(18) Tests of platelet aggregation were carried out in collaboration with Professors J. B. Smith and M. J. Silver of the Cardeza Foundation, Thomas Jefferson University, Philadelphia, Pa. 19107.
(19) The effect of 6,9-thiaprostacyclin on isolated cat coronary artery was determined in collaboration with Mr. Martin Ogletree and Professor A. M. Lefer, Department of Physiology, Thomas Jefferson Medical College, Philadelphia, Pa. 19107.
(20) M. L. Ogletree and A. M. Lefer, *Fed. Proc.*, **36**, 986 (1977).
(21) Details on the biological properties of 6,9-thiaprostacyclin will be reported elsewhere.
(22) This research was supported by the University of Pennsylvania, Merck Sharp and Dohme, U.S.A., and Ono Pharmaceutical Co., Japan.

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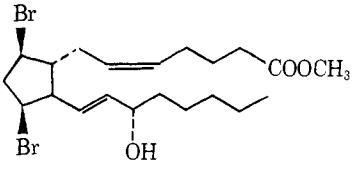
Synthesis of Prostaglandin H_2 Methyl Ester

Sir:

The prostaglandin (PG) endoperoxides, PGG_2 (**1**) and PGH_2 (**2**), are key intermediates in the bioconversion of arachidonic acid into a variety of physiologically active substances, including the prostaglandins,[1] thromboxane A_2,[2] 12-hydroxy-*cis*-5,*trans*-8,*trans*-10-heptadecatrienoic acid (HHT),[3] and prostacyclin (PGI_2).[4,5] Endoperoxides **1** and **2** were first isolated from biosynthetic preparations in 1973 and were characterized by chemical conversion into known, stable molecules.[6] More recently, the biosynthetic procedure has been modified and simplified to allow preparation of PGH_2 and PGH_1 on a multimilligram scale.[7] At the same time, several groups have reported preliminary results that clearly are aimed at providing a chemical synthesis of the endoperoxides.[8,9] In this report we outline the preparation of various 9,11-dihaloprostaglandins and describe the conversion of one of these, 9β,11β-dibromo-9,11-dideoxy-$PGF_{2\alpha}$ methyl ester (**3**), into prostaglandin H_2 methyl ester (**4**).



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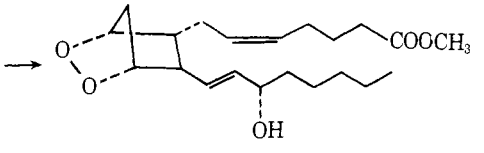

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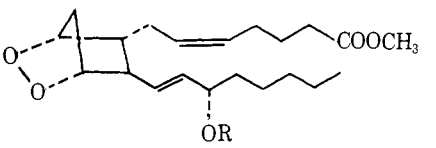
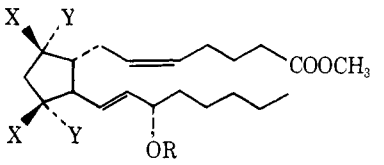
The following sequence of reactions was used to convert $PGF_{2\alpha}$ methyl ester (**5**), into the 9,11-ditosylate (**6**), the desired substrate for the preparation of 9,11-dibromoprostaglandins. Reaction of **5** and *n*-butylboronic acid (refluxing benzene, 2.5 h, azeotropic removal of water) gave the cyclic 9,11-*n*-butylboronic ester.[10] The 15-OH of this ester was derivatized with *tert*-butyldimethylsilyl chloride and imidazole (dimethylformamide, 40 °C, 20 h)[11] followed by removal of the cyclic 9,11-*n*-butylboronate with 30% aqueous hydrogen peroxide (acetone, 25 °C, 5 h) to give $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester (**7**). The ditosylate (**8**) of **7** was prepared by reaction of **7** with *p*-toluenesulfonyl chloride in pyridine and, following chromatography on silica gel, was hydrolyzed with 3:1:1 acetic acid–water–tetrahydrofuran to give **6**.

