useful in confirming the configuration of the PGB compounds at C_{15} and for estimating the composition of mixtures of enantiomers,[9,10] since the (+)-α-methoxy-α-trifluoromethylphenyl acetates (MTPA) of (15*R*)- and (15*S*)-PGB_2 methyl esters showed several differences in the proton and fluorine nuclear magnetic resonance spectra.[11]

The prostaglandins extracted from a specimen of the *S* form of *P. homomalla* after enzymatic hydrolysis were purified by column chromatography. Based on frozen wet weight of coral, the amounts of (15*S*)-PGA_2 (1.4%) and (15*S*)-PGA_2 methyl ester (0.4%) obtained are comparable to the amounts of (15*R*)-prostaglandins obtained from the (*R*) form of *P. homomalla*. In addition,[6] 0.06% of crystalline (15*S*)-PGE_2, mp 63–66.5°, was isolated and shown to be identical in physical and biological properties with mammalian PGE_2.[12]

These findings, in addition to providing a novel and possibly useful natural source of primary prostaglandins,[6] also raise many intriguing biochemical questions about the origin and role of prostaglandins in marine organisms, some of which are under investigation.

(9) J. Muenzer, Senior Thesis, Kalamazoo College, Kalamazoo, Mich., June 1970.

(10) U. Axen, J. E. Pike, and W. P. Schneider on "The Total Synthesis of Natural Products," Vol. III, J. ApSimon, Ed., Wiley, New York, N. Y., in press.

(11) In the proton magnetic spectrum, the doublet from the proton at C_{13} occurred centered at δ 6.79 (J = 16 Hz) for the (15*S*) isomer and at 6.89 (J = 16 Hz) for the (15*R*) isomer. The chemical-shift differences for the methoxyl protons were too small to be useful since they were closely coupled quartets due to splitting by the three fluorine atoms five bonds distant (Varian A-60-A, $CDCl_3$, tetramethylsilane internal reference). The fluorine magnetic resonance spectrum (obtained from Midwest Research Institute at 94.1 MHz in $CDCl_3$ relative to external trifluoroacetic acid) of the 15-epimers showed absorption frequencies of 675 ((*R*) isomer) and 687 ((*S*) isomer) for the trifluoromethyl groups, broadened enough by splitting from the methoxyl protons to make accurate integration difficult without comparison with computer-calculated spectra.

(12) Infrared and nuclear magnetic resonance spectroscopy, mixture melting point, and chromatographic behavior (several systems) all were identical. We are grateful to Dr. J. R. Weeks and coworkers, The Upjohn Company, for the biological assays.

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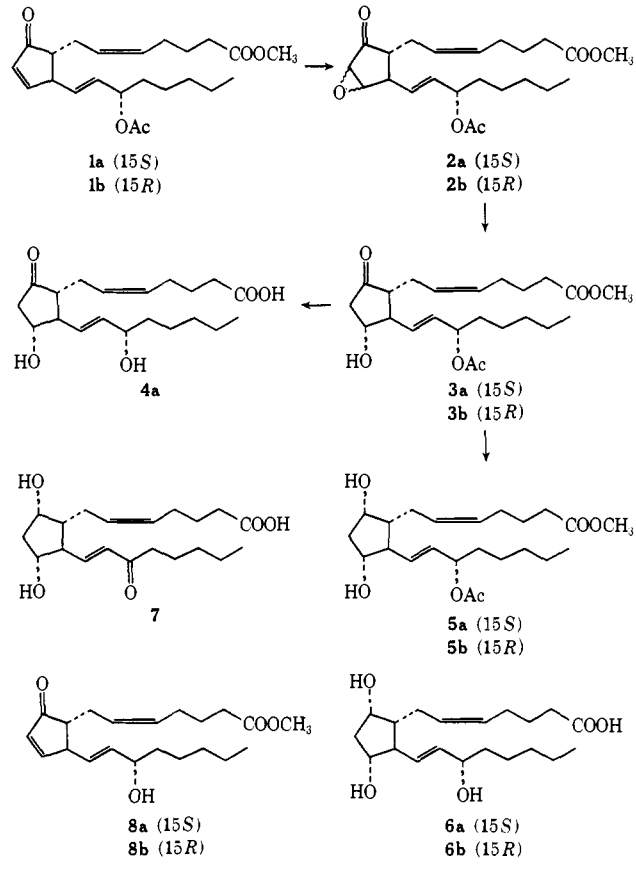
The Synthesis of Prostaglandins E_2 and $F_{2\alpha}$ from (15*R*)- and (15*S*)-PGA_2

Sir:

Ester derivatives of both (15*S*)- and (15*R*)-PGA_2 are readily obtainable from the gorgonian *Plexaura homomalla* found in the Caribbean area.[1,2] This communication describes the conversion of these materials to the biologically important[3] primary prostaglandins PGE_2 and $PGF_{2\alpha}$. (15*S*)-Prostaglandin A_2, acetate, methyl ester (**1a**) from coral extracts[2] was epoxidized with alkaline hydrogen peroxide[4] to a mixture of isomeric 10,11-epoxides (**2a**). Without separation, the mixture was reduced with chromous acetate[5] in acetic acid or aluminum amalgam[6] to give, after separation by silica gel chromatography, **3a**, the 15-acetate, methyl ester of PGE_2, in 56% yield along with 25% of the corresponding 11-epimer. The diester **3a** was hydrolyzed[7] to give PGE_2 (**4a**), obtained crystalline, mp 66–68°, in 90% yield, and identical in all respects[8] with PGE_2 obtained from mammalian sources. The 11β isomer of PGE_2 obtained similarly was noncrystalline, slightly less polar than **4a** on silica gel, showing characteristic downfield shifts of the $C_{13,14}$ olefinic protons in the nmr spectrum and characteristic fine structure differences in the circular dichroism curve.[9]



Reduction of PGE_2 with sodium borohydride leads directly to $PGF_{2\alpha}$.[10] Compound **3a** was also converted to its 11-trimethylsilyl ether and reduced with sodium borohydride to a mixture of 9α and 9β alcohols separated by silica gel chromatography; use of this protecting group increases the 9α:9β ratio obtained on reduction of the 9-ketone.[11] After hydrolysis $PGF_{2\alpha}$

(1) A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Lett.*, 5185 (1969).

(2) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem., Soc.*, 94, 2122 (1972).

(3) S. Bergström, L. A. Carlson, and J. R. Weeks, *Pharm. Rev.*, 20, 1 (1968).

(4) F. Weitz and A. Scheffer, *Chem. Ber.*, 54, 2327 (1921).

(5) W. Cole and P. L. Julian, *J. Org. Chem.*, 19, 131 (1954).

(6) L. F. Fieser and M. Fieser in "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967.

(7) The hydrolysis was effected by an acetone-insoluble esterase: E. G. Daniels, The Upjohn Company, unpublished observations.

(8) P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. F. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, 9, 231 (1968).

(9) Private communication, W. C. Krueger, The Upjohn Co.

(10) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, 34, 2139 (1969).

(11) The conversion of (15*R*)-PGA_2, acetate, methyl ester from coral to mammalian prostaglandins was first described at the N. Y. Academy of Sciences Meeting, Sept 17–19, 1970; G. L. Bundy, F. H. Lincoln, N. A. Nelson, J. E. Pike, and W. P. Schneider, *Ann. N. Y. Acad. Sci.*, 180, 76 (1971).

(**6a**), mp 25–35°, was obtained from **3a** in 60% yield and was converted to its tris(hydroxymethyl)aminomethane (THAM) salt,[12] mp 100–101°. Both $PGF_{2\alpha}$ and its THAM salt were identical with authentic materials.

Utilization of the (15*R*)-PGA_2 diester (**1b**) from coral as a precursor of PGE_2 and $PGF_{2\alpha}$ requires an inversion of configuration at C-15.[11] For the synthesis of $PGF_{2\alpha}$, **1b** was carried through the same sequence as above giving the corresponding intermediates **2b**, **3b**, and **5b**. On hydrolysis **5b** gave **6b**, the 15-epimer of $PGF_{2\alpha}$.

Selective oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[13] gave ketone **7** (λ_{max} 234 nm (ϵ 11,850)) which was reduced by zinc borohydride in dimethoxyethane[14] after temporary protection of the hydroxyl groups by trimethylsilylation, giving a 73:27 ratio of $PGF_{2\alpha}$ (**6a**) and its 15-epimer **6b**.

(15*R*)-PGA_2 methyl ester (**8b**), also available from coral, was treated with methanesulfonyl chloride in pyridine and the resulting crude 15-mesylate was solvolyzed in acetone–water to give modest yields of the C_{15} inverted product, (15*S*)-PGA_2 methyl ester (**8a**), along with some **8b** and several other products. Acetylation of **8a** in acetic anhydride–pyridine gave **1a** and thus ultimately PGE_2 and $PGF_{2\alpha}$.

Plexaura homomalla, var. (*R*) and var. (*S*), are thus both suitable sources of (coral) prostaglandins useful in the synthesis of PGE_2 and $PGF_{2\alpha}$. From the (*S*) variety, PGE_2 can be obtained in three steps and $PGF_{2\alpha}$ in four steps.

(12) This crystalline salt of $PGF_{2\alpha}$ was first prepared by W. Morozowich, The Upjohn Co.

(13) E. Änggård and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

(14) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

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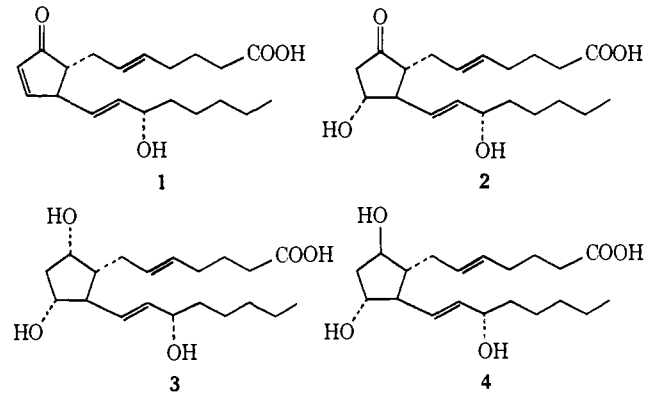
Isolation of a New Naturally Occurring Prostaglandin, 5-*trans*-PGA_2. Synthesis of 5-*trans*-PGE_2 and 5-*trans*-$PGF_{2\alpha}$

Sir:

During the chromatographic purification of (15*S*)-PGA_2 obtained from the gorgonian *Plexaura homomalla* var. (*S*),[1] a new natural prostaglandin was detected which was chromatographically less polar than PGA_2 on silver nitrate impregnated silica gel. We report here the purification of this material, its structure elucidation, and confirmation of the structure by chemical transformations.

