mixed anhydride (18) was then poured into the reaction vessel containing 19, and the coupling reaction was carried out by rocking the reaction vessel at room temperature for 18 hr. After this period, the reaction mixture was filtered and the resin-bound product was washed successively with DMSO, DMSO–THF mixture, and *p*-dioxane.

The resin was then suspended in 20 ml of 1:1 dioxane–2 *N* NaOH mixture, which was deaerated previously, and mixed well in a closed vessel for 1 hr at room temperature and for 20 min at 50°. The filtered solution was diluted to 100 ml and slowly acidified with 1 *N* HCl at 0° to pH 3.5. The yellow precipitate of 1 thus formed was collected by filtration, washed several times with distilled water, and dried under vacuum over P_2O_5: yield 80%; mp >300°; λ_{max} (0.1 *N* NaOH) 369 mm (ϵ 9638), 285 s (21,068), and 261 (32,850); NMR (D_2O–NaOD with SDSS as internal standard) 8.54, s (C_7 H), 7.8, d (J = 9 Hz, $H_{2'6'}$), 7.40, d (J = 9 Hz, $H_{3'5'}$), 4.42, t (α proton of glutamate moiety), and 1.0–2.5 ppm, c (four protons of glutamic acid). Anal. Calcd for $C_{19}H_{18}N_6O_6S$: C, 49.78; H, 3.93; N, 18.34; O, 20.96; S, 6.99. Found: C, 49.69; H, 3.96; N, 18.46; O, 21.08; S, 6.99.

10-Thioaminopterin, the 4-amino-4-deoxy analog of 1, has also been synthesized in this laboratory by a similar procedure and will be discussed in a later communication in this series.

Acknowledgments. This work was supported by Grant CI-86N of the American Cancer Society and by NIH Grant 1-R01-CA-16048. We are grateful to Miss Eleanor Braverman for her interest and assistance in this work and to Mr. D. J. Underwood for his technical assistance.

Registry No.—1, 54931-98-5; 3, 6302-65-4; 4, 35190-68-2; 6, 5455-98-1; 7, 6284-27-1; 8, 6284-26-0; 9, 54931-99-6; 10, 54932-00-2; 11, 54932-01-3; 12, 1007-99-4; 13, 54932-02-4; 14, 54932-03-5; 15, 54932-04-6; 16, 54932-05-7; 17, 54932-06-8; L-glutamic acid, 56-86-0.

References and Notes

(1) (a) Trivial names in general usage will be used for these compounds: 10-thiofolic acid = *N*-[*p*-[[(2-amino-4-hydroxy-6-pteridinyl)methyl]-thio]benzoyl]glutamic acid; 10-thiopterolc acid = 2-amino-4-hydroxy-6-(*p*-carboxythiophenoxymethyl)pteridine; homofolic acid = *N*-[*p*-[[(2-amino-4-hydroxy-6-pteridinyl)ethyl]amino]benzoyl]glutamic acid. Other abbreviations include: DHFR, dihydrofolate reductase; DEAE, diethylaminoethyl; *t*-Boc, *tert*-butyloxycarbonyl; SDSS, sodium 2,2-dimethyl-2-silapentane-5-sulfonate. (b) L. Goodman, J. DeGraw, R. L. Kisliuk, M. Friedkin, E. J. Pastore, E. J. Crawford, L. T. Plante, A. A. Nahas, J. F. Morningstar, G. Kwok, L. Wilson, E. F. Donovan, and J. Ratzan, *J. Am. Chem. Soc.*, **86**, 308 (1964).
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(22) Where analyses are indicated only by symbols of elements, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values.
(23) Increase in mean survival time of 27% at 8 mg/kg. We are thankful to Dr. H. B. Wood of NCI for the antitumor screening data.

Prostaglandins. VII. A Stereoselective Total Synthesis of Prostaglandin E_1[1]

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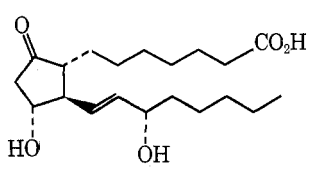
Received January 24, 1975

The stereoselective total synthesis of (±)- and (−)-prostaglandin E_1 (1) is described. Chromous sulfate reduction of 7-(2-formyl-3-tetrahydropyranyloxy-5-oxocyclopent-1-enyl)heptanoic acid (**3b**) afforded the saturated aldehyde **10b**, which was condensed with *n*-hexanoylmethylenetriphenylphosphorane (7) to form 11-*O*-tetrahydropyranyl-15-dehydroprostaglandin E_1 (11). Reduction of 11 with thexyl tetrahydrolimonyllithium borohydride followed by hydrolysis gave 1. The mechanism of stereochemical control is discussed in detail. The total synthesis was extended to the preparation of (±)-ω-homoprostaglandin E_1 (**32c**) and (±)-15-methyl-ω-homoprostaglandin E_1 (**32d**).

The prostaglandins,[2a,b] a family of oxygenated C_{20} fatty acids of widespread occurrence in animal tissues, exhibit a broad range of biological activities[2c] and presumably play an important role in several physiological processes. Prostaglandin E_1 (PGE_1, 1), one of the most active and ubiquitous hormones of this species, has been synthesized[3-10] chemically by several different groups. Some[4,7,8b,9b] of these total syntheses of PGE_1 were stereochemically controlled.



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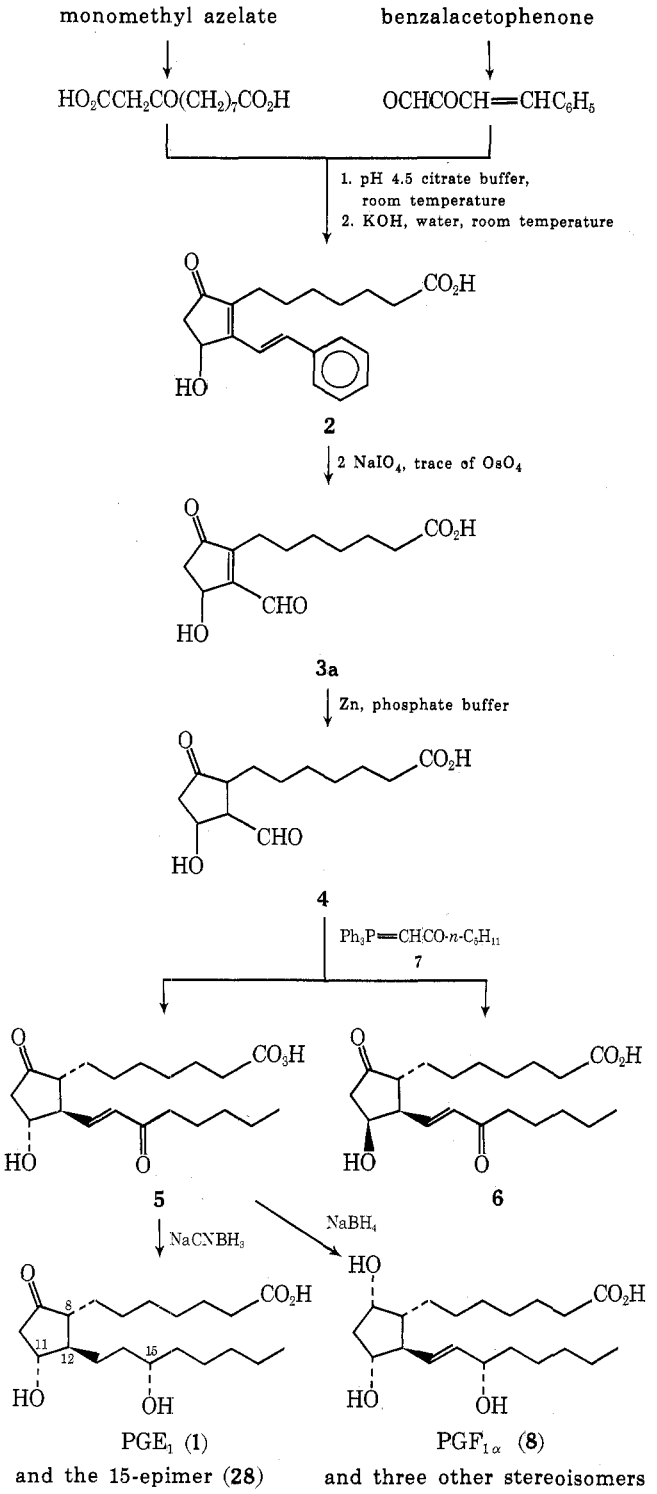
The primary objective of our study was to develop an efficient general route to new prostaglandin analogs which might possess more selective biological activities. This target was partly achieved with a facile seven-step total synthesis[8a,11] of racemic PGE_1 (1) and $PGF_{1\alpha}$ (8) along with their stereoisomers as outlined in Scheme I. This scheme was not stereoselective in some steps. Thus, almost equal amounts of **5** and **6** were obtained after the Wittig condensation. Also, comparable amounts of (±)-PGE_1 (1) and its 15 epimer (**28**) were formed in the reduction step. Some of the stereoisomers[11] exhibited interesting biological activities.[12]