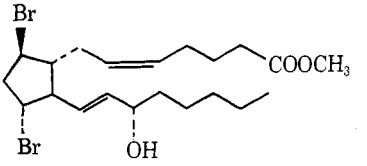
Reaction of **6** with lithium bromide (DMF, 65 °C, 1 h under N_2) followed by high pressure liquid chromatography on silica gel (15% acetone–hexane) gave, in increasing order of polarity



1, R = OH
2, R = H



5, X = R = H; Y = OH
6, X = R = H; Y = OTos
7, X = H; Y = OH; R = $OSi(CH_3)_2C(CH_3)_3$
8, X = H; Y = OTos; R = $OSi(CH_3)_2C(CH_3)_3$
10, X = R = H; Y = Br
11, X = Cl; Y = R = H
12, X = OTos; Y = R = H
13, X = R = H; Y = Cl



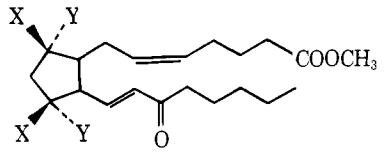
9

(silica gel TLC, 20% acetone in hexane), the following compounds as viscous oils. 9β,11α-Dibromo-9,11-dideoxy-$PGF_{1\alpha}$ methyl ester (**9**, 29% yield): R_f 0.33; mass spectrum (trimethylsilyl derivative), 564.1250, calcd for $C_{24}H_{42}{}^{79}Br_2O_3Si$ 564.1271, other ions at 549, 533, 521, 493, 485, 413, and 333 mass units. Anal. Calcd for $C_{21}H_{34}Br_2O_3$: Br, 32.33. Found: Br, 31.52. 9α,11α-Dibromo-9,11-dideoxy-$PGF_{2\alpha}$ methyl ester (**10**, 7.5%): R_f 0.27; mass spectrum (TMS derivative) 564.1272, remainder of spectrum nearly identical with that of **9**. Anal. Found: Br, 31.40. The desired **3**[12] (10%): R_f 0.25; mass spectrum (TMS derivative) 564.1261. Anal. Found: Br, 30.62. The order of appearance of these three products during the reaction, as detected by TLC, was **3** followed by **9** and then by **10**. One may reasonably expect formation of the 9β,11β isomer (**3**) to be kinetically most favored in this reaction, while the 9α,11α isomer will be least favored. Thermodynamically, the 9β,11α isomer (**9**), in which all substituents on the cyclopentane ring are trans, must be favored. These considerations lead to the tentative assignments of configuration given to the reaction products. These assignments were confirmed by comparison of the nuclear magnetic resonance (NMR) spectra of the dibromides with those of the dichlorides described below.

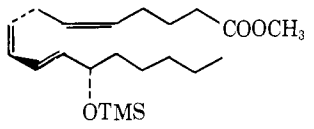
Reaction of 9α,11α-ditosylate **6** with lithium chloride (DMF, 65 °C, 2.5 h) gave a single dichloride (58% yield) that must be the 9β,11β-dichloro isomer **11**:[12] R_f 0.34 (20% acetone in hexane); mass spectrum (TMS derivative) 476.2279, calcd for $C_{24}H_{42}{}^{35}Cl_2O_3$ 476.2280. Anal. Calcd. for $C_{21}H_{34}Cl_2O_3$: C, 62.21; H, 8.45; Cl, 17.49. Found: C, 62.27; H, 8.91; Cl, 17.32. Likewise, reaction of lithium chloride with 11-epi-$PGF_{2\beta}$ methyl ester, 9,11-ditosylate (**12**, prepared from 11-epi-$PGF_{2\beta}$ methyl ester, by the same sequence of reactions used to prepare **6** from **5**) gave a single, isomeric dichloride (65% yield) that must be the 9α,11α-dichloro isomer **13**:[12] R_f 0.29 (20% acetone in hexane); mass spectrum (TMS derivative) 476.2279. Anal. Found: C, 62.72; H, 8.48; Cl, 17.91.

The NMR spectrum ($CDCl_3$) of 9β,11β-dibromo-9,11-dideoxy-15-keto-$PGF_{2\alpha}$ methyl ester (**14**,[12] obtained by Jones oxidation of **3** at −30 °C) (δ 6.81 (d of d, 1 H, J_{14} = 16 Hz, J_{12} = 8 Hz, $HC_{13}<$), 6.02 (d, 1 H, J_{13} = 16 Hz, $HC_{14}<$), 5.45 (m,

