Synthesis of Novel Bicyclic Prostaglandins by Photochemical Cycloaddition Reactions

By **Pierre Crabbé,*† Gustavo A. García, and Carlos Ríus,** Facultad de Química, Universidad Nacional Autonóma de Mexico, Mexico 20, D. F., Mexico

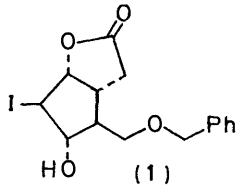
Light-induced addition reactions of cyclopentenone derivatives with ethylene, followed by elaboration of the alkyl chains at positions 8 and 12, give bicyclic prostanoic acid analogues belonging to the prostaglandin E_2 and $F_{2\alpha}$ series. Cycloaddition of ethylene to prostaglandin A_2 methyl ester yields simultaneously the α- and β-cycloadducts. Photochemical addition of allene to prostaglandin A_2 derivatives affords mixtures of photoadducts which vary with the nature of the functional group at position 15, thus illustrating the versatility of these photocondensation reactions.

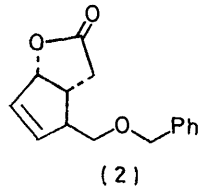
PROSTAGLANDINS ‡ of synthetic or natural origin containing the cyclopentenone unit are apparently suitable for photochemical cycloaddition reactions,[1] leading to bicyclic prostanoids of potential pharmacological utility. We report the addition of ethylene and allene to such systems and the stereochemical consequences.[2]

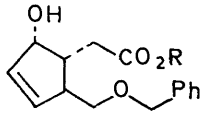
The first step consists of the preparation of an intermediate, obtained by photochemical reaction, which is then used in a total synthetic scheme. The lengthy but flexible synthesis developed at Harvard[3] was followed, since it has been shown that the iodo-lactone (1) can be converted into the olefin (2) in essentially quantitative yield.[4] The lactone group of the bicyclic intermediate (2) was carefully opened by treatment with base and the salt was neutralised, thus affording the hydroxy-acid (3a), which on esterification with ethereal diazomethane provided the hydroxy-ester (3b). This was readily oxidised with chromic acid[5] at low temperature to the conjugated ketone (4).

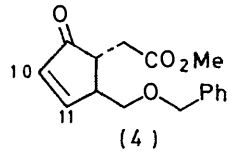
Irradiation of the substituted cyclopentenone (4) in methylene chloride solution saturated with ethylene, with a Hanau Q-18 high-pressure u.v. lamp at −70°, afforded the bicyclic keto-ester (5). This product is slowly converted into an equilibrium mixture of (5) and its 8β-acetate isomer (see later). For this reason, the carbonyl group of (5) was immediately reduced with sodium borohydride in methanol. T.l.c. then gave the expected lactone (6a) and a mixture of the hydroxy-esters (7a and b). The ester (7b) is only detected when the reduction is performed with an equilibrated sample of the ketone (5).

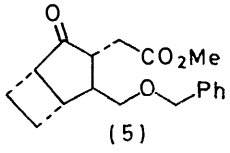
The mass spectrum of the tricyclic compound (6a) showed a molecular ion at *m/e* 272 and the n.m.r. spectrum displayed a triplet at 4·71 p.p.m. [C(9)H, $J_{8.9}$ 7, $J_{9.10}$ 7 Hz]. Examination of the geometry of the compound with molecular models indicates that such a triplet is only compatible with the α-configuration of the cyclobutane system,[6] which must also apply to the precursor (5).

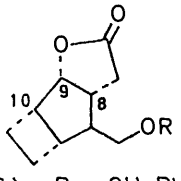

(1)

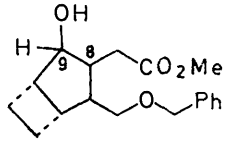

(2)


(3)a; R = H
b; R = Me


(4)


(5)


(6)a; R = CH_2Ph
b; R = H


(7)a; 8β-H, 9α-H
b; 8α-H, 9β-H

The crystalline 9β-hydroxy-ester (7a) could be oxidised with chromic acid[5] to regenerate the keto-ester (5); this can thus be recycled. In its n.m.r. spectrum, the ester (7a) shows a doublet (*J* 7 Hz) at 3·5 p.p.m. [C(13)H_2], whereas the isomer (7b) shows the corresponding doublet (*J* 5·5 Hz) at 3·3 p.p.m. The *trans*-stereochemistry of (7a and b) at positions 8 and 9 is supported by the fact that in solution neither of them suffers the transesterification observed with the hydroxy-ester (3b) or during the reduction of (5), which yield

† *Present address:* Laboratoire de Chimie Organique, C.E.R.M.O., Université Scientifique, Boite Postale 53, Grenoble 38.041, France.

‡ Throughout this paper, the numbering system illustrated in formula (16) is used for all compounds, except in systematic names.

[1] For recent theoretical discussions of photochemical cycloadditions, see N. D. Epiotis, *J. Amer. Chem. Soc.*, 1972, **94**, 1941; W. C. Herndon, *Chem. Rev.*, 1972, **72**, 157.

[2] Preliminary communication, P. Crabbé, G. A. García, and C. Ríus, *Tetrahedron Letters*, 1972, 2951.

[3] E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491, and references therein.

[4] P. Crabbé and A. Guzmán, *Tetrahedron Letters*, 1972, 115; A. Guzmán, P. Ortiz de Montellano, and P. Crabbé, *J.C.S. Perkin I*, 1973, 91.

[5] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

[6] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; *J. Amer. Chem. Soc.*, 1963, **85**, 2870.

directly the lactones (2) and (6a), respectively, without saponification.[7]