Later, large quantities of PGE_1 were required for biological study. Owing to the inevitable formation of the stereo-

Scheme I
Nonstereoselective Total Synthesis of PGE_1 (1) and $PGF_{1\alpha}$ (8)

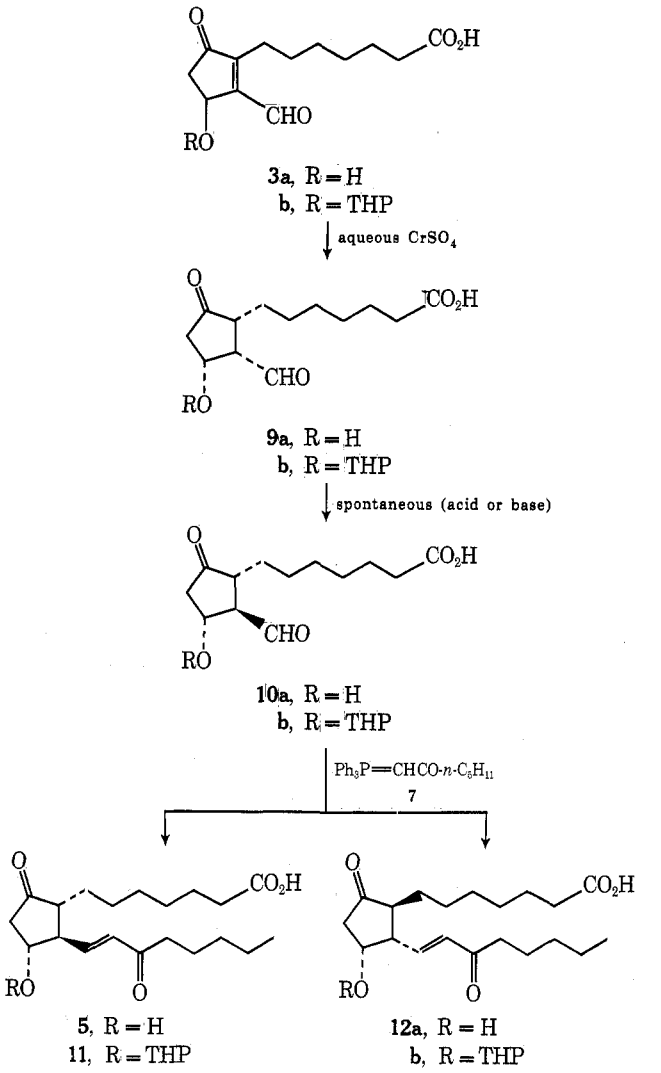


isomers, Scheme I was not practical for a large-scale production of PGE_1, and therefore we attempted to modify this synthetic route by incorporating more stereochemical control. A successful approach toward this goal is the subject of the present communication. For racemic compounds, only one enantiomer is depicted for convenience.

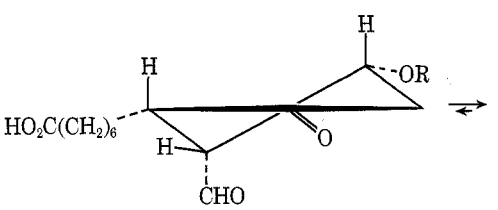
Results and Discussion

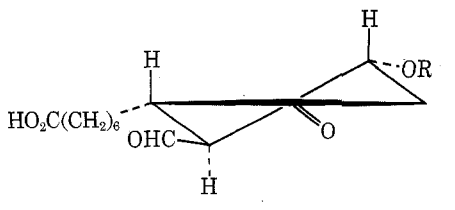
A unique feature of Scheme I is that the relative stereochemistry of C-8, C-11, and C-12 in the final product (1) is determined by a single step, that is, the reduction of **3a** to

Scheme II
Stereoselective Route to 15-Dehydro-PGE_1



4. In all likelihood, the reduction of **3a** occurs from the less hindered side[13] to afford the all-cis isomer **9a**, which is thermodynamically less stable than the trans isomer, and therefore is isomerized to the more stable "natural" configuration (**10a**) as depicted in **13** → **14**. To put this seemingly

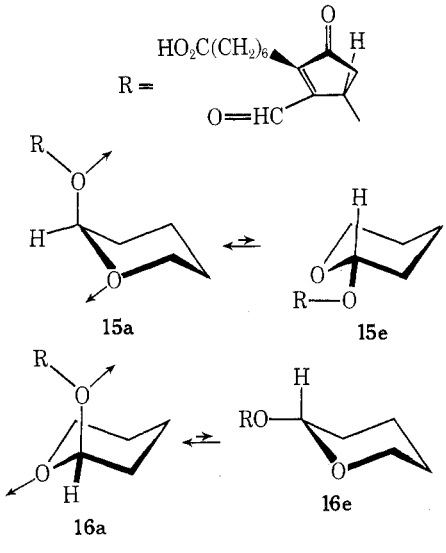




prosaic idea into practice, some pertinent problems were considered carefully. First, the hydroxyl group in **3a** may not be bulky enough to dictate satisfactory stereoselectivity.[14] Second, the reduced aldehyde (**9a, 10a**) may not be stable enough to survive the acid- or base-catalyzed equili-

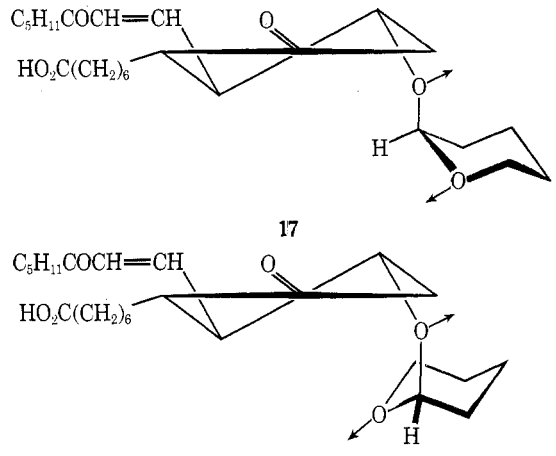
bration (**9a** → **10a**). Finally, as reported earlier,[11] the aldehyde (**10a**) does not exist as such, but in fact as a mixture of intra- and intermolecular acetal ketals in which isomer **10a** may not necessarily be more stable than **9a.** A logical solution to these problems was to use the tetrahydropyranyl (THP) derivatives (**3b, 9b, 10b**). The THP-oxy group is bulkier; hence it would dictate better stereoselectivity than the hydroxy group. It may be a less effective leaving group than hydroxy; thus **9b** and **10b** might be less susceptible to acid or base elimination. Also, **9b** and **10b** cannot participate in acetal formation owing to the absence of the hydroxy group.