2 H, C_5–C_6 olefinic protons), 4.42 (four-line pattern, 1 H, >HC_9Br), 3.97 (four-line pattern, 1 H, >HC_{11}Br), 3.63 (s, 3 H, -OCH_3), 0.90 (t, 3 H, J = 5 Hz, -CH_3)) (Anal. Calcd for $C_{21}H_{32}Br_2O_3$: C, 51.23; H, 6.55. Found: C, 51.27; H, 6.89) was compared with those of the 15-ketones derived from **11** and **13.** Oxidation of **11** gave 9β,11β-dichloro-9,11-dideoxy-15-keto-$PGF_{2\alpha}$ methyl ester (**15**) (NMR ($CDCl_3$) δ 6.85 (d of d, 1 H, J_{14} = 16 Hz, J_{12} = 8 Hz, H-C_{13}<), 6.07 (d, 1 H, J_{13} = 16 Hz, HC_{14}<), 5.46 (m, 2 H, C_5–C_6 olefinic protons), 4.38 (four-line pattern, 1 H, >HC_9Cl), 3.93 (four-line pattern, 1 H, >HC_{11}Cl), 3.67 (s, 3 H, -OCH_3), 0.90 (t, 3 H, J = 5.5 Hz, -CH_3)), while oxidation of **13** gave 9α,11α-dichloro-9,11-dideoxy-15-keto-$PGF_{1\alpha}$ methyl ester (**16**)[12] (NMR ($CDCl_3$) δ 6.68 (d of d, 1 H, J_{14} = 15.5 Hz, J_{12} = 8 Hz, HC_{13}<), 6.27 (d, 1 H, J_{13} = 15.5 Hz, HC_{14}<), 5.38 (m, 2 H, C_5–C_6 olefinic protons, 4.42 (m, 1 H, >HC_9Cl), 4.06 (six lines, 1 H, >HC_{11}Cl), 3.64 (s, 3 H, -OCH_3), 0.90 (t, 3 H, J = 5.5 Hz, -CH_3)). The similar chemical shifts for the C_{13} and C_{14} protons in **14** and **15** confirm the assignment of the 9β,11β-dibromo configuration to **3** and the 9α,11α configuration to **10.**



14, X = Br; Y = H
15, X = Cl; Y = H
16, X = H; Y = Cl



17

For the preparation of prostaglandin H_2 methyl ester (**4**), a solution of potassium superoxide (KO_2) in DMF was prepared by stirring a mixture of finely divided KO_2 (0.0060 mol) in DMF (10.0 mL) containing dicyclohexyl-18-crown-6 (0.0020 mol) for 2 h at room temperature.[9] After the solid KO_2 was allowed to settle for 20 min, 1.5 mL of the supernatent was cooled to −20 °C in an ice–methanol bath. To this was added dibromide **3** (26 mg) dissolved in 0.5 mL of DMF, reaction conditions under which the dibromide is present in excess.[13] The solution changed immediately to an orange-yellow color. After 2 min the reaction was quenched by addition to a water (8 mL)–ether (3 mL) mixture. TLC of the ether layer reveals a complex mixture that includes a spot having the same R_f[14] as authentic PGH_2 methyl ester.[7] This product spot furthermore gives the color characteristic of peroxides when sprayed with ferrous thiocyanate reagent.[9] The synthetic PGH_2 methyl ester was isolated by preparative TLC (silica gel, 10% acetone–methylene chloride and 30% acetone–hexane) and, following elution from the silica gel with acetone, gave prostaglandin H_2 methyl ester, (~400 μg, 3% yield based on recovered starting material) and recovered starting dibromide **6** (10 mg). The synthetic PGH_2 methyl ester (**4**) was further characterized as described below.

Gas chromatographic–mass spectral (GC–MS, LKB 9000) analysis of the freshly prepared trimethylsilyl (TMS) ether derivative of **4** (prepared with Regisil in pyridine) gave a major GC[15] peak from which the mass spectrum in Figure 1 (bottom) was obtained. Analysis of authentic PGH_2 methyl ester[7] under the same conditions gave the identical results shown in Figure 1 (top). The retention times and the mass spectra of these two samples are, in turn, identical with those of 12-hydroxy-*cis*-5,*trans*-8,*trans*-10-heptadecatrienoic acid methyl ester TMS ether (**17**).[3] The observed mass spectra (Figure 1) must arise from fragmentation of **4**-TMS to **17** and malondialdehyde, a process previously observed to occur both chemically and biologically.[3] As the freshly prepared TMS derivative of endoperoxide **4** aged (1–3 h), a more polar, minor peak (M^+ 510) increased in size at the expense of the major peak. This slow transformation of the TMS derivative to a new material suggests that the fragmentation most likely occurs during sample injection into the gas chromatograph.

