 (m), 3.68 (s), 3.38–3.12 (m), and 2.61–0.67 (m), including a singlet at 1.28; ir, 3440, 3000, 2940, 2920, 2860, 1735, 1705, 1585, 1540, 1435, 1365, 1350, 1240, 1200, 1120, 1095, 1045, and 975 cm^{-1}; the high resolution mass spectrum of the mono-TMS showed the parent ion at *m/e* 363.2031 (calcd for $C_{20}H_{31}O_4Si$: 362.1991), with other ions at 363, 344, 291, and 204.

(15*S*)-15-Methyl-*ent*-PGA_2 10ξ,11ξ-Oxide Methyl Ester, 95. To a stirred solution of 1.48 g (4.1 mmol) of (15*S*)-15-methyl-*ent*-PGA_2 methyl ester, **78**, in 20 ml of methanol at −25° (Dry Ice–acetone) under nitrogen was added a solution consisting of 6 ml of 30% aqueous hydrogen peroxide and 3 ml of 2 *N* sodium hydroxide. After 60 min, tlc (5% acetone–methylene chloride) showed the reaction to be complete. The reaction at −25° was quenched by dropwise addition of 10% acetic acid until the solution was between pH 5 and 6. The acidic solution was diluted with brine and extracted well with ether. The organic extracts were combined and washed with saturated sodium bicarbonate and brine and then dried (sodium sulfate) and evaporated to give 1.54 g (99%) of oil. Tlc in 5% acetone–methylene chloride showed two main components at R_f 0.6, differing only slightly in polarity.

(15*R*)-15-Methyl-*ent*-PGA_2 10ξ,11ξ-Oxide Methyl Ester, 96. To a stirred solution of 1.74 g (4.81 mmol) of (15*R*)-15-methyl-*ent*-PGA_2 methyl ester, 79, in 25 ml of methanol at −25° (acetone–Dry Ice) under nitrogen was added a solution consisting of 7 ml of 30% aqueous hydrogen peroxide and 3.5 ml of 2 *N* sodium hydroxide. After 60 min, tlc (5% acetone–methylene chloride) showed the reaction to be complete. The reaction at −25° was quenched by dropwise addition of 10% acetic acid until the solution was between pH 5 and 6. The acidic solution was diluted with brine and extracted well with ether. The organic extracts were combined, washed with saturated sodium bicarbonate and brine, then dried (sodium sulfate), and evaporated to give 1.98 g (109%) of oil. Tlc in 5% acetone–methylene chloride showed two main components at R_f 0.6, differing only slightly in polarity.

Example Preparation of Aluminum Amalgam. A 1.6-g sample of granular aluminum metal (20 mesh) was washed once each successively with ether, methanol, 80 ml of 2% aqueous mercuric chloride (contact time ~1 min or until gas evolution), methanol, and finally ether. The material was used immediately after preparation while still wet with ether.

11α-(15*S*)-15-Methyl-*ent*-PGE_2 Methyl Ester, 89. A mixture of 1.54 g (4.1 mmol theory) of (15*S*)-15-methyl-*ent*-PGE_2 10ξ,11ξ-oxide methyl ester, **95**, 1.23 g of aluminum amalgam, 120 ml of ether, 12 ml of methanol, and 12 drops of water was stirred at ambient temperature under nitrogen. After 67 hr, tlc (5% acetone–methylene chloride) showed the reaction to be complete. The reaction was quenched by filtration through Celite, washing well with ether. The filtrate was evaporated to give 1.31 g of oil. Tlc (30% acetone–methylene chloride) showed two spots (R_f ~0.5) of nearly equal intensity. The more polar compound was identical by tlc with (15*S*)-15-methyl-*ent*-PGE_2 methyl ester, **72**.