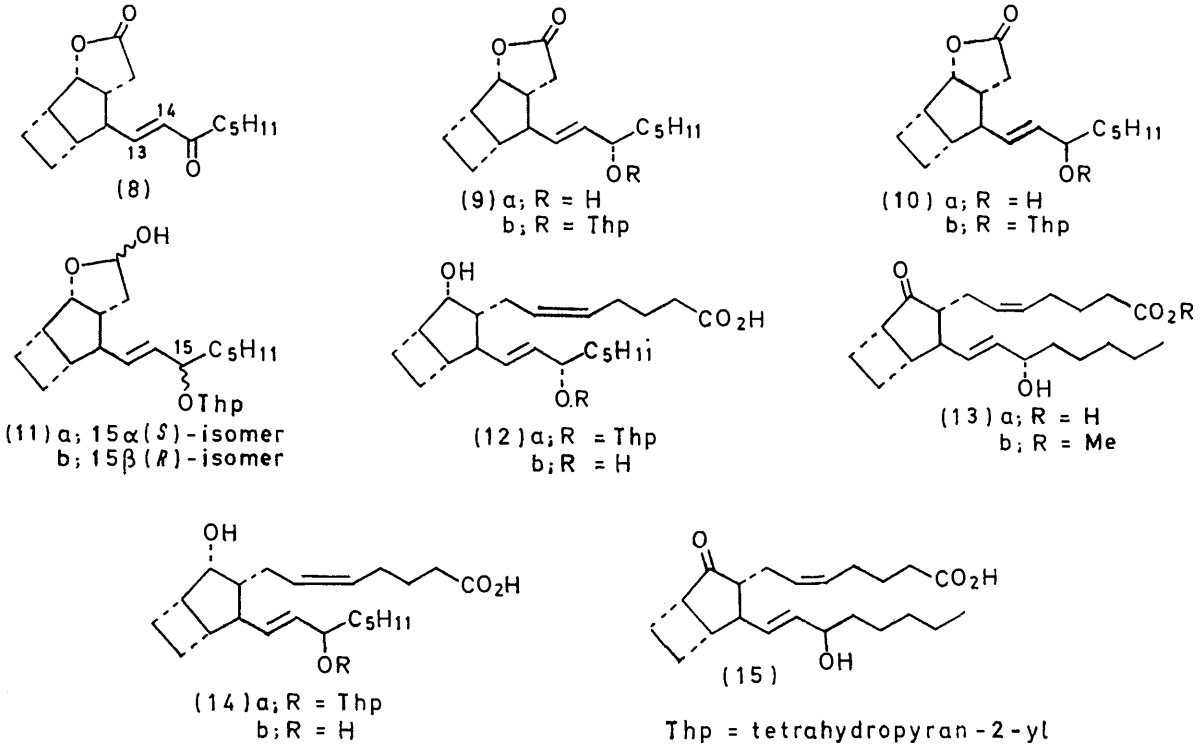
Hydrogenolysis of the benzyloxy-group of the tricyclic derivative (6a) with palladium–carbon in dimethoxyethane (DME) gave almost quantitatively the primary alcohol (6b). Oxidation of this with chromium trioxide–dipyridine complex in methylene chloride solution[8] gave the corresponding aldehyde, which was immediately alkylated under argon with the sodium salt of dimethyl 2-oxoheptylphosphonate[3] to afford the crystalline enone (8).

Reduction of the C-15 carbonyl group of compound (8) was performed with zinc borohydride in DME, under which conditions the lactone ring was not affected. The prostanoic acid as its 15-tetrahydropyranyl ether (12a). The protecting group was readily hydrolysed by brief exposure to aqueous acetic acid, thus completing the total synthesis of (±)-11-deoxy-10α,11α-ethylene-prostaglandin $F_{2\alpha}$ (12b).

Chromic acid oxidation[5] of the 9-hydroxy-group in (12a), followed by treatment with acid, provided the corresponding (±)-11-deoxy-10α,11α-ethyleneprostaglandin E_2 (13a).

Similarly, the (15*R*)-isomers belonging to the $F_{2\alpha}$ series (14b) and the E_2 series (15), respectively, were also prepared.

The noteworthy feature of the foregoing synthesis is the exclusive formation of the α-adduct (5) through the



required (15*S*)-alcohol (9a) was separated from its *R*-isomer (10a) by preparative t.l.c. The corresponding 15α-tetrahydropyranyl ether (9b) was easily prepared by treatment with dihydropyran in anhydrous methylene chloride–tetrahydrofuran, in the presence of a catalytic amount of toluene-*p*-sulphonic acid. Reduction of the lactone group of (9b) with di-isobutylaluminium hydride in toluene at −60°[9] then furnished the lactol (11a) (96%), which was immediately treated with the disodium salt of 5-triphenylphosphoniopentanoic acid in anhydrous dimethyl sulphoxide,[3] affording the novel stereochemical effectiveness of the photochemical cycloaddition reaction.

Parallel to our efforts to introduce a C_2 unit at positions 10 and 11 in the prostaglandin molecule by total synthesis, we also studied photochemical additions to naturally occurring prostanoids. The prostaglandin A_2 derivatives (16a and b),[10] isolated from the marine corals belonging to the *Plexaura homomalla* family,[11] originating from the Caribbean,[12] were investigated since their molecular framework possesses the enone system required.

[7] Examples of such internal transesterifications under these conditions are known, *e.g.* W. Darey and D. J. Tirey, *J. Chem. Soc.*, 1958, 1230; M. Julia, S. Julia, and B. Bémont, *Bull. Soc. chim. France*, 1960, 304; R. Lukes, S. Dolezal, and K. Capek, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2408; J. A. Marshall and N. Cohen, *J. Amer. Chem. Soc.*, 1965, **87**, 2773.

[8] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.

[9] L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Letters*, 1962, 619.

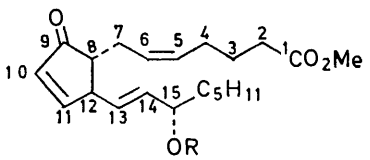
[10] W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, 1972, **94**, 2122.

[11] A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Letters*, 1969, 5185.

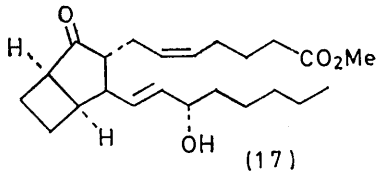
[12] Dr. O. Halpern, Syntex Research, Palo Alto, California, personal communication.

In contrast to the photocondensation of ethylene with the substituted cyclopentenone (4), which resulted exclusively in insertion from the α-side, irradiation of the ester (16a) in methylene chloride solution saturated with ethylene afforded a mixture of 30% of the 10α,11α-*cycloadduct* (13b) and 16% of its 10β,11β-isomer (17), besides unchanged starting material; the mixture was separated by preparative t.l.c.

