Preparation of Prostaglandin E_2 from *Plexaura homomalla*

By WILLIAM P. SCHNEIDER,* GORDON L. BUNDY, and FRANK H. LINCOLN
(*The Upjohn Company, Kalamazoo, Michigan* 49001)

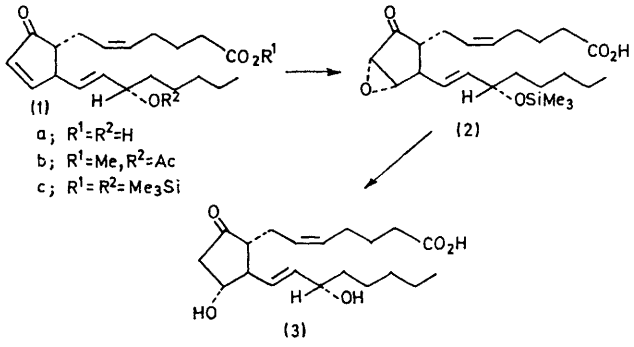
Summary An efficient method for enzymatic hydrolysis of esters of PGA_2 contained in the sea whip, *Plexaura homomalla* (var. S) and subsequent conversion of the released PGA_2 to PGE_2 *via* silylation, epoxidation, and reductive opening of the epoxide is described.

PROSTAGLANDIN E_2 (**3**), probably the most widely occurring and most highly active, biologically, of the mammalian prostaglandins, has been prepared from (15*S*)-PGA_2, acetate, methyl ester (**1b**), a prostaglandin derivative endogenous to some forms of the sea whip, *Plexaura homomalla*.[1] This route involved the conversion of (**1b**) into PGE_2, 15-acetate, methyl ester which was then hydrolysed enzymatically to PGE_2. An alternate method has now been devised which takes advantage of natural esterases of *P. homomalla* to initially hydrolyse (**1b**) into PGA_2 (**1a**) which is then converted chemically into PGE_2 without the necessity of purification at subsequent intermediate stages. This method facilitates the isolation of the acidic PGA_2 by extraction from other predominantly neutral products† of the coral and leads directly to PGE_2 in an overall yield of over 47% from PGA_2.

Fresh or frozen chopped *P. homomalla* was stirred in water at room temperature for 24 h and then extracted with

† These include batyl alcohol, fatty acid glycerides containing considerable amounts of arachidonic acid, and a mixture of at least seven sterols. This mixture may contain cholesterol, 24-methylenecholesterol, and compounds, $C_{28}H_{48}O$, $C_{29}H_{48}$, and $C_{30}H_{50}O$, as based on g.l.c.–mass spectral data obtained on the trimethylsilyl derivatives.

ethyl acetate. The acidic prostaglandins were extracted from the organic layer by equilibration with aqueous tris(hydroxymethyl)aminomethane and further purified if desired, by silica gel or argentation chromatography.[1b,c]



The PGA_2 thus obtained was converted into the trimethylsilyl derivative (**1c**)‡ with hexamethyldisilizane and trimethylchlorosilane and then into the epoxide with alkaline hydrogen peroxide§ in isopropyl alcohol at −40°. The mixture of epoxides, (**2**) and its 10β,11β-isomer was difficult to separate, was reduced with aluminium amalgam in a mixture of tetrahydrofuran, methanol, and aqueous sodium bicarbonate at 15° for about 1 h. After decanting from an excess of aluminium amalgam, the mixture was acidified and extracted to give a crude product which was shown by silica gel chromatography of an aliquot to consist of almost 70% PGE_2, 10% 11-epi-PGE_2, and small amounts of PGA_2, $PGF_2\alpha$ and other reduction products. Direct crystallization of the crude product from ether–Skellysolve B gave over 40% yield (based on PGA_2) of PGE_2 (**3**) m.p. 65—67·5°, identical in all respects to mammalian-derived PGE_2. More material of comparable quality (7% yield) was obtained by chromatography of filtrates followed by crystallization.

Thus, a simple, efficient method has been found for the preparation of the key prostaglandin, PGE_2, from the common Caribbean sea whip, *P. homomalla*.

(*Received*, 16*th February* 1973; *Com.* 217.)

‡ Derivatization at C-15 improves the α : β ratio of epoxides formed in the next step, see ref. 1b.

§ Slightly more than 1 equiv. of alkali (based on starting PGA_2) is required.

[1] (a) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, 1972, **94**, 2122; (b) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *ibid.*, p. 2123; (c) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *ibid.*, p. 2124.