Total Syntheses of Prostanoids

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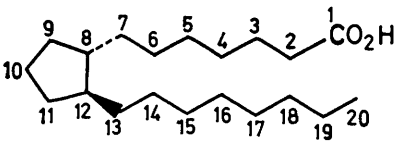
1 Introduction

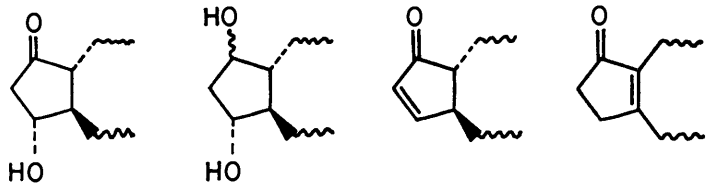
'Prostanoids' is a recently introduced[1] term used to designate the family of natural prostaglandins and prostaglandin-like compounds (*cf.* 'steroids'). The prostaglandins have been known for about forty years, but not until 1962 was the structure of prostaglandin E_1 announced by Bergström and co-workers.[2] Since then at least fourteen more have been isolated from various sources. Few other biologically potent, naturally occurring substances have such diverse biological effects, and it is reasonably certain that some clinical use will be found for at least one member or a synthetic analogue. The need for adequate amounts of the materials has led to several total syntheses of these substances and it is with this aspect that the review is concerned. Literature to April, 1972 is included. For other aspects the reader is referred to a recent review by Horton[3] as well as to an earlier chemical review.[4]

2 Nomenclature and Structures

The structures of the prostaglandins (PG's) are derivable from prostanoic acid (1). They occur in four series, designated by the letters *E*, *F*, *A*, and *B* [partial structures (2)—(5)], depending on the substitution within the ring.



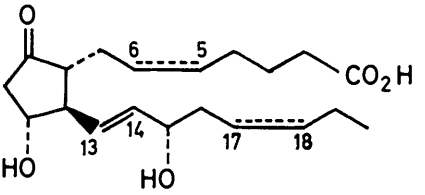
(1)



E Series (2) *F* Series (3) *A* Series (4) *B* Series (5)

[1] E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Amer. Chem. Soc.*, 1971, **93**, 4326
[2] S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *Acta Chem. Scand.*, 1962, **16**, 501
[3] E. W. Horton, 'Prostaglandins', Vol. 7 of Monographs on Endocrinology, Springer Berlin, 1972.
[4] J. E. Pike, *Fortsch. Chem. Org. Naturstoffe*, 1970, **28**, 313.

As well as a 15-hydroxy-group, up to three double bonds may be present in the side-chains. Thus E_1, E_2, and E_3 have one, two, and three double bonds respectively in the positions and with the configurations shown in (6)—(8).



(6) PGE_1, no 5,6-or 17,18-double bond

(7) PGE_2, 5,6-*cis*, no 17,18-double bond

(8) PGE_3, 5,6-*cis*, 17,18-*cis*-double bond

The 13,14-double bond is *trans*

In the *F* series the 9-hydroxy-group can be either α, and hence *cis* to the C-8 side-chain, or β, when it is *trans*. Only the former occurs naturally. Prostaglandins with a 19α-hydroxy-group also occur naturally. Structure (6) shows the absolute stereochemistry of PGE_1 as determined by *X*-ray analysis. PGE_1 is therefore (−)-11α,15(*S*)-dihydroxy-9-oxo-13-*trans*-prostenoic acid. The six prostaglandins of the *E* and *F* series are termed the primary prostaglandins.

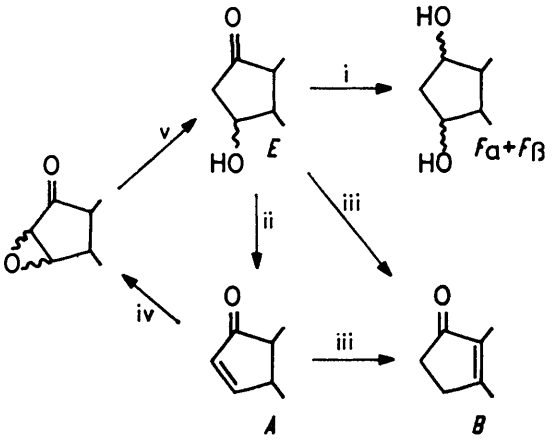
3 Chemical Syntheses

The salient features of PGE_1 (6) are the four chiral centres, the β-ketol function in the five-membered ring, the all-*trans* arrangement of the three ring substituents, and the allylic alcohol group at C-15. The additional *cis*-double bonds and the configuration of the 9-hydroxy-group in the *F* series add further problems to the design of a general synthesis. Furthermore, prostaglandins of the *E* and *A* series both give rise to *B*-prostaglandins under basic conditions, whereas under acidic conditions *E*-prostaglandins dehydrate to *A*-prostaglandins. Final steps in any synthesis must therefore be conducted under mild conditions.