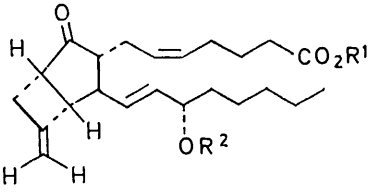
The 11-deoxy-10α,11α-ethyleneprostaglandin E_2 analogue (13b) showed no intense u.v. absorption. Furthermore, its n.m.r. spectrum was similar to that of the



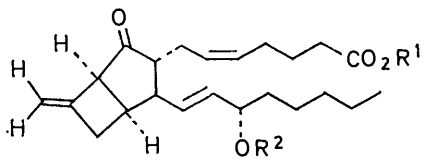
(16) a; R = H
b; R = Ac



(17)



(18) a; R^1 = Me, R^2 = H
b; R^1 = R^2 = H
c; R^1 = Me, R^2 = Ac



(19) a; R^1 = Me, R^2 = H
b; R^1 = R^2 = H
c; R^1 = Me, R^2 = Ac

synthetic material (13a). Since the keto-ester (13b) was prepared from the natural prostaglandin A_2 methyl ester (16a), it is optically active, displaying a weakly negative Cotton effect at *ca.* 300 nm. Definite proof of the structure and stereochemistry of (13b) resulted from the esterification of the acid group of the total synthesis product (13a) with diazomethane, which gave the ester (13b); this sample was identical with the material obtained from (16a) except for its optical activity.

The spectroscopic properties of the 10β,11β-cycloadduct (17) were similar to those of its isomer (13b). However, whereas the specific rotation of the α-ethyleneadduct (13b) is positive, that of the β-isomer (17) is negative. In addition, the β-adduct (17) exhibits an intense negative Cotton effect in the 300 nm region, because the cyclobutane group falls into a negative octant.[13]

The cycloaddition of prostaglandin A_2 methyl ester (16a) to allene,[14,15] induced by u.v. irradiation, was also attempted. This reaction yielded a mixture of isomeric methylene-substituted 11-deoxy-10,11-ethyleneprostaglandin E_2 methyl esters. Preparative t.l.c. gave the major prostanoic acid derivative (18a) (22% yield) and its isomer (19a) (19%), besides 34% of unchanged starting material.

Compound (18a) showed a cyclopentanone-like carbonyl absorption in its i.r. spectrum. The absence of an intense u.v. maximum above 220 nm and the n.m.r. signals of the methylene substituent are similar to the properties of 6-methylenebicyclo[3.2.0]heptan-2-one.[14] Furthermore, the configuration of the ethylene bridge appears to be α in (18a) since its negative Cotton effect is reminiscent of that exhibited by the derivative (13b).

As in the case of 7-methylenebicyclo[3.2.0]heptan-2-one,[14] the structure of the photoadduct (19a) is based on the appearance of the methylene signal in the n.m.r. spectrum, and on its u.v. maximum at 302 nm, typical of a βγ-unsaturated ketone system. In addition, the β-stereochemistry of the ethylene bridge in the prostanoic ester (19a) is supported by the intense negative chiroptical properties associated with the homoconjugated chromophore, in agreement with the extension of the octant rule for βγ-unsaturated ketones.[15,16]

Alkaline hydrolysis of the esters (18a) and (19a) afforded the novel bicyclic prostaglandin E_2 derivatives (18b) and (19b), respectively.

Photochemical addition of allene to prostaglandin A_2 1-methyl ester 15α-acetate (16b) was also studied. In this case, the major compound isolated was the β-adduct (19c) (20%); also obtained were the α-adduct (18c) (16%) and 31% of unchanged starting material. The structure and stereochemistry of these compounds was confirmed by basic hydrolysis of their acetoxy-groups, which afforded the esters (19a) and (18a), respectively.

Since all the novel optically active bicyclic prostanoid derivatives (13b), (17), (18), and (19) reported here exhibit a negative Cotton effect in the 300 nm region, it is reasonable to assume that no isomerisation occurs at C-8 during the photochemical process. Indeed, it is

[13] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013; W. Klyne, *Tetrahedron*, 1961, **13**, 29.

[14] Ph. E. Eaton, *Tetrahedron Letters*, 1964, 3695.

[15] P. Crabbé, A. Cruz, and J. Iriarte, *Photochem. Photobiol.*, 1968, **7**, 829; P. Sunder-Plassman, P. H. Nelson, P. H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, 1969, **34**, 3779.

[16] E. Bunnenberg, C. Djerassi, K. Mislow, and A. Moscowitz, *J. Amer. Chem. Soc.*, 1962, **84**, 2823.

known that 8-*iso*-prostaglandin E derivatives display an intense positive Cotton effect in this region.[17]

Worth emphasising is the influence exercised by the substituents at positions 8 and 12 on the course of these photochemical additions. Whereas addition of ethylene to the enone (4) gave exclusively the α-adduct, substitution for the acetic ester system at C-8 and (more important) the β-benzyl ether system at C-12 of longer aliphatic substituents, such as these of the enone (16a), not only decreased the photochemical yield, but also gave a 2 : 1 mixture of α- and β-[2 + 2] cycloadducts. The situation was also complicated in the photochemical addition of allene to the enone (16a), which afforded a *ca.* 1 : 1 mixture of α- and β-photoproducts. Finally, substitution of an α-acetoxy-group at C-15 for the hydroxy-group increased the proportion of 10β,11β-adduct, thus showing the subtle effects of groups apparently remote from the enone system.

The novelty of these syntheses resides in the photochemical addition of two- or three-carbon units to appropriate cyclopentenones, thus leading to new prostaglandin [2 + 2] cycloadducts with various structural and stereochemical features.

Besides their intrinsic pharmacological potential, the bicyclic prostaglandins reported here may also be important intermediates for conversion into modified prostanoic acids *via* microbiological hydroxylation.

EXPERIMENTAL

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. M.p.s were determined with a Fisher–Johns apparatus. T.l.c. was performed with silica gel GF-254 (Merck). Rotations were taken between 16 and 22 °C with a 1 dm tube at the sodium D-line. I.r. spectra were taken with a Perkin-Elmer model 21 (NaCl prism) instrument. U.v. spectra were obtained with a Beckman DU spectrophotometer. O.r.d. curves were taken with an automatic recording JASCO/UV-5 spectropolarimeter and c.d. curves were obtained with a Bendix dichrograph. Unless otherwise stated, the n.m.r. spectra were recorded with Varian A-100 and T-60 instruments, for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants are accurate to ±1 Hz. Mass spectra were recorded with an Atlas CH-4 spectrometer equipped with an EFO-4B ion source; ionising energy 70 eV.

Esterification of 2-*Benzyloxymethyl*-5-*hydroxycyclopent*-3-*enylacetic Acid* (3a).—To a suspension of the acid (3a) [4] (500 mg) in ether (2 ml), cooled to −10°, ethereal diazomethane was added until all the material had dissolved and the yellow colour persisted. The solution was washed with aqueous 10% sodium hydrogen carbonate and then with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and evaporated to give the methyl ester (3b) (520 mg, 98%). Recrystallisation from ether–hexane gave material of m.p. 45°; $\nu_{max.}$ 3350, 1730, and 1600 cm^{-1}; δ 1·92 (OH), 3·42 (d, *J* 6 Hz, CH_2·O·CH_2Ph), 3·66 (CO_2Me), 4·50 (O·CH_2Ph), 4·83 (m, CH·OH), 5·93 (2 vinylic H), and 7·33 p.p.m. (5 aromatic H); *m/e* 245 (M^+ − OCH_3), 244 (M^+ − CH_3OH), and 91 ($C_7H_7^+$).