The readily available **3a**[11] was converted into the THP ether **3b.** To our surprise, however, **3b** was not reduced with zinc in aqueous acid under conditions used in the reduction[11] of **3a** to **4.** It was discovered that the calculated amount of aqueous chromous sulfate solution[15] effected reduction of the double bond of **3b** in a few minutes at room temperature. No purification of the reduction product was attempted. It was instead promptly treated with *n*-hexanoylmethylenetriphenylphosphorane in benzene to afford **11** as the major product accompanied by a small amount of 8,12-bisepi isomer[16] (**12b**). The ratio of **11** to **12b** was usually 80:20 or better. Isomerization of **9b** to **10b** must have taken place prior to the Wittig condensation, possibly during the work-up of the chromium reduction. Presumably, the more stable conformation of **3b** contains an axial THP-oxy group such as **15a** or **16a,** rather than the equatorial counterparts **15e** or **16e.** Only in the axial conforma-



tions can two ether linkages be stabilized by two ethereal dipoles taking an antiparallel relationship. A similar situation is encountered in the configuration of pyranoside sugars[17a,b] with regard to the "anomeric effect". The energy difference of an axial (α-glycoside) and equatorial (β-glycoside) isomer was estimated to be 0.9 (in polar solvent) to 1.3 kcal (in nonpolar solvents)/mol.[17a] The THP-oxy group in **15a** or **16a** would shield the α side of the molecule much more effectively than the equatorial counterparts (**15e** and **16e**). Hence, after electron transfer from Cr^{II}, a water molecule (proton donor) would approach from the β side to afford all-cis **9b.**

The NMR spectrum of **11** showed that this substance is approximately a 1:1 mixture of two diastereoisomers (**17, 18**) both of which exist in the axial conformations in deuteriochloroform. The NMR signal of the acetal protons of both isomers appeared as a narrow multiplet ($W_{1/2}$ <6.5 Hz) at δ 4.65 ppm which is compatible only with an equatorial acetal proton, that is, the axial THP-oxy structure.



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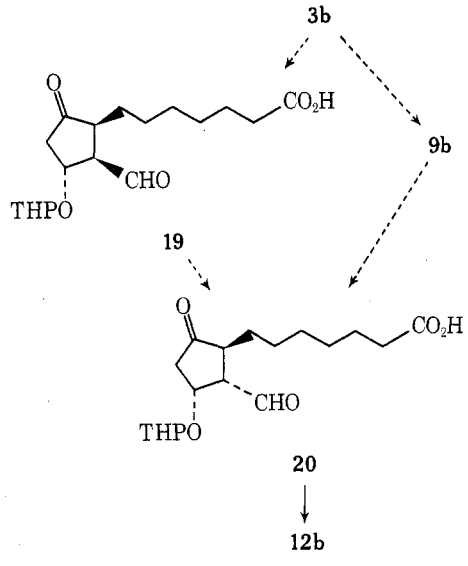
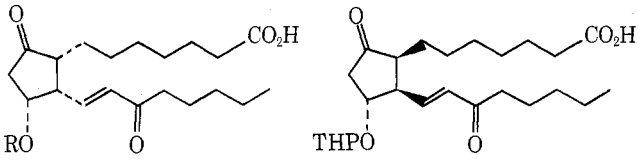
Formation of a small amount of **12b** might be rationalized by either formation of **19** followed by the isomerization to **20** or isomerization of **9b** to **20.** The Wittig condensation



(**10b** → **11**) is slightly inhibited by a weak base (pyridine), strongly inhibited by a strong base (imidazole), and accelerated by a weak acid (isobutyric acid). Since **10b** is a weak acid, the self-catalyzed condensation takes place at 25° in benzene. Contrary to the nonstereoselective scheme,[11] very little 12 epimer (**21b**) was formed in the present scheme, but a small amount of 8 epimer (**22**) was found. The 15-



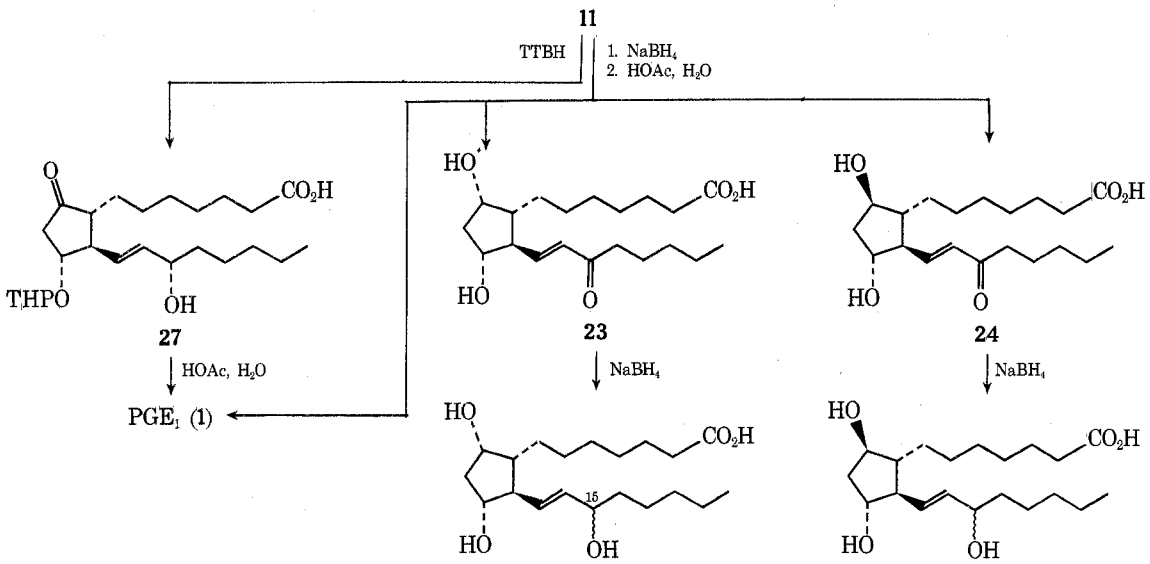
21a, R = H
b, R = THP

22

dehydro-PGE_1 THP ether (**11**) thus obtained (25–30% from **3a**) was sufficiently pure to be used for the next step. The analytical sample of **11** was prepared by hydrolysis of the THP group, chromatography, and retetrahydropyranylation.