The crude product was chromatographed on 150 g of silica gel, packed in 25% ethyl acetate–hexane. Taking 11-ml fractions, elu-

tion was with 75% ethyl acetate–hexane. Fractions 6–10 contained the less polar epimer, 340 mg of oil, identified as 11α-(15*S*)-15-methyl-*ent*-PGE_2 methyl ester, **89**. Fractions 11–14 contained a mixture (190 mg) of C-11 epimers while fractions 15–40 contained 250 mg (16%) of the more polar epimer, identical with (15*S*)-15-methyl-*ent*-PGE_2 methyl ester, **72**. This compound was free of its C-15 epimer (**73**) by tlc in 20% acetone–methylene chloride (twice up). The less polar epimer was chromatographed on 34 g of silica gel, packed in 5% acetone–methylene chloride. Taking 11-ml fractions elution was with 20% acetone–methylene chloride. Fractions 26–60 contained 230 mg (15%) of good product: 11α-(15*S*)-methyl-*ent*-PGE_2 methyl ester, **89**, as an oil $[\alpha]D$ +36° (*c* 1.26, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.5 (indistinguishable from its C-15 epimer, **90**). The following spectral data were obtained: uv, neutral ethanol, end absorption, and basic ethanol, λ_{max} 278 nm (ε 23,400); ir, 3430, 3000, 2930, 2860, 1740, 1455, 1435, 1370, 1315, 1280, 1240, 1220, 1165, 1045, and 980 cm^{-1}; nmr, δ 5.84–5.24 (m), 4.50–4.22 (m), 3.68 (s), and 3.08–0.62 (m), including a singlet at 1.28; high resolution mass spectrum, parent ion of the bis-TMS derivative at 509.3124 (calcd for $C_{27}H_{49}O_5Si_2$: 509.3118), with other ions at 493, 453, 434, 419, 363, 344, and 309.

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.74; H, 9.43.

11α-(15*R*)-15-Methyl-*ent*-PGE_2 Methyl Ester, 90. A mixture of 1.98 g (4.81 mmol theory) of (15*R*)-15-methyl-*ent*-PGA_2 10ξ,11ξ-oxide methyl ester, **96**, 1.60 g of aluminum amalgam, 150 ml of ether, 15 ml of methanol, and 15 drops of water was stirred at ambient temperature under nitrogen. After 168 hr, tlc (5% acetone–methylene chloride) showed complete reaction. The reaction was quenched by filtration through Celite, washing well with ether. The filtrate was evaporated to give 1.75 g of oil. Tlc (30% acetone–methylene chloride) showed two spots (R_f ~0.5) of nearly equal intensity. The more polar compound was identical by tlc with (15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **73**.

The crude product was chromatographed on 175 g of silica gel, packed in 25% ethyl acetate–Skellysolve B. Taking 11-ml fractions, elution was with 300 ml of 50% ethyl acetate–Skellysolve B, 1 l. of 75%, and 300 ml of 100%. Fractions 77–91 contained the less polar epimer, 450 mg of oil, identified as 11α-(15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **90**. Fractions 92–110 contained a mixture (270 mg) of C-11 epimers, while fractions 111–190 contained 440 mg (24%) of the more polar epimer, identical with (15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **73**. This compound was free of its C-15 epimer (**72**) by tlc in 20% acetone–methylene (twice up).

The less polar epimer was chromatographed on 40 g of silica gel packed in 25% ethyl acetate–Skellysolve B. Taking 2-ml fractions, elution was with 25% ethyl acetate–Skellysolve B. Fractions 9–25 contained 424 mg (23%) of good product: 11α-(15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **90**, as an oil, $[\alpha]D$ +37°, (*c* 0.81, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.5 (indistinguishable from its C-15 epimer **89**). The following spectral data were obtained: uv, neutral ethanol, end absorption, and basic ethanol, λ_{max} 278 nm (ε 21,650); nmr, 5.84–5.60 (m), 5.48–5.24 (m), 4.50–4.24 (m), 4.50–4.25 (m), 3.68 (s), and 3.20–0.67 (m), including a singlet at 1.28; high resolution mass spectrum, parent ion of the bis-TMS derivative 509.3118 (calcd for $C_{27}H_{49}O_5Si_2$: 509.3119), with other ions at 537, 535, 493, 453, 434, 419, 363, 344, and 309.