Conversion of the Ester (3b) *into* 4-*Benzyloxymethyl*-3,3a,4,6a-*tetrahydrocyclopenta*[b]*furan*-2-*one* (2).—A solution of the ester (3b) (20 mg) in methylene chloride (or chloroform, or ether) (10 ml) kept at room temperature for a few days (the time depends on the amount of acid or base present). After removal of the solvent *in vacuo*, the lactone (2) was isolated quantitatively as an oil; $\nu_{max.}$ 1770 and 1615 cm^{-1}; δ 6·0 p.p.m. (2 vinylic H).[4]

Oxidation of the Alcohol (3b) *to Methyl* 2-*Benzyloxymethyl*-5-*oxocyclopent*-3-*enylacetate* (4).—To a solution of the alcohol (3b) in acetone (100 ml), cooled to −5°, 8N-chromic acid [5] (2 ml) was added dropwise. The reaction was followed by t.l.c. After completion of the oxidation, a few drops of propan-2-ol were added. The salts were filtered off and the solution was concentrated *in vacuo*. Ether (150 ml) was added and the ethereal solution was washed with aqueous sodium chloride, dried ($MgSO_4$), filtered, and evaporated to give the *keto-ester* (4) (2·34 g, 97%), which was purified by preparative t.l.c. to afford an oil, $\lambda_{max.}$ 209 nm (log ε 4·11); $\nu_{max.}$ 1735, 1710, and 1595 cm^{-1}; δ 3·56 (m, CH_2·O·CH_2Ph), 3·60 (CO_2Me), 4·52 (O·CH_2Ph), 6·21 (dd, $J_{1,2}$ 6, $J_{1,3}$ 2 Hz, C-10 vinylic H), 7·3 (5 aromatic H), and 7·61 p.p.m. (dd, $J_{2,1}$ 6, $J_{2,3}$ 2·5 Hz, C-11 vinylic H); *m/e* 274 (M^+) and 91 ($C_7H_7^+$) (Found: C, 70·35; H, 6·7. $C_{16}H_{18}O_4$ requires C, 70·05; H, 6·6%).

Photochemical Cycloaddition of Ethylene to the Enone (4).—Into a solution of the enone (4) (700 mg) in methylene chloride (100 ml) in a quartz vessel, cooled to −70°, ethylene was bubbled for 0·5 h. The solution was then irradiated through Pyrex with a 70 W Hanau Q-81 high-pressure mercury lamp for 2 h.[15] The solvent was removed *in vacuo* and the residue was chromatographed on silica gel plates (hexane–ethyl acetate, 7 : 1) to give methyl 2-benzyloxomethyl-4-oxobicyclo[3.2.0]heptan-3-ylacetate (5) and unchanged starting material (4) (160 mg). The adduct (5) was an oil, $\nu_{max.}$ 1740 and 1610 cm^{-1}; δ 3·53 (d, *J* 5 Hz, CH_2·O·CH_2Ph), 3·63 (CO_2Me), 4·50 (O·CH_2Ph), and 7·33 p.p.m. (5 aromatic H); *m/e* 302 (M^+), 271 (M^+ − OMe), and 91 ($C_7H_7^+$); it was unstable and was therefore used immediately for the next reaction.

Reduction of the Keto-ester (5).—To a solution of the ester (5) (1·1 g) in methanol (40 ml), kept below 10°, sodium borohydride (2 g) was added in small portions with stirring. The mixture was then stirred for 3 h at room temperature. 2N-Hydrochloric acid was added and the mixture was stirred for another 15 min. The solution was concentrated under reduced pressure, ethyl acetate (100 ml) was added, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by t.l.c. (hexane–ethyl acetate, 3 : 2).

The less polar compound (350 mg, 36%) was the lactone (6a), an oil; $\nu_{max.}$ 1770 and 1610 cm^{-1}; δ 3·27 (dd, J_{ab} 9, J_{ac} 6 Hz), 3·47 (dd, J_{ba} 9, J_{bc} 5·5 Hz) (CH_c·CH_aH_b·O·CH_2Ph), 4·41 (O·CH_2Ph), 4·71 (t, $J_{8,9}$ 7, $J_{9,10}$ 7 Hz, 9-H), and 7·21 p.p.m. (5 aromatic H); *m/e* 272 (M^+), 181 (M^+ − C_7H_7), and 91 ($C_7H_7^+$). The more polar product (400 mg) was a 2 : 1 mixture of the *trans*-esters (7a and b), which were separated by t.l.c.

Methyl 2β-*benzyloxymethyl*-4β-*hydroxybicyclo*[3.2.0]*heptan*-3α-*ylacetate* (7a) was recrystallised from ether, m.p. 49°; $\nu_{max.}$ 3450 and 1725 cm^{-1}; δ 3·5 (d, *J* 7 Hz, CH_2·O·CH_2Ph),

[17] E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *J. Amer. Chem. Soc.*, 1968, **90**, 5894; O. Korver, *Rec. Trav. chim.*, 1969, **88**, 1070; N. H. Andersen, *J. Lipid Res.*, 1969, **10**, 320; H. Shio, P. W. Ramwell, N. H. Andersen, and E. J. Corey, *Experientia*, 1970, **26**, 355.

3·66 (CO_2Me), 4·0 (m, C*H*·OH), 4·45 (O·CH_2Ph), and 7·33 p.p.m. (5 aromatic H); *m/e* 304 (M^+), 286 ($M^+ - H_2O$), 273 ($M^+ - OMe$), 244 ($M^+ - HCO_2Me$), 231 ($M^+ - CH_2{\cdot}CO_2Me$), 213 ($M^+ - C_7H_7$), and 91 ($C_7H_7^+$) (Found: C, 71·4; H, 7·6. $C_{18}H_{24}O_4$ requires C, 71·1; H, 7·8%).