Earlier reductions of the 9-keto function of the *E* series yielded a separable mixture of the *F*α and the biologically less active *F*β-prostaglandins. However, more sophisticated reducing agents furnish the desired *F*α compounds exclusively[5] so that a synthesis of the *E*-prostaglandins becomes a more general one. A conversion of a PGA_2 derivative into a mixture of PGE_2 and its 11β-epimer

[5] E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 7319.

by an epoxidation and reduction sequence has also been reported.[6] These interconversions are shown in a general form in Scheme 1.



Reagents: i, $LiBHR_3$ (for R see ref. 5); ii, H_2O—AcOH or HCl-H_2O-THF; iii, KOH—MeOH; iv, H_2O_2—KOH—MeOH; v, Cr^{2+}

Scheme 1

Commercially it would be desirable for a synthesis to be as adaptable as possible and ideally to provide in high yield all the resolved primary prostaglandins and desirable analogues from a single intermediate. So far only the latest Harvard synthesis is likely to meet all these requirements.

In this review prostanoid syntheses have been divided into those in which the cyclopentane ring is formed from precursors which incorporate at least one of the carbon side-chains and those where both side-chains are elaborated from initially 'simple' cyclopentane derivatives. The object of the review is not to be comprehensive but to illustrate the diversity of the schemes and to suggest which are of commercial importance.

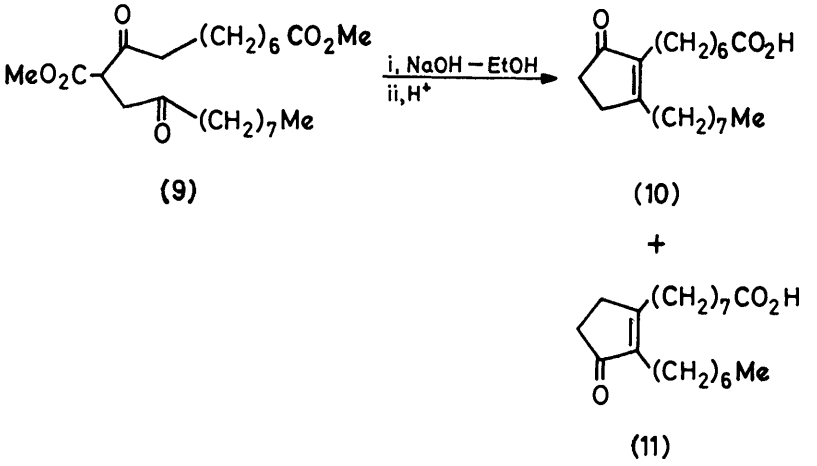
4 Prostanoids from Single-chain Precursors

It is convenient to subdivide this section according to which carbon–carbon bond of the ring is formed.

A. C-8—C-12 Bond Formation.—Historically this section includes the first synthesis of a prostanoid by Samuelsson and Ställberg.[7] Base-catalysed cycliza-

[6] G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Amer. Chem. Soc.*, 1972, **94**, 2123.
[7] B. Samuelsson and G. Ställberg, *Acta Chem. Scand.*, 1963, **17**, 810.

tion of (9), followed by ester hydrolysis and decarboxylation, afforded 15-deoxy-13,14-dihydro-PGB_1 (10) and an isomer (11) arising from an alternative mode of cyclization. These isomers were critically compared with a degradation product of natural PGE_1, the results supporting the earlier proposed structure (6).