11α-(15*S*)-15-Methyl-*ent*-$PGF_2\alpha\beta$ Methyl Esters, 92 and 91. To a stirred slurry of 38.8 mg (1.02 mmol) of sodium borohydride in 12 ml of methanol at −15° under nitrogen was added a solution of 0.26 g (0.68 mmol) of 11α-(15*S*)-15-methyl-*ent*-PGE_2 methyl ester, **89**, in 12 ml of methanol. After 45 min, the reaction while at −15° was quenched by dropwise addition of 12 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and then ethyl acetate added. This solution was washed sequentially with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, dried (sodium sulfate), and evaporated to give 0.26 g of oil. Using boric acid impregnated silica gel plates, tlc in 95:5:1 (chloroform–methanol–acetic acid) showed two main spots with a ratio of less polar–more polar of ~4:1.

The crude product was chromatographed on 26 g of acid washed, boric acid impregnated silica gel, packed in 95% chloroform–5% methanol (saturated with boric acid). A solution (300 ml) of 95% chloroform–5% methanol (saturated with boric acid) was used for elution, taking 5-ml fractions. Fractions 14–25 gave 149 mg of the less polar material of low purity. Fractions 26–40 gave 56 mg of impure more polar material. On the basis of the relative tlc mobility on boric acid plates,[28] the less polar compound was assigned the structure 11α-(15*S*)-15-methyl-*ent*-$PGF_2\beta$ methyl ester, **91**. This material was purified further by chromatography on 15 g of neutral silica gel, packed in 5% acetone–methylene chloride. Taking 6-ml fractions, elution was with 20 ml of 5%, 100 ml of 20%, 100 ml of 30%, and 200 ml of 50% acetone–methylene chloride. Fractions 31–48 contained good material, 101 mg (39%): 11α-(15*S*)-15-methyl-*ent*-$PGF_2\beta$ methyl ester, **91**, as an oil; $[\alpha]D$ −43° (*c* 0.71, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.1 and by boric acid tlc in 95:5:1 (chloroform–methanol–acetic acid) with R_f 0.3 (indistinguishable from its C-15 epimer, **93**). The following spectral data were obtained: ir, 3380, 3000, 2930, 2860, 1740, 1455, 1435, 1365, 1315, 1240, 1215, 1170, 1150, 1120, 1090, 1055, and 980 cm^{-1}; nmr, δ 5.82–5.35 (m), 4.26–3.77 (m), 3.68 (s), and 3.17–0.68 (m), including a singlet at 1.28; high resolution mass spectrum (parent C_5H_{11}) ion of the tris-TMS derivative at *m/e* 527.3038 (calcd for $C_{26}H_{51}O_5Si_3$: 527.3044), with other ions at 508, 455, 418, and 217.

The more polar material **92** was purified further by chromatography on 5.6 g of acid-washed, boric acid impregnated silica gel packed in 95% chloroform–5% methanol (saturated with boric acid). A solution of 200 ml of 95% chloroform and 5% methanol (saturated with boric acid) was used for elution, taking 5-ml fractions. Fractions 4–6 gave 10 mg of the less polar material, **91**. Fractions 8–12 gave 23 mg of the more polar material of low purity. This material was purified further by chromatography on 2.5 g of neutral silica gel, packed in 5% acetone–methylene chloride. Taking 2-ml fractions, elution was with 45 ml of 30% and 70 ml of 50% acetone–methylene chloride. Fractions 27–38 contained good material, 11 mg (4%): 11α-(15*S*)-15-methyl-*ent*-$PGF_2\alpha$ methyl ester, **92**, as an oil, homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.13 and by boric acid tlc in 95:5:1 (chloroform–methanol–acetic acid) with R_f 0.1. The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at 598.3865 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3905), with other ions at 583, 567, 527, 508, 493, and 477.

11α-(15*R*)-15-Methyl-*ent*-$PGF_2\alpha\beta$ Methyl Esters, 94 and 93. To a stirred slurry of 48 mg (1.26 mmol) of sodium borohydride in 15 ml of methanol at −15° under nitrogen was added a solution of 0.32 g (0.84 mmol) of 11α-(15*R*)-15-methyl-*ent*-PGE_2 methyl ester, **90**, in 15 ml of methanol. After 45 min, the reaction while at −15° was quenched by dropwise addition of 15 ml of acetic acid. The resulting solution was allowed to warm to ambient temperature and then ethyl acetate added. This solution was washed with 0.2 *M* sodium bisulfate, saturated sodium bicarbonate, and brine, dried (sodium sulfate), and evaporated to give 0.37 g of oil. Using boric acid impregnated silica gel plates, tlc in 95:5:1 (chloroform–methanol–acetic acid) showed two main spots with a ratio of less polar–more polar of 4:1.