The *isomer* (7b), only isolated when the reduction was performed with the keto-ester (5) after equilibration, crystallised from ether to afford a sample of m.p. 65°; $\nu_{max.}$ 3450 and 1730 cm^{-1}; δ 3·3 (d, *J* 5·5 Hz, CH_2·O·CH_2Ph), 3·66 (CO_2Me), 4·0 (m, C*H*·OH), 4·43 (O·CH_2Ph), and 7·33 p.p.m. (5 aromatic H); *m/e* 286 ($M^+ - H_2O$), 273 ($M^+ - OMe$), 244 ($M^+ - HCO_2Me$), 231 ($M^+ - CH_2{\cdot}CO_2Me$), 213 ($M^+ - C_7H_7$), and 91 ($C_7H_7^+$) (Found: C, 70·8; H, 7·9%).

Hydrogenolysis of the Benzyl Ether (6a).—A mixture of the ether (6a) (460 mg) in DME (15 ml) was stirred in hydrogen over 10% palladium–carbon with perchloric acid (2 drops). After filtration and evaporation ethyl acetate (50 ml) was added; the solution was washed with aqueous 10% sodium hydrogen carbonate, dried, filtered, and concentrated under vacuum. The residual alcohol (6b) (293 mg, 95%) was an oil, homogeneous by t.l.c., $\nu_{max.}$ 3400 and 1770 cm^{-1}; δ 2·7 (OH, disappears with D_2O), 3·6 (CH_2·O), and 4·91 p.p.m. (t, *J* 7 Hz, 9α-H); *m/e* 182 (M^+) and 154 ($M^+ - CO$).

Oxidation and Alkylation at C-13.—To methylene chloride (8 ml) cooled to 0°, Celite (4·5 g) and chromium trioxide–dipyridine complex [8] (2·73 g, 10·5 mmol) were added, followed, with stirring, by the alcohol (6b) (200 mg) dissolved in methylene chloride (2·5 ml). After 10 min stirring at 0°, sodium hydrogen sulphate (5 g) was added and the mixture was stirred for an additional 10 min at 0°. It was filtered over anhydrous magnesium sulphate (which was washed with methylene chloride) and the solution was concentrated *in vacuo* at 0°. The oily aldehyde obtained was used as such for the next reaction.

Sodium hydride (50% suspension in oil; 67·4 mg) was washed twice with hexane (under argon). Then anhydrous DME (14 ml) was added, followed by the sodium salt of dimethyl 2-oxoheptylphosphonate [3] (308 mg) in DME (6·5 ml).* The mixture was stirred for 0·5 h, then the foregoing aldehyde dissolved in DME (6·5 ml) was added. The mixture was stirred for 2 h under argon. The excess of base was neutralised with acetic acid (2 drops) and the solvent was removed under reduced pressure without heating. The residue was purified by t.l.c. (hexane–ethyl acetate, 7 : 3), thus affording 6-(3-*oxo*-*oct*-1-*enyl*)-10-*oxatricyclo*[5.3.0.0^{2,5}]*decan*-9-*one* (8) (180 mg). Recrystallisation from ethyl acetate–hexane afforded a sample of m.p. 38—39°; $\lambda_{max.}$ 228 nm (log ε 4·19); $\nu_{max.}$ 1770, 1690, and 1625 cm^{-1}; δ 0·88 (Me), 6·12 (d, *J* 16 Hz, 14-H), and 6·66 p.p.m. (dd, *J* 16 and 8 Hz, 13-H); *m/e* 276 (M^+), 221 ($M^+ - C_4H_7$), and 205 ($M^+ - C_5H_{11}$) (Found: C, 73·8; H, 8·8; O, 17·4. $C_{17}H_{24}O_3$ requires C, 73·95; H, 8·7; O, 17·35%).

Reduction of the Ketone (8) *with Zinc Borohydride*.—To sodium borohydride (1·95 g) in redistilled DME (50 ml) was added recently fused zinc chloride (3·4 g). The mixture was stirred overnight at 0—5°. After filtration under nitrogen, the clear solution (*ca.* 0·5M) was used immediately.

To the ketone (8) (530 mg) dissolved in anhydrous DME (4 ml) was added 2 ml of the solution of zinc borohydride. The mixture was stirred at room temperature until the reduction was complete (50 min) (followed by t.l.c.). Saturated sodium hydrogen tartrate solution was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the solution was dried ($MgSO_4$), filtered, and evaporated to dryness. The mixture of 15-alcohols (9a) and (10a) (480 mg) (90%) was separated on preparative silica gel plates (ethyl acetate–hexane, 55 : 45), to give 200 mg of each isomer, in addition to a mixture of (9a) and (10a) (50 mg).

The 15α-ol (9a) was an oil, $\nu_{max.}$ 3450, 1770, and 1666 cm^{-1}; δ 0·88 (Me), 4·07 (C*H*·OH), 4·81 (dd, $J_{9.10}$ 6, $J_{8.9}$ 8 Hz, 9-H), and 5·52 p.p.m. (m, 2 vinylic H); *m/e* 278 (M^+), 250 ($M^+ - C_2H_4$), and 207 ($M^+ - C_5H_{11}$). The spectroscopic properties of the 15β-ol (10a) were identical.

The 15-*Tetrahydropyranyl Ethers* (9b) *and* (10b).—To a solution of the alcohol (9a) (98 mg) in anhydrous methylene chloride (1 ml) was added freshly distilled dihydropyran (0·046 ml) and a solution (0·2 ml) of toluene-*p*-sulphonic acid in tetrahydrofuran (50 mg in 10 ml). The mixture was stirred for 20 min at room temperature; the reaction was followed by t.l.c. Pyridine (2 drops) was added, then ether (40 ml). The solution was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and evaporated to leave the ether (9b) as an oil (120 mg, 95%), shown to be homogeneous by t.l.c., $\nu_{max.}$ 1770 and 1666 cm^{-1}; δ 0·88 (Me), 3·6—4·2 (m, 15-H, CH_2·O of Thp), 4·5—4·9 (m, 9-H, O·CH·O), and 5·5 p.p.m. (m, 2 vinylic H).

The 15β-alcohol (10a) (190 mg) similarly gave the ether (10b) (225 mg), showing physical properties essentially identical with those of its isomer (9b).

Reduction of the γ-Lactone (9b).—To a solution of the lactone (9b) (100 mg) in anhydrous toluene (3 ml) cooled to −60° was added (in argon atmosphere) a solution (0·44 ml) of di-isobutylaluminium hydride in toluene (1 ml in 3 ml).[9] The mixture was stirred for 15 min at −60°. The excess of reagent was destroyed by dropwise addition of methanol until the evolution of gas ceased. Stirring was continued for an additional 20 min at room temperature. Ether (40 ml) was added and the insoluble material was filtered off and washed with ether. The ethereal fractions were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual lactol (11a) (96 mg) was an oil, shown to be homogeneous by t.l.c., $\nu_{max.}$ 3450 and 1666 cm^{-1}. Since this hemiacetal (11a) was unstable it was immediately used for the next step.