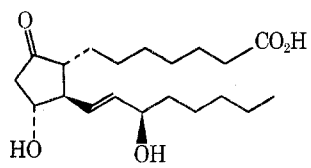
Reduction of **11** with sodium borohydride in cold methanol followed by hydrolysis gave rise to three products in comparable amounts. The least polar substance of mp 81–82° exhibited a uv (methanol) absorption at 233 nm (ϵ 13,500). The NMR (100 MHz, CD_3OD) spectrum suggested that the C-9 carbinol proton (δ 3.64, m, $W_{1/2}$ = 13 Hz) was equatorial; that is, the 9-OH was axial. The structure (**23**)

Scheme III
Reduction of 15-Dehydro-PGE_1 Tetrahydropyranyl Ether



was unequivocally proven by formation of $PGF_{1\alpha}$ (**25a**) and 15-epi-$PFG_{1\alpha}$ (**25b**)[11] upon reduction with borohydride. The polar fraction was readily separated by partition chromatography[11] into two pure compounds. The less polar substance of mp 112–113° was indistinguishable from (±)-PGE_1 in its melting point, 100-MHz NMR in deuteriomethanol, its TLC, and its biological activities. The more polar substance showed the uv (methanol) absorption at 232 nm (ϵ 13,100). The NMR (100 MHz, CD_3OD) spectrum suggested that the C-9 carbinol proton (δ 3.58, q, J = 7.5 Hz) was axial; that is, 9-OH was equatorial. Structure **24** was unambiguously confirmed by formation of $PGF_{1\beta}$ (**26a**) and 15-epi-$PGF_{1\beta}$ (**26b**)[11] upon reduction with borohydride. The optically active form of **23** and its borohydride reduction has been recorded.[18]

Although 15-epi-PGE_1 (**28**) was not isolated, its presence



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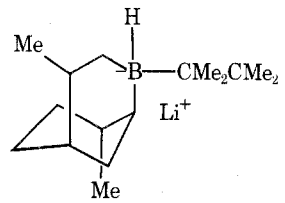
in a minute amount cannot be precluded. Although **11** was not reduced regioselectively, there was little doubt that the 15-keto group was reduced stereoselectively. Corey and his coworkers demonstrated[19] that the reduction of the 15-keto group of one of the prostaglandin derivatives with thexyl tetrahydrolimonyllithium borohydride (**29**, TTBH) took



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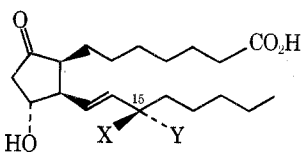
place to afford preferentially the 15(*S*) carbinol (natural) in a ratio of 9:2. This reagent[19,4e] was successfully applied to the regio- and stereoselective reduction of **11**. In our hands treatment of **11** with 1.5 equiv of TTBH in THF at −78° gave rise to **27** as the only major reduction product. A small amount of 15-epi compound was formed. The extent of conjugate reduction (reduction of the 13,14 double bond) appeared to be negligible, though it was not investigated quantitatively.

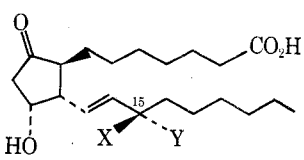
The THP group of crude **27** was hydrolyzed with aqueous acetic acid at room temperature to afford (±)-PGE_1 (**1**) in 27% yield from **11**.

The total synthesis of PGE_1 outlined in Schemes II and III possessed, in addition to enhanced stereoselectivity, several advantages. First, the THP derivatives (**11, 12b, 22**) were found to be reasonably stable substances which could be set aside at room temperature for a couple of weeks without any recognizable decomposition. The corresponding hydroxy compounds, especially **5** and **6**, were very unstable and underwent a series of complicated irreversible reactions even in a freezer. Second, the THP group modified solubility; thus, **10b** (or **9b**) was substantially less soluble in water compared with its hydroxy counterpart, hence easier to handle. Finally, the THP group modified the elution pattern from the column. More specifically, chromatography of the Wittig condensation product afforded **11** (desired and major product, equatorial[20] THP-oxy group), **12b** (a minor product, axial[20] THP-oxy), and triphenylphosphine oxide in this sequence. In the hydroxyl series, triphenylphosphine oxide, **6** (axial hydroxy), and **5** (desired product, equatorial hydroxy) were eluted in this sequence, which was inconvenient as the desired material came off last.

Pure 8 epimer **22** could not be obtained. TTBH reduction of a mixture containing (±)-**22** afforded (±)-8,15-bisepi-PGE_1 (**30a**) after hydrolysis of the THP group. Al-



30a, X = OH; Y = H
b, X = H; Y = OH



31a, X = OH; Y = H
b, X = H; Y = OH

though it could not rigorously be determined, much more **30a** (15*R*) than **30b** (15*S*) appeared to be formed; that is, the stereoselectivity of TTBH reduction is reversed in the

8-epi series. The configuration of **30a** was readily confirmed by the isomerization to 15-epi-PGE_1 (**28**) upon mild base treatment.[18] The TTBH reduction of (±)-8,12-bis epimer (**12b**)[16] afforded comparable amounts of (±)-11-epi-PGE_1 (**31a**) and (±)-11,15-bisepi-PGE_1 (**31b**). Here the stereoselectivity of the reduction appeared to be lost.

The natural PGE_1, (−)-11α,15(*S*)-dihydroxy-9-oxo-13-*trans*-prostenoic acid, was prepared from (−)-7-[2-*trans*-styryl-3(*R*)-hydroxy-5-oxocyclopentenyl]heptanoic acid[1] in the same manner. The synthetic PGE_1 was indistinguishable from natural PGE_1 in melting point, NMR in deuteriomethanol or deuterioacetone, optical rotation in tetrahydrofuran, and in a variety of TLC systems. The synthetic PGE_1 exhibited equal (within experimental error) biological activities to the authentic natural PGE_1 prepared from bishomo-γ-linolenic acid by sheep seminal tissue.

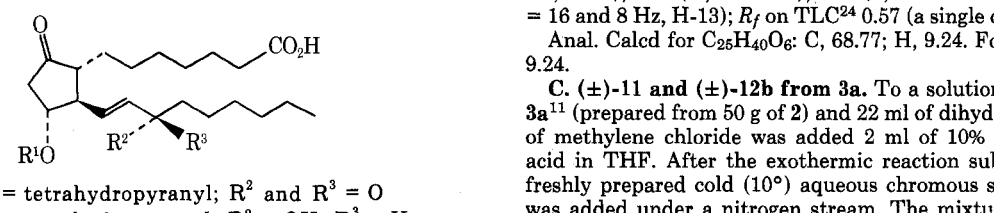
Optically active **5** and **12a** were obtained by hydrolysis of the corresponding THP derivatives (**11** and **12b**). The CD data of **5** and **12a** (Table I) demonstrates that **5** takes the same conformation as natural PGE_1 whereas **12a** takes the enantiomeric conformation rendering additional evidence for the configurations previously proposed[11] for the racemic compounds.

Table I
ORD[a] and CD[b] of PGE_1 (1), 5, and 12a

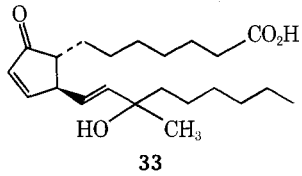
	(−)-PGE_1 (1)	5	12a
ORD n→π*			
peak	272 nm	~260 nm	315 nm
	+7161	+6000	+3870
trough	314 nm	315 nm	254 nm
	−6168	−4400	−14,100
CD n→π*			
	296 nm	297 nm	296 nm
	−11,100	−12,000	+10,200

[a] Molecular rotation. [b] Molecular ellipticity.