The crude product was chromatographed on 37 g of acid washed, boric acid impregnated silica gel, packed in 95% chloroform–5% methanol (saturated with boric acid). A solution of 500 ml of 95% chloroform–5% methanol (saturated with boric acid) was used for elution, taking 10-ml fractions. Fractions 9–18 gave 220 mg of the less polar material of low purity. Fractions 21–36 gave 90 mg of the impure more polar material. On the basis of the relative tlc mobility on boric acid plates,[28] the less polar compound was assigned the structure 11α-(15*R*)-15-methyl-*ent*-$PGF_2\beta$ methyl ester, **93**. This material was purified further by chromatography on 22 g of neutral silica gel, packed in 25% ethyl acetate–hexane. Taking 5-ml fractions, elution was with 100 ml of 75% ethyl acetate–hexane, 100 ml of 100% ethyl acetate, and 100 ml of 3% methanol in ethyl acetate. Fractions 49–73 contained good material, 219 mg (68%): 11α-(15*R*)-15-methyl-*ent*-$PGF_2\beta$ methyl ester, **93**, as an oil, $[\alpha]D$ −44° (*c* 0.97, chloroform), homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.1 and by boric acid tlc in 95:5:1 (chloroform–methanol–acetic acid) with R_f 0.3 (indistinguishable from its C-15 epimer, **91**). The following spectral data were obtained: ir, 3400, 2950, 1740, 1412, 1210, 1083, 976, and 758 cm^{-1}; nmr, δ 5.80–5.10 (m), 4.24–3.80 (m), 3.68 (s), 3.16 (m), and 2.57–0.62 (m), including a singlet at 1.28; high resolution mass spectrum, parent ion of the tris-TMS derivative at 598.3947 (calcd for $C_{31}H_{62}O_5Si_3$: 598.3905), with other ions at 583, 527, 508, 455, and 418.

The more polar material, **94**, was purified further by chromatography on 6 g of silica gel, packed in 50% ethyl acetate–hexane. Taking 8-ml fractions, elution was with 250 ml of ethyl acetate. Fractions 6–22 were combined to give 15 mg (5%) of pure 11α-(15*R*)-15-methyl-*ent*-$PGF_2\alpha$ methyl ester, **94**, as an oil, homogeneous by tlc in 30% acetone–methylene chloride with R_f 0.10 and by boric acid tlc in 95:5:1 (chloroform–methanol–acetic acid) with R_f 0.1.

The high resolution mass spectrum of the tris-TMS derivative showed the parent ion at 598.3935 (calcd for $C_{21}H_{62}O_5Si_3$: 598.3905) with other ions at 583, 567, 527, 508, 493, and 477.

Acknowledgment. The authors gratefully acknowledge Mr. P. A. Meulman and Mr. R. J. Wnuk for the ir and mass spectra. We especially acknowledge Dr. H. A. Karnes and associates for the preparation of generous supplies of intermediates.

Intramolecular Mechanism of the Allylic Rearrangement from O^6 to C-8 in the Guanine Series. Double Labeling Experiments