Column chromatography of crude (15*S*)-PGA_2 on Amberlyst-15 Ag^+ form[2] or on silver nitrate impregnated silica gel gave a minor component to which the structure (15*S*)-15-hydroxy-9-oxo-5-*trans*,10,13-*trans*-prostatrienoic acid (5-*trans*-PGA_2) (**1**) is assigned. Content of the trans isomer usually ranged between 5 and 15% of the PGA_2 present. 5-*trans*-PGA_2 is an oil [λ_{max} 217 nm (ϵ 9050); $[\alpha]D$ +128° ($CHCl_3$); molecular ion at 478.2998 for TMS derivative (calcd for $C_{26}H_{46}O_4Si_2$, 478.2932); mass spectrum identical with that of PGA_2]. Conversion of **1** to the β-ketol was effected by a modification of the epoxidation–reduction sequence[3] to give (15*S*)-11α,15-dihydroxy-9-oxo-5-*trans*,13-*trans*-prostadienoic acid (5-*trans*-PGE_2) (**2**)[4] together with the 11β isomer. 5-*trans*-PGE_2 was crystalline: mp 76–77° (*Anal.* Found: C, 68.52; H, 9.23); $[\alpha]D$ −66° (*c* 0.983, ethanol); mass spectrum identical with PGE_2. After conversion to a trimethylsilyl (TMS) derivative, reduction of **2** with sodium borohydride[5] and hydrolysis gave a mixture of (15*S*)-9α,11α,15-trihydroxy-5-*trans*,13-*trans*-prostadienoic acid (5-*trans*-$PGF_{2\alpha}$) (**3**) and (15*S*)-9β,11α,15-trihydroxy-5-*trans*,13-*trans*-prostadienoic acid (5-*trans*-$PGF_{2\beta}$) (**4**),



which were separated by silica gel chromatography. 5-*trans*-$PGF_{2\alpha}$ was crystalline: mp 94.8–95.8° (*Anal.* Found: C, 67.99; H, 9.64); $[\alpha]D$ +9° (ethanol); mass spectrum *m/e* at 354 (M^+), 336, 318, 264, 247, 191, 137. 5-*trans*-$PGF_{2\beta}$ was also crystalline: mp 68–69° (*Anal.* Found: C, 67.89; H, 9.78); $[\alpha]D$ −8° (ethanol).

Irradiation of prostaglandin E_2 in oxygen-free benzene–methanol solution with 3500-Å light for 24 hr in a Rayonet photochemical reactor in the presence of diphenyl sulfide[6,7] gave, after careful chromatography on acid-washed silica gel, a 22% yield of 5-*trans*-PGE_2, mp 75–77°, which was identical with the material derived from *P. homomalla*. In a similar fashion and in similar yield, crystalline 5-*trans*-$PGF_{2\beta}$ and 5-*trans*-$PGF_{2\alpha}$ were prepared from the corresponding 5-*cis*-prostaglandins and were also identical with the coral-derived compounds.

A reexamination of the extracts of *P. homomalla* var. (*S*) prior to hydrolysis shows that, while small amounts of the free acids are present, the 5-trans isomer is predominantly in the form of its 15-acetate methyl ester. It is not clear at this time whether the presence of this isomer represents biosynthetic formation from 5-*trans*-arachidonic acid endogenous to *P. homomalla*, or a subsequent transformation product of 5-*cis*-PGA_2.

(1) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, **94**, 2122 (1972).

(2) E. G. Daniels and J. E. Pike, *Proc. Prostaglandin Symp. Worcester Found. Exp. Biol.*, 379 (1968).

(3) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Amer. Chem. Soc.*, **94**, 2123 (1972).

(4) The preparation and biological activity of 5-*trans*-PGE_2 obtained by biosynthesis from 5-*trans*,8-*cis*,11-*cis*,14-*cis*-eicosatetraenoic acid (5-*trans*-arachidonic acid) have been described by D. A. van Dorp, *Ann. N. Y. Acad. Sci.*, **180**, 181 (1971).

(5) G. L. Bundy, F. H. Lincoln, N. A. Nelson, J. E. Pike, and W. P. Schneider, *ibid.*, **180**, 76 (1971).

(6) C. Mousseboisand J. Dale, *J. Chem. Soc.*, 260 (1966).

(7) F. D. Gunstone and I. A. Ismail, *Chem. Phys. Lipids*, **1**, 264 (1967).

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