The total synthesis (Schemes II and III) was readily applied to the preparation of (±)-ω-homo-PGE_1 (**32c**) by replacing the Wittig reagent with *n*-heptanoyl triphenylphosphorane (**10b** → **32a** → **32b** → **32c**). The total synthesis could be modified for the preparation of 15-alkyl prostaglandins. Thus, the 15-keto intermediate (**32a**) in this sequence was treated with methylmagnesium bromide in tetrahydrofuran at −78° to give, after mild hydrolysis, an approximately 55:45 mixture of (±)-15(*S*)-15-methyl-ω-homo-PGE_1 (**32d**) and (±)-15(*R*)-15-methyl-ω-homo-PGE_1 (**32e**). It is noteworthy that the unsaturated ketone **32a** reacted preferentially in the presence of the saturated ketone. The latter did not undergo Grignard reaction at all under these conditions. The configuration at C-15 was determined by comparison with the biological activities of 15(*S*)- and 15(*R*)-15-methyl-PGE_1.[21] The major by-product in the Grignard reaction was the elimination product (**33**).[22] A small amount of (±)-8-epi-15(*R,S*)-15-methyl-PGE_1 (**34**) was also obtained as a minor by-product which could be isomerized to **32d** and **32e** with potassium acetate in ethanol.[18]



32a, R^1 = tetrahydropyranyl; R^2 and R^3 = O
b, R^1 = tetrahydropyranyl; R^2 = OH; R^3 = H
c, R^1 = H; R^2 = OH; R^3 = H
d, R^1 = H; R^2 = OH; R^3 = CH_3
e, R^1 = H; R^2 = CH_3; R^3 = OH



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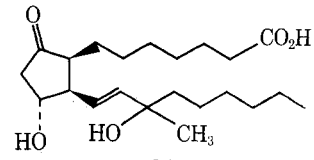

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Experimental Section[23-26]

(+)-9,15-Dioxo-11α-tetrahydropyranyl-13-*trans*-prostenoic Acid (11) and Its (±)-8(*S*),12(*S*) Isomer (12b). A. (+)-11 from 5. To a solution of 1.014 g of **5**[11] and 0.42 ml of dihydropyran in 2.5 ml of methylene chloride was added 0.10 ml of 10% *p*-toluenesulfonic acid in THF. The reaction mixture was set aside for 2 hr, then diluted with methylene chloride and washed with aqueous sodium sulfate. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed[25] on 75 g of CC-4. The desired material **11** (982 mg) was found in the 15% ethyl acetate eluate: uv (MeOH) 228.5 nm (ε 12,400); ir ($CHCl_3$) 1746, 1713, 1632, 1039, 979, 913 cm^{-1}; NMR (100 MHz, $CDCl_3$) for one diastereomer (**17** or **18**) δ 4.10 (q, *J* = 8.5 Hz, H-11), 4.65 (m, $W_{1/2}$ < 6.5 Hz, acetal H), 6.27 (d, *J* = 16 Hz, H-14), 6.81 (q, *J* = 16 and 8.5 Hz, H-13); NMR for the other diastereomer (**18** or **17**) δ 4.26 (q, *J* = 8.5 Hz, H-11), 4.65 (m, $W_{1/2}$ < 6.5 Hz), 6.31 (d, *J* = 16 Hz, H-14), 6.86 (q, *J* = 16 and 8.5 Hz, H-13); R_f on TLC[24] 0.623 (a single dark-brown spot).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.55; H, 9.55.

B. (±)-12b from 12a. Pure **12b** (330 mg, inseparable mixture of two diastereomers similar to **17**, **18**) was prepared from 420 mg of **(±)-12a** in the same manner as in A: uv (MeOH) 228.5 nm (ε 12,900); ir ($CHCl_3$) 1746, 1714, 1632, 1121, 1029, 989 cm^{-1}; NMR (100 MHz, $CDCl_3$) for one diastereomer δ 4.47 (t, *J* = 4 Hz, H-11), 4.65 (m, acetal H), 6.22 (d, *J* = 16 Hz, H-14), 7.11 (q, *J* = 16 and 8.5 Hz, H-13); NMR for the other diastereomer δ 4.35 (t, *J* = 4.5 Hz, H-11), 4.60 (m, acetal H), 6.22 (d, *J* = 16 Hz, H-14), 6.92 (q, *J* = 16 and 8 Hz, H-13); R_f on TLC[24] 0.57 (a single dark-brown spot).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.55; H, 9.24.

C. (±)-11 and (±)-12b from 3a. To a solution of 40 g of crude **3a**[11] (prepared from 50 g of **2**) and 22 ml of dihydropyran in 120 ml of methylene chloride was added 2 ml of 10% *p*-toluenesulfonic acid in THF. After the exothermic reaction subsided, 700 ml of freshly prepared cold (10°) aqueous chromous sulfate solution[15b] was added under a nitrogen stream. The mixture was vigorously stirred under nitrogen at room temperature for 30 min. To this mixture was added in sequence with vigorous stirring 60 g of ammonium sulfate, 500 g of sucrose, 300 ml of 1 *M* citric acid, and 1 l. of ether. The ethereal extract (total 4 l.) was washed with 200 ml of saturated ammonium chloride solution, then with a saturated sodium chloride solution, and dried over sodium sulfate. Upon evaporation of the solvent, 44 g of crude **10b** was obtained, which was treated immediately with 100 g of triphenyl-*n*-hexanoylmethylenephosphorane[28] in 500 ml of benzene for 6 days at 25°. The reaction mixture was washed with cold 2% citric acid, then with 1% salt solution, and dried over sodium sulfate. Concentration gave 77 g of product. This was chromatographed on 1.4 kg of CC-4. The desired material was found in the 15% ethyl acetate eluates, which were pooled in three fractions: I (4.12 g, **11b** containing the 8 epimer **22**, the latter R_f on TLC[24] 0.685); II (13.7 g, **11** identified by NMR with pure **11b** prepared in A); and III (11.5 g, **11** containing **12b**). I, II, and III were reduced with TTBH separately to produce **27**.

D. Determination of Ratio of 11 and 12b. Crude **3a** (2.0 g, 8 mmol) was converted into a mixture containing **11** and **12b** by the

procedure described in C. The THP group was removed by treatment with 150 ml of HOAc–water–THF (20:10:3)[4d] at 38–40° for 4 hr. The hydrolysis mixture was diluted with water and extracted with benzene. The benzene extract was washed with 1% sodium chloride solution, dried over sodium sulfate, and concentrated to give 3.2 g of residue. Separation[26] on a partition column made from 75 g of CC-4 afforded 670 mg of **5**,[11] 44 mg of **12a**,[11] and 57 mg of $\Delta^{8(12)}$ derivative.[28]

(±)-9,15-Dioxo-11α-tetrahydropyranyloxy-13-*trans*-12(*S*)-prostenoic Acid (21b) from 21a. **21b** was prepared in the usual manner (see A for preparation of **11**) from 207 mg of crystalline **21a**.[11] R_f on TLC[24] (0.554) was almost identical with that of **12b** but the NMR spectrum was evidently different, demonstrating that no isomerization[11] (**21** → **12**) took place during the reaction: NMR (100 MHz, $CDCl_3$) of one diastereoisomer δ 6.20 (d, J = 16 Hz, H-14), 6.64 (q, J = 6.76 (q, J = 16 and 10.5 Hz, H-13).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.21; H, 8.90.

(±)-15-Dehydro-PGF$_{1\alpha}$ (23), (±)-15-Dehydro-PGF$_{1\beta}$ (24), and (±)-PGE$_1$ (1) by Reduction of 11. A solution of 208 mg of crude **11** (fraction II, procedure C, vide supra) in 20 ml of methanol was chilled to −78° to which 1.5 ml of 3.2% methanolic triethylamine was added followed by 18.2 mg of sodium borohydride in 1 ml of water. The mixture was warmed to 0°. After 2 hr, the reaction mixture was treated with acetone to destroy excess borohydride, diluted with ether, washed with cold 2% citric acid and with 1% sodium chloride, dried over sodium sulfate, and concentrated. The product was chromatographed on 5 g of CC-4 and eluted with 20% ethyl acetate–benzene. The first 40 ml gave 52 mg (R_f on TLC[24] 0.62) of the starting material which was recycled, the next 36 ml gave 40 mg of a reduction product (I, R_f on TLC[24] 0.48), and the last 132 ml gave 63 mg of a reduction product (II, R_f on TLC[24] 0.47). Fraction I was dissolved in 10 ml of HOAc–water–THF (20:10:3),[4d] left at 25° for 20 hr, stripped of the solvent, and chromatographed on a partition column.[26] The half-crystalline product was recrystallized from ethyl acetate–cyclohexane to give pure **23**: mp 81–82°; uv (MeOH) 233 nm (ε 13,500); NMR (100 MHz, $CDCl_3$) δ 2.27 (t, 2, J = 7 Hz, H-2), 2.60 (t, 2, J = 7 Hz, H-16), 3.96 (complicated q, J = 7 Hz, H-11), 4.14 (m, $W_{1/2}$ = 13 Hz, H-9), 6.19 (d, J = 16 Hz, H-14), 6.80 (q, J = 16 and 9 Hz, H-13).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.61; H, 10.00.