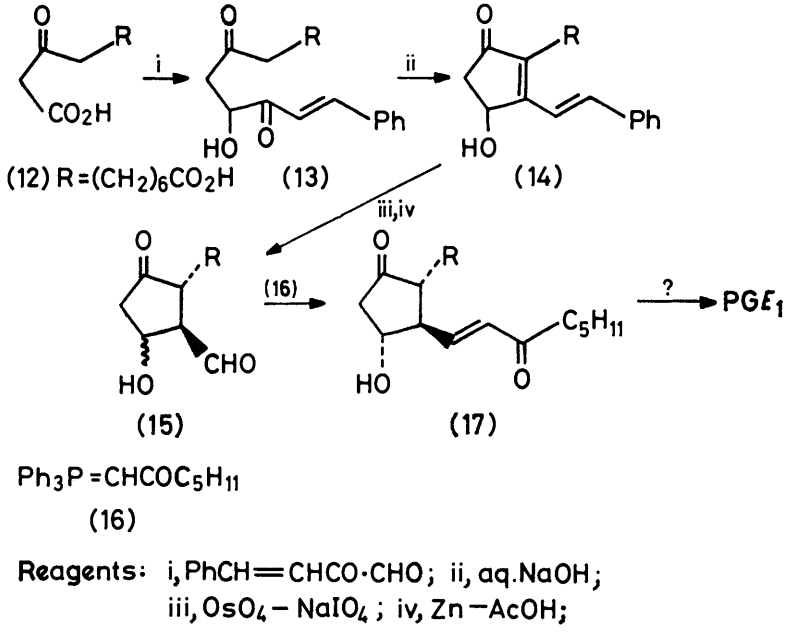
(9) (10) + (11)

Miyano and Dorn[8] effected a similar cyclization of (13), available from a condensation of styrylglyoxal and the diacid (12). The product (14) on hydroxylation and cleavage of the side-chain and reduction of the ring double bond afforded the aldehyde (15). This underwent a Wittig condensation with the phosphorane (16) to furnish 15-dehydro-PGE_1 (17), together with the 11β-epimer and small amounts of dehydration products, all separable by chromatography (Scheme 2). Although the selective reduction of the 15-oxo-group in (17) remained to be solved, and recent work[9] suggests that this may be possible microbiologically, the small number of steps and good yields make the synthesis otherwise attractive.

Syntheses of PGB_1 are presently of less commercial interest because it has low biological activity and it has not yet been converted into the primary prostaglandins. A total synthesis was achieved by three groups[10–12] utilizing the diketone (19). The latter was prepared either by selective reduction[10,11] of (18), available from a condensation of 9-oxo-decanoic acid and oxalate, or by cyclization[12] of (20) (Scheme 3). Reaction of the corresponding enol ether (21) with the acetylenic Grignard reagent (22), followed by acidic work-up, afforded (23) as a mixture of C-15-epimers. Partial reduction of the latter gave (±)-PGB_1 or

[8] M. Miyano and C. R. Dorn, *Tetrahedron Letters*, 1969, 1615.
[9] M. Miyano, C. R. Dorn, F. B. Colton, and W. J. Marsheck, *Chem. Comm.*, 1971, 425.
[10] P. Collins, C. J. Jung, and R. Pappo, *Israel J. Chem.*, 1968, **6**, 839.
[11] J. Katsube and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1969, **33**, 1078.
[12] Y. Yura and J. Ide, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 408.

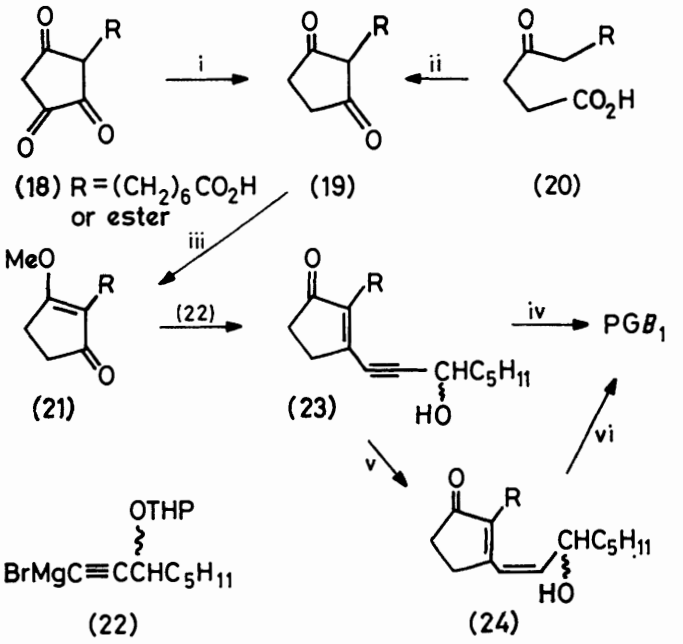
the *cis*-isomer (24), which was isomerized to PGB_1 by dilute alkali. Use of optically active (22) has also afforded natural PGB_1.[13]