Alkylation of the Hemiacetal (11a).—To 4-carboxybutyltriphenylphosphonium bromide (326 mg; dried under vacuum for 3 h), dissolved in dimethyl sulphoxide (DMSO) (0·6 ml; freshly distilled over calcium hydride) was added a solution (0·65 ml) of the sodium salt of dimethyl sulphoxide [from NaH (880 mg) dissolved in DMSO (10 ml) and heated at 70° for 1 h].* To the deep red solution was added, at room temperature, the lactol (11a) (97 mg) dissolved in DMSO (0·6 ml). The mixture was stirred for 15 h. The DMSO was removed under vacuum at 35°. Water was added to the residue, and the mixture was washed with ethyl acetate–ether (four times) to eliminate neutral impurities. The aqueous phase was acidified with oxalic acid to pH 2, and then extracted with pentane–ether (1 : 1). The organic layer was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and evaporated to give the crude acid (12a) (80 mg), which showed *ca.* 10% of a slightly more polar impurity by t.l.c.

Since compound (12a) is a mixture of isomeric tetrahydropyranyl ethers it was not purified further, but immediately subjected to acid hydrolysis.

* All the alkylation reactions were performed with freshly redistilled, anhydrous solvents in an inert atmosphere (dry nitrogen or argon).

(±)-11-*Deoxy*-3′,4′,10β,11β-*tetrahydrocyclobuta*[10,11]-*prostaglandin* $F_{2\alpha}$ (12b).—A solution of the tetrahydropyranyl ether (12a) (10 mg) in acetic acid–water (7 : 3; 1 ml) was stirred at room temperature for 4 h (hydrolysis followed by t.l.c.). The mixture was concentrated in vacuum without heating. Ethyl acetate was added and then removed under high vacuum. This operation was repeated until all traces of acetic acid had been removed. The residue was dissolved in toluene. The solvent was removed and the material was dried under high vacuum for 1 h. The residual material was purified by t.l.c. to give the acid (12b), an oil, $\nu_{max.}$ 3450 and 1710 cm^{-1}; δ 0·88 (Me), 4·12 (9-H, 15-H, CO_2H, 9-OH, 15-OH), and 5·46 p.p.m. (4 vinylic H); *m/e* 346 ($M^+ - H_2O$), 328 ($M^+ - 2H_2O$), and 293 ($M^+ - C_5H_{11}$).

(±)-11-*Deoxy*-3′,4′,10β,11β-*tetrahydro*-15-epi-*cyclobuta*-[10,11]*prostaglandin* $F_{2\alpha}$ (14b).—The lactone (10b) (170 mg) was reduced with di-isobutylaluminium hydride as for compound (9b),[9] affording the lactol (11b) (140 mg). The lactol (11b) (170 mg) was alkylated under identical conditions, thus affording the acid (14a) (140 mg).

Hydrolysis of compound (14a) (25 mg) with acetic acid–water (7 : 3) at room temperature, as before, provided compound (14b), which was purified by t.l.c. to give amorphous material, $\nu_{max.}$ 3450 and 1710 cm^{-1}; δ 0·88 (Me), 4·14 (9-H, 15-H), 4·56 (CO_2H, 9-OH, 15-OH), and 5·45 p.p.m. (4 vinylic H); *m/e* 346 ($M^+ - H_2O$), 328 ($M^+ - 2H_2O$), and 293 ($M^+ - C_5H_{11}$).

(±)-11-*Deoxy*-3′,4′,10β,11β-*tetrahydrocyclobuta*[10,11]-*prostaglandin* E_2 (13a).—To a solution of compound (12a) (10 mg) in acetone (1 ml) cooled to −13° was added Jones reagent (0·02 ml).[5] The mixture was stirred for 90 min; the reaction was followed by t.l.c. A few drops of propan-2-ol were added, then ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), filtered, and evaporated, affording the 9-oxo-derivative.

The tetrahydropyranyl group was removed by treatment with aqueous acetic acid (see before) for 4 h at room temperature; the reaction was followed by t.l.c. After removal of the acetic acid, the material was dried with toluene and then under high vacuum, thus affording the product (13a) (6 mg), purified by preparative t.l.c. to give an oil, $\nu_{max.}$ 3450, 1740, and 1710 cm^{-1}; δ 0·88 (Me), 4·1 (m, C*H*·OH), 5·44 (m, *cis* vinylic H), and 5·58 p.p.m. (m, *trans* vinylic H); *m/e* 344 ($M^+ - H_2O$) and 291 ($M^+ - C_5H_{11}$).

(±)-11-*Deoxy*-3′,4′,10β,11β-*tetrahydro*-15-epi-*cyclobuta*-[10,11]*prostaglandin* E_2 (15).—A solution of the ether (14a) (24 mg) in acetone (1 ml) was treated with Jones reagent (0·04 ml) [5] at −10° for 90 min. Extraction by the usual procedure gave the 9-oxo-15-ether (15 mg), which was subjected to acid hydrolysis as before. Isolation and t.l.c. gave the amorphous product (15) (10 mg), $\nu_{max.}$ 3450, 1735, and 1710 cm^{-1}; δ 0·88 (Me), 4·08 (m, C*H*·OH), and 5·44 p.p.m. (m, 4 vinylic H); *m/e* 344 ($M^+ - H_2O$) and 291 ($M^+ - C_5H_{11}$).

Purification of the Extracts from Marine Corals.—The crude extracts (2·86 g) from the gorgonians *Plexaura homomalla*,[10] were purified by t.l.c. on 8 plates (1 m × 20 cm) of silica gel (methylene chloride–ethyl acetate, 4 : 1). Two major u.v.-absorbing substances were isolated. The less polar material corresponded to the 15-acetate 1-ester (16b) of prostaglandin A_2 (16b) (734 mg). A second chromatography (methylene chloride–ethyl acetate, 95 : 5) gave an oil, $[\alpha]_D$ +104° ($CHCl_3$); $\lambda_{max.}$ 217 nm (log ε 4·02); $\nu_{max.}$ 1735, 1715, and 1595 cm^{-1}; δ 0·88 (Me), 2·09 (Ac), 3·66 (CO_2Me), 5·5 (m, 4 vinylic H), 6·2 (dd, $J_{1,2}$ 6, $J_{1.3}$ 2·0 Hz, 10-H), and 7·55 p.p.m. (dd, $J_{2.1}$ 6, $J_{2.3}$ 2·2 Hz, 11-H).