Fraction II was hydrolyzed in the same manner and chromatographed on a partition column[26] made from 10 g of CC-4, and fractions of 13 ml were collected. Fractions 14–16 (R_f on TLC[24] 0.138, dark brown spot) gave crystalline (±)-PGE$_1$ melting at at 112–113° (lit.[7a] mp 112–113°, lit.[4a] mp 112.8–113.1°) after recrystallization from ethyl acetate–cyclohexane. Its NMR (100 MHz, CD_3OD) was indistinguishable from that of natural PGE$_1$ in every detail: δ 4.05 (m, 2, H-11 and H-15), 6.58 (complicated q, 2, $J \cong$ 2.5 Hz, H-13 and H-14).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.61; H, 9.96.

Fractions 17–19 (R_f on TLC[24] 0.185, blue spot) of the partition column gave **24** as a colorless gum: uv (MeOH) 232 nm (ε 13,100); NMR (100 MHz, CD_3OD) δ 2.25 (t, 2, J = 7 Hz, H-2), 2.59 (t, 2, J = 7 Hz, H-16), 3.91 (complicated q, $J \cong$ 5 Hz, H-11), 4.08 (q, J = 5.5 Hz, H-9), 6.14 (d, J = 16 Hz, H-14), 6.84 (q, J = 16 and 9 Hz, H-13).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.24; H, 9.54.

Sodium Borohydride Reduction of 23. The procedure followed was that described by Pike.[18] The reduction product was found to be a mixture of PGF$_{1\alpha}$ (**25a**) and 15-epi-PGF$_{1\alpha}$ (**25b**) by careful examination of TLC [silica gel plate and uppler layer of EtOAc–HOAc–2,2,4-trimethylpentane–water (22:4:3:20)] against authentic PGF$_{1\alpha}$[11] and 15-epi-PGF$_{1\alpha}$.[11]

Sodium Borohydride Reduction of 24. The reduction product was identified as a mixture of PGF$_{1\beta}$ (**26a**) and 15-epi-PGF$_{1\beta}$ (**26b**). For the procedure employed, see the preceding paragraph.

(±)-PGE$_1$ (1) by Thexyl Tetrahydrolimonyl Borohydride Reduction of 11. A. From Crude 11. Over a period of 1 hr, a solution of 26.8 mmol of TTBH (**29**)[19] in 88 ml of THF–*n*-pentane was added to a solution of 7.258 g of **11** (fractions I and II of procedure C, vide supra) in 50 ml of THF at −78° under a nitrogen stream. The reaction mixture was immediately diluted with 100 ml of ether and treated with 10% citric acid while it was still cold. The ethereal extract was washed with 1% sodium chloride solution, dried over sodium sulfate, concentrated, and chromatographed[25] on 500 g of CC-4. Results were as follows: recovered starting material (15% ethyl acetate–benzene, 3.048 g); a mixture (I, 1.396 g, 25% ethyl acetate) containing impure **27**; pure **27** (II, 1.798 g, 25–35% ethyl acetate); a mixture (III, 0.767 g, 50% ethyl acetate) containing impure **27**; and finally free PGE$_1$ (IV, 0.158 g, crystalline, 75–100% ethyl acetate). Fraction II was hydrolyzed with 200 ml of HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°. The solvent was removed and the residue was recrystallized from ethyl acetate to give 588 mg of (±)-PGE$_1$. The mother liquor gave a second crop (200 mg) after chromatography on CC-4. Fraction III, upon hydrolysis, gave (±)-PGE$_1$ containing PGF$_{1\alpha}$. Fraction I, upon hydrolysis followed by chromatography[25] on CC-4, gave 75 mg of 8,15-bisepi-PGE$_1$ (**30a**), less than 255 mg of crude 15-epi-PGE$_1$ (**28**), and 52 mg of crystalline (±)-PGE$_1$.

(±)-PGE$_1$ obtained in this experiment (946 mg, 27% based on consumed **11**) melted at 112–113° and was identical with the specimen obtained by sodium borohydride reduction. Thus the stereospecificity of the reduction (ratio of PGE$_1$ to **28**) was better than 4:1.

(±)-15-epi-PGE$_1$ was oily: NMR (60 MHz, CD_3OD) δ 4.10 (m, 2, H-11 and H-15), 5.69 (m, 2, H-13 and H-14).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.95; H, 10.05.

B. From Pure 11. Pure **11** (3.834 g, prepared from **5** as in procedure A) in 150 ml of THF was reduced with 15 mmol of TTBH (**29**)[19] in 40 ml of THF–*n*-pentane at −78° under nitrogen. After the addition of the reagent was completed the reaction mixture was stirred at −78° for 20 min and worked up as in A. Chromatographic separation[25] gave 1.95 g of recovered starting material, 1.5 g of **27**, 1.0 g of crude **27**, 0.185 g of 15-epi-PGE$_1$ (**28**), and 740 mg of crystalline PGE$_1$.

(−)-PGE$_1$. Cleavage[11] of 21.6 g of the 3(*R*)-(−) enantiomer[1] of **2** afforded 15 g of 3(*R*)-**3a** which was then converted into the THP derivative **3b**, reduced to **9b**, and finally treated with the Wittig reagent in the same manner as described for the racemic series. Chromatographic separation on 500 g of CC-4 using 15% ethyl acetate gave fraction A [0.948 g, a mixture containing 11(*R*)-**11** and 11(*R*)-**22**], fraction B [2.980 g, 11(*R*)-**11**], fraction C [5.378 g, 11(*R*)-**11** containing a small amount of 11(*R*)-**12b**], and fraction D [0.401 g, ca. 1:1 mixture of 11(*R*)-**11** and 11(*R*)-**12b**] in order of increasing polarity. Fraction B exhibited an identical NMR spectrum (100 MHz, $CDCl_3$) with that of the corresponding racemic **11**.

Fraction C, which was mostly **11** as demonstrated by the NMR, was dissolved in 50 ml of THF and treated with 12.2 mmol of TTBH (**29**)[19] in 40 ml of THF–*n*-pentane for 1.5 hr at −78° under nitrogen. An additional 12.2 mmol of TTBH was added and the solution was stirred for an additional 30 min at −78°. The reaction mixture was worked up as in the racemic series and chromatographed[25] on 220 g of CC-4. The 35% ethyl acetate fraction gave 138 mg of crude 11(*R*)-**27** (fraction I), 970 mg of pure 11(*R*)-**27** (fraction II), and 307 mg of crude 11(*R*)-**27** (fraction III). Fraction II was analyzed: NMR δ 4.73 (m, acetal H), 5.67 (m, H-13 and H-14); [α] −5.0 (*c* 0.993, MeOH).

Anal. Calcd for $C_{25}H_{42}O_6$: C, 68.46; H, 9.65. Found: C, 69.21; H, 10.10.

A portion (875 mg) of fraction II (**27**) was hydrolyzed with 70 ml of HOAc–water–THF[4d] and chromatographed[25] as in the racemic series. The crystalline (−)-PGE$_1$ (255 mg) was recrystallized from ethyl acetate: mp 114–114.5° (lit.[4e] mp 113.5–114°, lit.[9] mp 115–116°); $[\alpha]^{24}D$ −53.2 (*c* 0.977, THF) (lit.[9] −54.3, natural PGE$_1$ purchased from Unilever −55.8); NMR (100 MHz, CD_3OD) identical with that of the natural product.