Scheme 2

B. C-11—C-12 Bond Formation.—Two general syntheses by Corey and co-workers were characteristically outstanding in that pure crystalline prostaglandins of the *E* and *F* series were obtained for the first time and, in the case of PGE_1, a resolution step provided both enantiomeric forms. In addition, completely new chemistry of general applicability was devised. The important synthetic concepts of these elegant syntheses were: (i) the use of the 9-nitro-group as a precursor of the 9-keto function, into which it was transformed under mild conditions; (ii) the successful use of the tetrahydropyranyl (THP) protecting group which suggested that the *E* series might be obtainable from 11,15-bis-THP-prostaglandin *F* derivatives, an important concept of the Harvard bicyclic route; and (iii) the use of aldol cyclizations at a late stage of the synthesis, leading directly to the C-11—C-15 ene-diol unit or its equivalent.

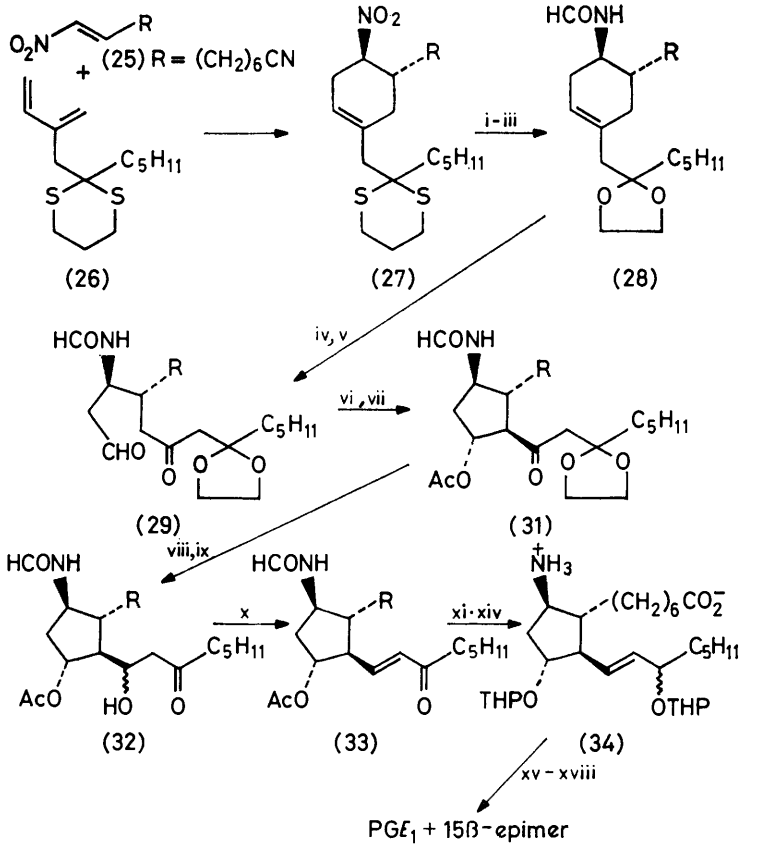
[13] R. Pappo, P. Collins, and C. J. Jung, *Ann. New York Acad. Sci.*, 1971, **180**, 64.



Scheme 3

In the first of these syntheses,[14] the key intermediate (29) was constructed by a six-stage process commencing with the Diels–Alder addition of (25) and (26), which gave the adduct (27) as the major product. The latter was modified to (28) (Scheme 4), the cyclohexene ring oxidatively cleaved, and the product (29) cyclized using the base (30). Acetylation of the product furnished (31) along with small amounts of the 11β-epimer. Reduction of the ketone function and ketal hydrolysis gave (32), which was dehydrated to (33) under neutral conditions by a new and useful reaction with dicyclohexylcarbodi-imide, catalysed by cupric chloride. On reduction, the enone (33) yielded both C-15-epimeric alcohols, which were further transformed, *via* (34), to racemic PGE_1 and its C-15-epimer. After separation PGE_1 was converted into $PGF_{1\alpha}$, $PGF_{1\beta}$, PGA_1, and PGB_1 by reactions shown in Scheme 1.