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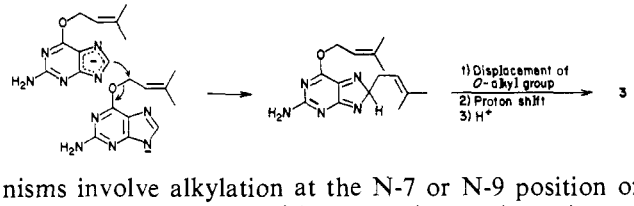
Abstract: The displacement reaction of 2-amino-6-chloropurine with the sodium salts of allylic alcohols proceeds through an intermediate O^6 ether to yield an 8-substituted guanine. The O^6 to C-8 rearrangement occurs with overall allylic retention, is partially controlled by the degree of methyl substitution on the allylic group and by the temperature, and proceeds with greatest facility through anionic species. In examining the general mechanism for the rearrangement of O^6-allylic guanines to 8-allylic guanines, several inter- and intramolecular pathways were considered. All were eliminated except for a double [3,3] sigmatropic shift *via* C-5. The intramolecular nature of the rearrangement was established by mass spectrometric analysis of the 8-substituted guanines formed from the reactions of 2-amino-6-chloropurine with the sodium salts of 3-methyl-2-buten-1-ol-^{18}O, 3-methyl-d_3-2-buten-1-ol-4,4,4-d_3, and mixtures of these having known ^{18}O and ^2H composition. Other intramolecular routes could be eliminated on the basis of the stability of postulated intermediates, *e.g.*, 7- or 9-substituted guanines, under the reaction conditions.

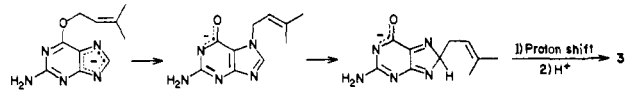
In an attempt to synthesize O^6-(3-methyl-2-butenyl)-guanine (**1**) by a substitution reaction of sodium 3-methyl-2-butenoxide upon 2-amino-6-chloropurine (**2**) in dioxane (101°), we obtained as the sole product 8-(3-methyl-2-butenyl)guanine (**3**).[1] The uniqueness of this $O^6 \rightarrow 8$ ring arrangement stimulated our curiosity concerning its mechanism. Complications are apparent both in proposing possible mechanisms and in showing which mechanisms could not be operative. The large number of heteroatoms forces the consideration of many possible pathways, and the rearrangement by our method occurs in heterogeneous phase. To keep the mechanistic considerations within reasonable bounds, two experimental facts should be noted. First, an overall retention of allylic structure of the isopentenyl side chain results from the rearrangement. Second, the initial displacement step places the oxygen of the alkoxide at the 6 position of the purine ring, and allylic C–O bond cleavage and rearrangement of the anion result in an 8-substituted guanine as the sole product. By contrast, the neutral O^6-allylic guanine requires higher temperatures for rearrangement and gives other products in addition to the 8-substituted guanine.[1]

One possible *intermolecular* rearrangement route can be visualized as involving a nucleophilic displacement upon the ether bond of first-formed **1** by the C-8 of another molecule of **1** as the anion, as illustrated in Scheme I. Two other possible intermolecular mechanisms involve alkylation at the N-7 or N-9 position of one purine by **1** with either retention or inversion of the allylic system, followed by movement of the isopentenyl group to C-8 while the C-8 hydrogen moves to neighboring nitrogen, in a manner similar to the final stages of the intramolecular pathways diagrammed in Schemes II and III.

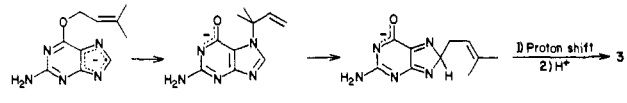
SCHEME I



SCHEME II



SCHEME III



Among the reasonable *intramolecular* rearrangement routes that can be visualized, the allylic side chain of **1** may be involved in an intramolecular alkylation of the nearby N-7 with either retention or inversion of the allylic group, followed by a transfer of the allylic group to C-8, as illustrated in Schemes II and III. A distinctly different mechanism starting with **1** would involve two consecutive [3,3] sigmatropic shifts *via* C-5, as illustrated in Scheme IV. The overall result resembes a para-Claisen rearrangement and can be viewed as a combined Claisen–Cope rearrangement. Local-

(1) C. R. Frihart and N. J. Leonard, *J. Amer. Chem. Soc.*, **95**, 7174 (1973); see especially ref 7; *cf.* the statement by B. S. Thyagarajan, *Advan. Heterocycl. Chem.*, **8**, 143 (1967): "Rearrangements of allyl ethers in the purines have been reported as early as 1935. However, there is little scope for unusual migrations in this ring system owing to the nonavailability of positions other than ring nitrogens for the attachment of the allyl moiety."