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.60; H, 9.46.

Fraction B (pure **11**, 2.980 g) was reduced with 11.7 mmol of TTBH (**29**) and worked up in the same manner to give 355 mg of the starting material, 1.4 g of **27**, 270 mg of crystalline PGE$_1$, and 210 mg of a mixture of PGE$_1$ and PGF$_{1\alpha}$.

(−)-9,15-Dioxo-11α-hydroxy-13-*trans*-prostenoic Acid (5) and (−)-9,15-Dioxo-11α-hydroxy-13-*trans*-8(*S*),12(*S*)-prostenoic Acid (12a). Approximately a 1:1 mixture of optically active **11** and **12b** (401 mg, fraction D of the preceding preparation) was hydrolyzed with HOAc–water–THF (20:10:3)[4d] for 20 hr at 25° and worked up as in the racemic series. Chromatographic separation[25] on 50 g of CC-4 afforded 30 mg of crystalline **12a** (R_f on TLC[24] 0.323, 30% ethyl acetate fraction) followed by a mixture of **5** and **12a**, and then 47 mg of pure **5** (R_f on TLC[24] 0.300).

Recrystallization from ether–*n*-pentane gave **12a**: mp 67°; $[\alpha]^{25}D$ −10.12 (*c* 1.038, MeOH). This specimen was spectroscopically indistinguishable from the racemic compound used (**6**)[11] and was for the ORD–CD study (see Table I). Oily **5** was used for the

optical study: $[\alpha]^{25}D$ −41.6 (c 1.009, MeOH); see Table I for ORD and CD.

(±)-11-epi-PGE_1[16] and (±)-11,15-bisepi-PGE_1.[16] Pure (±)-**12b** (2.495 g) prepared from **12a** was reduced with 12.7 mmol of TTBH (**29**)[19] in the usual manner (vide supra) and chromatographed[25] on 700 g of CC-4. The 30% ethyl acetate fractions gave rise to 851 mg of 11,15-bisepi compound (R_f on TLC[24] 0.50, fraction I) followed by 888 mg of crude 11-epi compound (R_f on TLC[24] 0.49, fraction II). Fraction I, upon hydrolysis with HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°, afforded 199 mg of crystalline (±)-11,15-bisepi-PGE_1 (recrystallized from ethyl acetate), mp 91–92° (lit.[4b] mp 88.6–89.3°), R_f[24] on TLC 0.228, identical with a specimen obtained by sodium cyanoborohydride reduction[8a] of **12a**.

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.70; H, 9.80.

Fraction II was also hydrolyzed with HOAc–water–THF and recrystallized from ethyl acetate to give 193 mg of 11-epi-PGE_1, mp 92.5° (lit.[4b] mp 92.5–93°), R_f on TLC[24] 0.160, identical with the specimen obtained from **12a** by sodium cyanoborohydride reduction.[8a]

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.64; H, 9.79.

(±)-9-Oxo-11α,15(*S*)-dihydroxy-8(*S*)-13-*trans*-prostanoic Acid (8-epi-PGE_1, 30b)[18] and (±)-9-Oxo-11α,15(*R*)-dihydroxy-8(*S*)-13-*trans*-prostenoic Acid (8,15-Bisepi-PGE_1, 30a). The pure starting material (**22**) could not be prepared. Crude **11** (chromatographic fraction I in procedure C was rechromatographed[25] to produce **22** which still contained a small amount of **11**. This substance (584 mg) was reduced with 9 ml of 0.3 *M* **29** in 40 ml of THF (−78°, 1.5 hr). The reaction mixture was worked up in the usual manner and chromatographed on 200 g of SilicAR CC-4; 129 mg of the THP ether of **30a** (30% ethyl acetate–benzene), 97 mg of the THP ether of **30b** (30–50% ethyl acetate–benzene), 106 mg of **30a** (50% ethyl acetate–benzene), 41 mg of **30b** (ethyl acetate), and 19 mg of **1** (ethyl acetate) were obtained. The partial hydrolysis had apparently taken place on the CC-4 column. The THP ethers were hydrolyzed in HOAc–water–THF (20:10:3) (25°, 24 hr)[4d] to **30a** and **30b**, respectively. In a similar experiment, 4.5 g of crude **22** afforded 939 mg of the THP ether of **30a**, 554 mg of the THP ether of **30b**, 1.204 g of **30a**, and 282 mg of **30b**. **30a** was oily: R_f[24] on TLC 0.262; NMR (60 MHz, CD_3OD) δ 5.73 (q, *J* = 15.5 and 5 Hz, H-14), 5.30 (q, *J* = 15.5 and 8.5, H-13), 4.25 (m, H-11), 4.05 (m, H-15).

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 68.08; H, 9.52.

Isomerization of 30a and 30b to 28 and 1. The structure of **30b**[18] was confirmed by potassium acetate induced isomerization[18] to **1**. Under the same conditions, **30a** was isomerized to **28** (R_f on TLC[24] 0.200) confirming the structure of **30a**.

(±)-9,15-Dioxo-11α-tetrahydropyranyloxy-20-methyl-13-*trans*-prostenoic Acid (32a). This was prepared in the same manner as in procedure C for **11** starting from **10b** and *n*-heptanoylmethylenetriphenylphosphorane.[28] The desired material was eluted[25] with 15% ethyl acetate–benzene and used for the next step without further purification.

(±)-ω-Homo-PGE_1 (32c). Reduction of 5.511 g of **32a** with **29**[19] was similar to the reduction of **11**. The THP ether (**32b**, 1.928 g) was eluted[25] with 35% ethyl acetate–benzene: NMR (60 MHz, $CDCl_3$) δ 5.65 (m, 2, H-13 and H-14), 4.77 (m, acetal H), 4.07 (m, 2, H-11 and H-15), 3.67 (m, 2, OCH_2– in THP).

Anal. Calcd for $C_{26}H_{44}O_6$: C, 67.57; H, 9.93. Found: C, 67.67; H, 9.98.

The THP group was removed by treatment of 1.707 g of **32b** with 100 ml of HOAc–water–THF (20:10:3)[4d] for 20 hr at 25°. The hydrolysis solution was concentrated in vacuo and the residue was chromatographed.[25] Crystalline (±)-ω-homo-PGE_1 (**32c**, 752 mg) was found in the 75% ethyl acetate–benzene fractions. It was recrystallized from ethyl acetate (mp 100.5–101°).[29] The NMR (60 MHz, CD_3OD) was identical with that of authentic (−)-ω-homo-PGE_1 kindly provided by the Unilever Co.: δ 5.64 (m, 2, H-13 and H-14), 4.08 (m, 2, H-11 and H-15).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.80; H, 10.07.