The more polar compound corresponded to prostaglandin A_2 methyl ester (16a) (341 mg). A second purification by t.l.c. (hexane–ethyl acetate, 3 : 2) gave an oil, $[\alpha]_D$ +108° (MeOH); $\lambda_{max.}$ 216 nm (log ε 3·86); $\nu_{max.}$ 3400, 1735, and 1715 cm^{-1}; δ 0·88 (Me), 3·66 (CO_2Me), 4·1 (m, 15-H); 5·4 (m, C-5 and C-6 vinylic H), 5·6 (m, C-13 and C-14 vinylic H), 6·18 (dd, $J_{1,2}$ 6, $J_{1.3}$ 2·0 Hz, 10-H), and 7·51 p.p.m. (dd, $J_{2,1}$ 6, $J_{2.3}$ 2·2 Hz, 11-H).

Photochemical Cycloaddition of Ethylene to Prostaglandin A_2 Methyl Ester (16a).—To a solution of compound (16a) (200 mg) in methylene chloride (60 ml), cooled to −70°, in argon, ethylene was bubbled for 15 min. This solution, kept at −70°, was irradiated for 2 h through Pyrex with a 70 W Hanau Q-81 high-pressure mercury lamp. The solvent was removed and the crude products were separated by preparative t.l.c. to give the α-adduct (13b) (65 mg, 30%), its β-isomer (17) (35 mg, 16%), and starting material (70 mg).

The adduct (13b), purified by t.l.c., was a liquid, $[\alpha]_D$ +23° ($CHCl_3$); c.d. (MeOH) $[\theta]_{302}$ −2050, $[\theta]_{217}$ +1950, $[\theta]_{210}$ +6200, $[\theta]_{204}$ +15,180; $\nu_{max.}$ 3400, 1740, and 1720 cm^{-1}; δ 0·88 (Me), 3·64 (CO_2Me), 4·06 (C*H*·OH), 5·41 (C-5 and C-6 vinylic H), and 5·54 p.p.m. (C-13 and C-14 vinylic H); *m/e* 376 (M^+), 358 ($M^+ - H_2O$), and 345 ($M^+ - OMe$).

The adduct (17), after purification by t.l.c., was an oil, $[\alpha]_D$ −51° ($CHCl_3$); c.d. (MeOH) $[\theta]_{304}$ −10,800, $[\theta]_{238}$ +1450, $[\theta]_{206}$ +20,460; $\nu_{max.}$ 3450 and 1730 cm^{-1} (broad); δ 0·88 (Me), 3·64 (CO_2Me), 4·08 (C*H*·OH), 5·36 (C-5 and C-6 vinylic H), and 5·58 p.p.m. (C-13 and C-14 vinylic H); *m/e* 376 (M^+), 358 ($M^+ - H_2O$), and 345 ($M^+ - OMe$).

Photochemical Cycloaddition of Allene to Prostaglandin A_2 Methyl Ester (16a).—To a solution of the ester (16a) (290 mg) in methylene chloride (70 ml), cooled to −70°, in argon, allene (10 g) was slowly added. This solution, kept at −70°, was irradiated for 1 h, through Pyrex with a 70 W Hanau Q-81 high-pressure mercury lamp. The solvent was removed under reduced pressure and the photoproducts were separated by preparative t.l.c. (methylene chloride–ethyl acetate, 85 : 15) to give starting material (16a) (100 mg) and two new compounds, less polar than (16a).

The first substance (62 mg) (19%), the photoadduct (19a), was purified further by t.l.c. (ethyl acetate–methylene chloride, 9 : 1), to give a liquid; c.d. (MeOH) $[\theta]_{304}$ −14,850, $[\theta]_{229}$ −1020, $[\theta]_{212}$ +3530; o.r.d. (*c* 0·001 in dioxan) $[\phi]_{700}$ ±0°, $[\phi]_{589}$ ±0°, $[\phi]_{328}$ −5382°, $[\phi]_{308}$ ±0°, $[\phi]_{282}$ +8794°, $[\phi]_{240}$ +9812°, $[\phi]_{230}$ +13,257°, $[\phi]_{222}$ +23,627° (*a* − 142); $\lambda_{max.}$ 302 nm (log ε 2·39); $\nu_{max.}$ 3430, 1745—1730br, 1670, 972 (*trans*-CH=CH), 880 (C=CH_2), and 720 cm^{-1} (*cis*-CH=CH); δ 0·89 (Me), 3·40 (10-H), 3·66 (CO_2Me), 4·10 (C*H*·OH), 4·79 and 4·95 (C=CH_2), 5·36 (C-5 and C-6 vinylic H), and 5·61 p.p.m. (C-13 and C-14 vinylic H); *m/e* 370 ($M^+ - H_2O$), 357 ($M^+ - OMe$), and 339 ($M^+ - H_2O - OMe$).

The second, major substance, slightly more polar, was the photoadduct (18a) (72 mg, 22%). A pure sample was an oil, c.d. (MeOH) $[\theta]_{302}$ −5570, $[\theta]_{225}$ +2340, $[\theta]_{212}$ −10,920; o.r.d. (*c* 0·001 in dioxan) $[\phi]_{700}$ +106°, $[\phi]_{589}$ −64°, $[\phi]_{320}$ −3390°, $[\phi]_{295}$ ±0°, $[\phi]_{274}$ +2911°, $[\phi]_{266}$ +2997°, $[\phi]_{235}$ ±0°, $[\phi]_{226}$ −1815° (*a* − 63); $\nu_{max.}$ 3430, 1745—1730br, 1660, 972 (*trans*-CH=CH), 890 (C=CH_2), and 725 cm^{-1} (*cis*-CH=CH); δ 0·89 (Me), 3·60 (11-H), 3·65

(CO_2Me), 4·10 (C*H*·OH), 4·90 and 5·02 ($C{=}CH_2$), 5·35 (C-5 and C-6 vinylic H), and 5·56 p.p.m. (C-13 and C-14 vinylic H); *m/e* 388 (M^+), 370 ($M^+ - H_2O$), 357 ($M^+ - OMe$), and 339 ($M^+ - H_2O - OMe$).

Photochemical Addition of Allene to Prostaglandin A_2 Acetate Ester (16b).—To a solution of compound (16b) (465 mg) in methylene chloride (100 ml) kept at −70°, allene (20 g) was slowly added, the mixture being kept under argon. This solution, at −70°, was irradiated for 80 min through Pyrex with a 70 W Hanau Q-81 high-pressure mercury lamp.[17] The solvent was removed under vacuum and the residue was separated by preparative t.l.c. (hexane–ethyl acetate, 85 : 15) to give starting material (16b) (145 mg) and two major photoproducts.