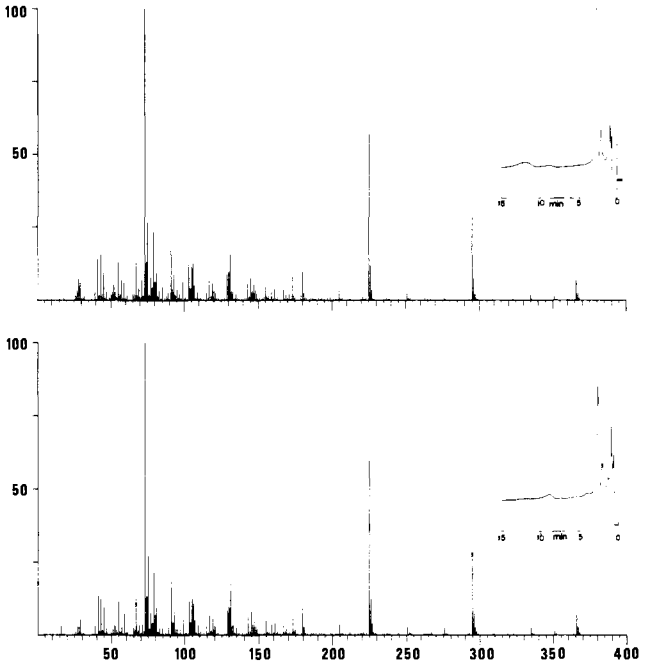


Figure 1. Top, GC tracing (inset) and mass spectrum obtained from the TMS derivative of PGH_2 methyl ester, from a biosynthetic source. Bottom, GC tracing (inset) and mass spectrum obtained from the TMS derivative of PGH_2 methyl ester, prepared by chemical synthesis.

The synthetic PGH_2 methyl ester (**4**) was reduced with triphenylphosphine.[16] This reduction gave a more polar product which was identical with authentic $PGF_{2\alpha}$ methyl ester by TLC[17] and mass spectral comparisons (the latter on the tri-TMS derivatives).

The synthetic PGH_2 methyl ester also is comparable with a biosynthetic sample in its ability to aggregate human platelets. In addition, this aggregation is (a) effectively blocked by addition of 9,11-azoprosta-5,13-dienoic acid, a known inhibitor of the enzymic transformation of endoperoxides into thromboxane A_1,[18] and (b) is enhanced by the addition of human platelet microsomes, known to accelerate the enzymatic conversion of PGH_2 to thromboxane A_2,[19] to the aggregation experiment.

These results demonstrate that the chemical synthesis of endoperoxide **4** has been achieved and illustrate methods by which such endoperoxides may be isolated and characterized. Improvement of the yield from this reaction may be limited. The nature of several by-products[20] suggests that the desired S_N2 displacement of bromide by hydroperoxide anion[9] suffers from serious competition by an intramolecular elimination process.

References and Notes

(1) (a) P. F. Beal, G. S. Fonken, and J. E. Pike, U.S. Patent 3 296 091 (filed Feb 19, 1964); (b) B. Samuelsson, *J. Am. Chem. Soc.*, **87**, 3011 (1965); (c) D. H. Nugteren, R. K. Beerthuis, and D. A. vanDorp, *Recl. Trav. Chim. Pays-Bas*, **85**, 405 (1966); (d) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **242**, 5344 (1967).
(2) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975).
(3) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 3400 (1974).

(4) (a) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, **263**, 663 (1976); (b) R. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, *Prostaglandins*, **12**, 685 (1976); (c) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *ibid.*, **12**, 715 (1976); (d) S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, *ibid.*, **12**, 897 (1976); (e) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *ibid.*, **12**, 915 (1976); (f) R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, **99**, 4182 (1977).
(5) For a review of the physiological role of the endoperoxides and substances derived therefrom, see R. R. Gorman, *MTP Int. Rev. Sci.: Biochem., Ser., Two*, in press.
(6) (a) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 899 (1973); (b) D. H. Nugteren and E. Hazelhof, *Biochem. Biophys. Acta*, **326**, 448 (1973).
(7) R. R. Gorman, F. F. Sun, O. V. Miller, and R. A. Johnson, *Prostaglandins*, **13**, 1043 (1977).
(8) (a) N. A. Porter and M. O. Funk, *J. Org. Chem.*, **40**, 3614 (1975); (b) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975); (c) R. G. Salomon and M. F. Salomon, *J. Am. Chem. Soc.*, **99**, 3501 (1977); (d) N. A. Porter and D. W. Gilmore, *ibid.*, **99**, 3503 (1977).
(9) (a) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975); (b) R. A. Johnson, E. G. Nidy, and M. V. Merritt, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 29–Sept 3, 1976. Abstract ORGN-107.
(10) (a) C. Pace-Asciak and L. S. Wolfe, *J. Chromatogr.*, **56**, 129 (1971); (b) E. E. Nishizawa, W. L. Miller, R. R. Gorman, G. L. Bundy, J. Swensson, and M. Hamberg, *Prostaglandins*, **9**, 109 (1975).
(11) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(12) The corresponding free acid of this compound has also been prepared and completely characterized.
(13) Control experiments have shown that endoperoxide **4** is unstable to excess KO_2 under these reaction conditions.
(14) The identity of R_f values was found in five distinctly different solvent systems.
(15) A 4-ft glass column of 1% QF 1 was used for the GC analysis. The GC–MS operating conditions were as follows: column temperature, 170 °C; flash heater, 225 °C; separator, 240 °C; ion source 250 °C; trap current, 65 μA; ionizing voltage, 70 eV.
(16) M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 345 (1974).
(17) The TLC system used (two times in methylene chloride–acetonitrile–methanol–water, 60:35:5:2.5 by volume) also differentiated $PGF_{2\alpha}$ methyl ester from 11-epi-$PGF_{2\beta}$ methyl ester. The latter would have been formed if the 9α,11α-dibromide (**10**) had been incorrectly used for the endoperoxide synthesis.
(18) R. R. Gorman, G. L. Bundy, D. C. Peterson, F. F. Sun, O. V. Miller, and F. A. Fitzpatrick, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 4007 (1977).
(19) P. Needleman, S. Moncada, S. Bunting, J. R. Vane, M. Hamberg, and B. Samuelsson, *Nature*, **261**, 558 (1976).
(20) A pair of hydroperoxy olefins and a pair of hydroxy olefins have been tentatively identified by mass spectrometry as products of the reaction.