(±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-15(*S*)-13-*trans*-prostenoic Acid (32d) and (±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-15(*R*)-13-*trans*-prostenoic Acid (32e). A solution of 3.20 g of crude **32a** in 50 ml of THF was added to a stirred solution of 20 ml of 3 *M* ethereal methylmagnesium bromide in 150 ml of THF at −70°. After 20 min, the reaction mixture (−78°) was poured into aqueous citric acid and extracted with ether. The ethereal extract was washed with 5% ammonium chloride and water, dried over sodium sulfate, and concentrated. The residue was treated with 100 ml of HOAc–water–THF (20:10:3)[4d] for 24 hr at 25°. The aqueous acetic acid solution was concentrated in vacuo and chromatographed.[25] A mixture of **32d** and **32e** was eluted with 50–60% ethyl acetate–benzene and was recrystallized from ethyl acetate–Skelly B to give approximately a 1:1 mixed crystal of **32d** and **32e**, mp 73–76°. **32d** and **32e** form a mixed crystal at any ratio. The separation of **32d** and **32e** was carried out by Misses Linda Petrosky and Janet Mueller of the Chromatography Department using 4% deactivated Woelm silica as the adsorbent and ethyl acetate–acetic acid–cyclohexane (100:1:99) as the solvent. The "unnatural" **32e** was eluted first closely followed by the "natural" isomer (**32d**). (±)-15(*S*) isomer (**32d**) was recrystallized from ether–Skelly B (mp 88–89°): NMR (100 MHz, CD_3OD) δ 5.64 (m, 2, H-13 and H-14), 4.07 (q, *J* = 8 Hz, H-11), 2.70 (q, *J* = 18 and 7.5, H-10β), 2.12 (q, *J* = 18 and 9.5 Hz, H-10α), 1.285 (s, 15-CH_3).

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.80; H, 9.91.

(±)-15(*R*) isomer (**32e**) was recrystallized from ethyl acetate–Skelly B (mp 83–84°): NMR (100 MHz, CD_3OD) δ 5.64 (m, 2, H-13 and H-14), 4.07 (q, *J* = 8 Hz, H-11), 2.70 (q, *J* = 18 and 7.5 Hz, H-10β), 2.12 (q, *J* = 18.5, 9 Hz, H-10α), 1.280 (s, 15-CH_3(/

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.80; H, 9.88.

The ratio of **32d** and **32e** obtained was approximately 55:45. R_f on TLC (Woelm silica gel F on an 8-in. plate, 2% acetic acid in ethyl acetate) for **32d** and **32e** was 0.214 and 0.243, respectively.

(±)-9-Oxo-11α,15-dihydroxy-15,20-dimethyl-8(*S*),15(*R,S*)-13-*trans*-prostenoic Acid (34). This compound was obtained as a minor product in the preparation of **32d** and **32e**. It was not clear whether the epimerization at C-8 took place during the Grignard reaction, or whether the starting **32a** contained a small amount of 8 epimer. The earlier chromatographic fractions[25] (50% ethyl acetate–benzene) in preparation of **32d,e** were purified by the partition column[11] to afford oily **34** which was a mixture of 15(*R*) and 15(*S*) isomers: NMR (100 MHz, CD_3OD) δ 5.73 (d, *J* = 16 Hz, H-14), 5.24 (q, *J* = 16 and 10 Hz, H-13), 3.03 (broad t, *J* = 8 Hz, H-12), 1.22 (s, 15-CH_3).

Isomerization of 34 to 32d and 32e. A solution of 21 mg of **34** in 10 ml of 4.2% ethanolic potassium acetate was allowed to stand at 25° for 70 hr. Approximately one-half of **34** had been isomerized to a mixture of **32d** and **32e** as demonstrated by TLC.[24] The R_f values[24] of **32d**, **32e**, and **34** were 0.19, 0.19, and 0.28, respectively.

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Registry No.—(±)-**1**, 20348-58-7; (−)-**1**, 745-65-3; (±)-**3a**, 34388-79-9; 3(*R*)-**3a**, 41693-78-1; (±)-**5**, 34402-60-3; (−)-**5**, 22973-19-9; (±)-**11**, 52163-83-4; 11(*R*)-**11**, 41638-40-8; (±)-**12a**, 34388-82-4; (−)-**12a**, 54984-02-0; (±)-**12b**, 41638-39-5; 11(*R*)-**12b**, 55028-41-6; (±)-**21a**, 34388-90-4; (±)-**21b**, 54984-03-1; (±)-**22**, 54984-04-02; (±)-**23**, 52087-42-0; (±)-**24**, 52087-41-9; 11(*R*)-**27**, 54889-37-1; (±)-**28**, 20897-96-5; (±)-**30a**, 23203-65-8; (±)-**32a**, 54984-05-3; (±)-**32b**, 54984-06-4; (±)-**32c**, 55028-42-7; (±)-**32d**, 54889-38-2; (±)-**32e**, 54931-78-1; (±)-15(*R*)-**34**, 55028-43-8; (±)-15(*S*)-**34**, 55028-51-8; (±)-11,15-bisepi-PGE_1, 20348-69-0; (±)-11-epi-PGE_1, 20348-68-9.

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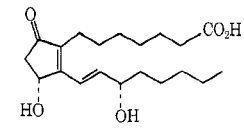

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(20) With respect to the five-membered ring. It is always axial with respect to the THP ring.
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(22) Mr. C. R. Dorn of these laboratories found that the trimethylsilyl group is a better protecting group than THP for the Grignard reaction, reducing the elimination product to a negligible amount.
(23) Melting points were taken on a Thomas-Hoover Unimelt in open capillaries and were not corrected. The NMR spectra were recorded at 60 MHz on Varian A-60 or at 100 MHz on Varian XL-100 NMR spectrometers in either deuteriochloroform or deuteriomethanol, using Me_4Si as an internal reference. $W_{1/2}$ denotes peak width at half-height of the multiplets. All uv spectra were determined in a 1 mg % methanol solution.
(24) R_f values for thin layer chromatography were determined on a 1 × 3 in. silica gel plate using benzene–ethyl acetate–acetic acid (25:25:1) sprayed with ethanolic phosphomolybdic acid.
(25) Unless otherwise mentioned adsorption column chromatography was carried out on Mallinckrodt SilicAR CC-4 (100–200 mesh) using benzene containing increasing percentages of ethyl acetate.
(26) Partition column chromatography was carried out by the procedure described in ref 11.
(27) Two diastereoisomers, **17** and **18**, were inseparable.
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(29) The melting point of (±)-ω-homo-PGE_1 could not be found in the literature.

Total Synthesis of (±)-β-Gorgonene

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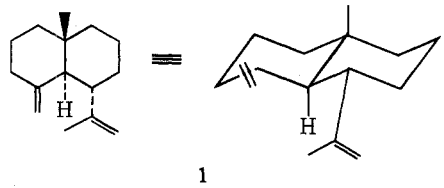
A synthetic approach to a novel nonisoprenoid sesquiterpene skeleton is described. The skeleton is derived from a rearrangement of the cationic intermediate leading to the germacrane skeleton resulting in a misplaced isopropenyl group. The key construction sequence involves the stereoselective introduction of the isopropenyl to 10-methyl-8(9)-octal-1-one. This intermediate was synthesized by two routes, both proceding through *cis*- and *trans*-10-methyl-1-decalone.

A considerable amount of synthetic chemistry has been directed toward the preparation of various members of the decalin-derived bicyclic sesquiterpenes.[1] One particular member of this general class, (+)-β-gorgonene (1), isolated



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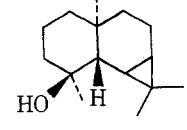
by Weinheimer and coworkers,[2] was of particular interest to us since it apparently represented an example of the violation of the usually observed biogenetic substitution pattern. Since the initial report of our synthesis,[4] a biogenetic-like conversion of maaliol (2) to (−)-β-gorgonene by dry HCl presumably through cation 3 has been reported which



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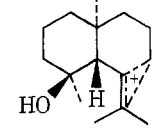

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confirms the absolute stereochemistry of (+)-β-gorgonene (1) and supports the rearrangement hypothesis for its biosynthesis.[5]

A synthetic approach to this class of molecules requires that one deal with the problem of stereoselective introduction of the required equatorial isopropenyl group. This problem is compounded by the presence of the angular methyl group and the fact that the point of attachment is a peri-like position in the decalin ring system in a 1,3 relation to the angular group.

We felt that octalone (4) represented one plausible pre-