The ester (19c) (63 mg, 20%) was purified by a second preparative t.l.c. (methylene chloride–ethyl acetate, 95 : 5) to give an oil, c.d. (MeOH) $[\theta]_{305}$ −11,950, $[\theta]_{228}$ −2740; $\lambda_{max.}$ 300—302 nm (log ε 2·38); $\nu_{max.}$ 1740br, 1720br, 1670, 970 (*trans*-CH=CH), 880 ($C{=}CH_2$), and 725 cm^{-1} (*cis*-CH=CH); δ 0·88 (Me), 2·0 (OAc), 3·4 (10-H), 3·65 (CO_2Me), 4·80 and 4·95 ($C{=}CH_2$), 5·22 (C*H*·OAc), 5·35 (C-5 and C-6 vinylic H), 5·45 (C-14 vinylic H), and 5·77 p.p.m. (C-13 vinylic H); *m/e* 370 (M^+ — AcOH), 339 (M^+ — OMe), and 299 ($M^+ - C_5H_{11}$).

The isomeric cycloadduct (18c) (52 mg, 16%) was purified by t.l.c. (methylene chloride–ethyl acetate, 95 : 5) to give an oil, c.d. (MeOH) $[\theta]_{299}$ −3860, $[\theta]_{224}$ +1650, $[\theta]_{207}$ −18,500; $\nu_{max.}$ 1740br, 1720br, 1670, 970 (*trans*-CH=CH), 890 ($C{=}CH_2$), and 720 cm^{-1} (*cis*-CH=CH); δ 0·88 (Me), 2·05 (OAc), 3·62 (11-H), 3·66 (CO_2Me), 4·90, 5·04 ($C{=}CH_2$), 5·22 (C*H*·OAc), 5·35 (C-5 and C-6 vinylic H), 5·43 (C-14 vinylic H), and 5·70 p.p.m. (C-13 vinylic H); *m/e* 370 (M^+ — OAc), 339 (M^+ — OAc — OMe), and 299 (M^+ — OAc — C_5H_{11}).

Hydrolysis of the Acetate Esters (19c) *and* (18c) *to the Alcohol Esters* (19a) *and* (18a).—The acetate ester (19c) (30 mg) in methanol (4 ml) containing potassium carbonate (30 mg) was stirred for 90 min at room temperature. Saturated aqueous ammonium chloride was added. The methanol was removed *in vacuo*, and the residue was extracted three times with ethyl acetate. The organic layer was washed, dried, filtered, and concentrated under reduced pressure. T.l.c. of the residue gave the pure alcohol ester (19a) (20 mg), identical with an authentic sample (see before).

The acetate ester (18c) was similarly hydrolysed to the alcohol ester (18a), identical with an authentic sample (t.l.c., i.r., and n.m.r. analysis).

Alkaline Hydrolysis of the Ester (19a).—A solution of the ester (19a) (52 mg) in methanol (5 ml) containing potassium carbonate (120 mg) was stirred at room temperature for 12 h, then evaporated to dryness *in vacuo*. Water was added and the solution was extracted with ethyl acetate to remove neutral impurities. Dilute hydrochloric acid (10%) was then added and the free acid was extracted with ethyl acetate. Washing with water, drying ($MgSO_4$), filtration, and concentration under reduced pressure gave the acid (19b) (41 mg). Preparative t.l.c. (ethyl acetate–methanol–formic acid, 95 : 4·5 : 0·5) gave 11-deoxy-3′,4′,10α,11α-tetrahydro-4′-methylenecyclobuta[10,11]-prostaglandin E_2 (19b) as an oil, $\lambda_{max.}$ 302—304 nm (log ε 2·38), $\nu_{max.}$ 3500, 1740, 1720, 1670, 972, 880, and 725 cm^{-1}; δ 0·88 (Me), 3·43 (10-H), 4·15 (C*H*·OH), 4·80 and 4·95 ($C{=}CH_2$), 5·36 (C-5 and C-6 vinylic H), 5·60 (C-13 and C-14 vinylic H), and 5·70 p.p.m. (CO_2H and OH); *m/e* 374 (M^+), 356 ($M^+ - H_2O$), and 303 ($M^+ - C_5H_{11}$).

Alkaline Hydrolysis of the Ester (18a).—A solution of the ester (18a) in methanol (5 ml) containing potassium carbonate (120 mg) was stirred at room temperature for 12 h, then concentrated under reduced pressure. Water was added and the solution was extracted with ethyl acetate to remove neutral material. Hydrochloric acid (10%) was added and the product extracted with ethyl acetate. The usual work-up gave the acid (18b) (35 mg).

T.l.c. furnished 11-deoxy-3′,4′,10β,11β-tetrahydro-3′-methylenecyclobuta[10,11]prostaglandin E_2 (18b) as a liquid, $\nu_{max.}$ 3500, 1740, and 1715 cm^{-1}; δ 0·88 (Me), 3·56 (11-H), 4·10 (C*H*·OH), 4·95 and 5·02 ($C{=}CH_2$), 5·43 (C-5 and C-6 vinylic H), 5·63 (C-13 and C-14 vinylic H), and 5·86 p.p.m. (CO_2H and OH); *m/e* 374 (M^+), 356 ($M^+ - H_2O$), 338 ($M^+ - 2H_2O$), and 303 ($M^+ - C_5H_{11}$).

Esterification of the Free Acid (19b) *with Diazomethane*.—To a solution of the acid (19b) (40 mg) in anhydrous ether (5 ml) saturated ethereal diazomethane was added carefully. When the yellow colour persisted, the mixture was left at room temperature for 2 min. The solvent was removed *in vacuo*, affording the crude ester (19a) (47 mg). T.l.c. gave material identical (t.l.c., i.r.) with an authentic sample.

We thank Professor Ph. E. Eaton, University of Chicago, for providing u.v. and n.m.r. data for the allene–cyclopentenone photoadducts. We also thank Professor W. Klyne and Dr. P. M. Scopes, University of London, for the c.d. curves, and Mr. E. Díaz, Instituto de Química (U.N.A.M.) and Dr. L. Tökés, Syntex Research, Palo Alto, for several n.m.r. and mass spectra. We express our gratitude to Dr. O. Halpern, Syntex Research, Palo Alto, for a supply of extracts of gorgonians and for informing us of his findings about the (15*S*)-configuration of prostaglandin A_2 isolated from marine corals. G. A. G. and C. R. are grateful to the U.N.A.M. for predoctoral fellowships.

[2/2050 *Received*, 30*th August*, 1972]