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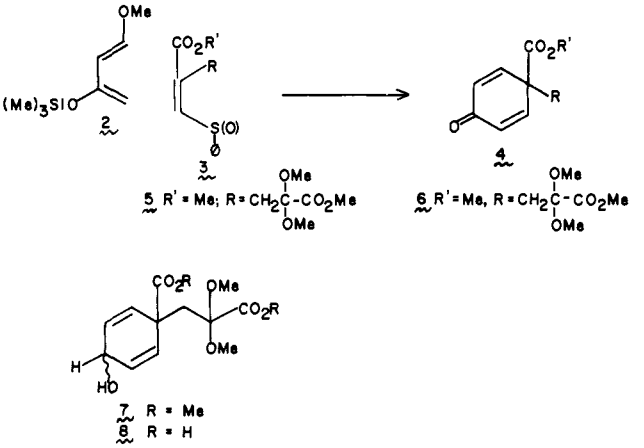
Total Synthesis of Disodium Prephenate

Sir:

Prephenic acid (**1**), stable only in its dicarboxylate form (**1a, 1b**), is the central intermediate in the biological production of the aromatic rings of phenylalanine and tyrosine.[1] Its existence was inferred and established after extensive research by Davis.[2] Given the fragility of prephenate and the paucity of degradative and analytical data, the formulation of its structure by Weiss et al.[3] was an accomplishment of considerable magnitude. The stereochemistry of prephenic acid was surmised to be that shown in **1** by Plieninger and co-workers[4,5] by the paper chromatographic comparison of the 2,4-DNP derivative of tetrahydroprephenic acid, with a sample of known stereochemistry obtained through synthesis.

The lability of prephenate and its compactly arranged functionality pose an implicit challenge to its total synthesis. Below we describe the total synthesis of disodium prephenate.

Our general approach was recently described.[6] It involves a new synthesis of compounds such as **4,** themselves systems of marginal stability to acids[7] and bases.[8a] Such systems are obtained by unraveling of the Diels–Alder adducts of diene **2**[8b] with dienophiles of the type **3.** Through the use of the specific dienophile, **5,** we obtained dienone **6.** This was converted to a 7:5 mixture (separated into its components) of **7.** Unfortunately, the side-chain ketone could not be redeemed from the dimethyl acetal by treatment of either epimer of **7** with acids, under a variety of conditions, owing to dienol–benzene rearrangement.[9] Moreover, both epimers of **8** suffered rapid conversion of phenylpyruvic acid dimethyl acetal even at pH 3.5 under conditions where the ketal was stable.[6]



We reasoned that it would be advantageous to store the C_{10}-carboxy and C_8-keto functions in a concurrently protected form from which both groups might be unmasked in a single step under alkaline circumstance. Methoxylactone **15** seemed eminently suitable for this purpose. Its precursor dienone **14,** might be expected to arise from a Diels–Alder dynamic using **2** and **13.** This proposition was reduced to practice.

Saponification (5 equiv of KOH, 1:1 methanol–water, room temperature, 36 h) of the readily available **9**[6] afforded a 92% yield of **10,**[10] mp 108–110 °C. Treatment of **10** with 2:1 aqueous HCl (0.012 N)–THF (room temperature, 73 h) afforded acid **11** which upon reaction with diazomethane and