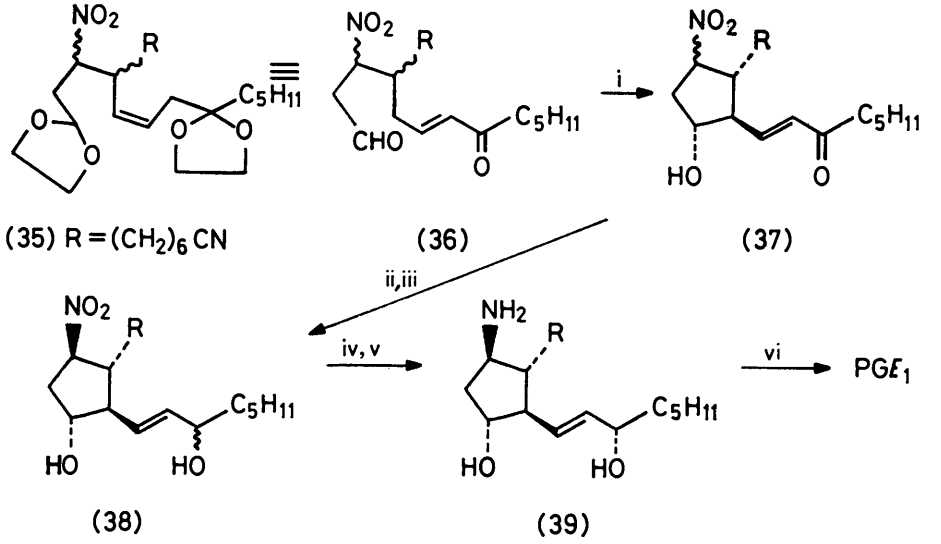
[14] E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, 1968, **90**, 3245.



Reagents: i, Al–Hg ($NO_2 \rightarrow NH_2$); ii, HCO_2Ac ($NH_2 \rightarrow HCONH$);
iii,  , Hg^{2+} (ketal exchange); iv, OsO_4; v, $Pb(OAc)_4$;
vi,  (30); vii, Ac_2O; viii, $NaBH_4$; ix, H^+;
x, $C_6H_{11}NCNC_6H_{11}$–$CuCl_2$; xi, $ZnBH_4$; xii, KOH (OAc → OH);
xiii,  (OH → OTHP); xiv, KOH (CN → CO_2H and HCONH → NH_2);
xv, NBS ($NH_2 \rightarrow NHBr$); xvi, OH^- (-HBr);
xvii, H^+ ( )NH →)O and OTHP → OH); xviii, chromatography

Scheme 4

In a second synthesis[15] stannic chloride-catalysed cyclization of (35), which reacted as the aldehyde (36), led to the enone (37), essentially free of the 11β-epimer (Scheme 5). Other acidic catalysts gave both C-11-epimers. Following



Reagents: i, $SnCl_4$; ii, $ZnBH_4$; iii, base; iv, chromatography; v, Al – Hg; vi, HCO_2Ac, then xiii – xvii of Scheme 4

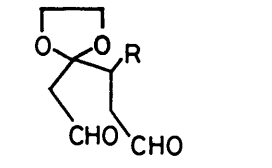
Scheme 5

reduction of the ketone function in (37) with zinc borohydride, mild base treatment of the products placed the nitro-group and C-8 side-chains in the more stable *trans*-orientation, enabling the C-15-epimers (38) to be separated by chromatography. The synthesis of PGE_1 was completed essentially as before, but in addition the amine (39) was resolved and each enantiomer reacted separately. The natural forms of the prostaglandins were thereby obtained for the first time. The later bicyclic route was the result of the need for a general synthesis, particularly of the higher prostaglandins (PGE_2, PGE_3 *etc.*), to which the above routes were not easily adaptable.

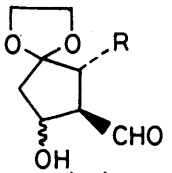
Several potential PGE_1 syntheses were described by Morin and co-workers.[16] Thus it was envisaged that dialdehyde (40), which had been obtained from

[15] E. J. Corey, I. Vlattas, and K. Harding, *J. Amer. Chem. Soc.*, 1969, **91**, 535.
[16] R. B. Morin, D. O. Spry, K. L. Hauser, and R. A. Mueller, *Tetrahedron Letters*, 1968, 6023.

aromatic precursors, might undergo intramolecular aldol cyclization to furnish (41). In the event no aldols were isolable. Moreover, the alternative mode of cyclization was preferred, so that at best a separable mixture of (42) and (43) was produced. Further reactions of (42) afforded PGB_1, but added difficulties were encountered in removing the protecting ketal group, and only low yields were obtained.



(40) R = $(CH_2)_6CO_2Me$



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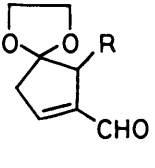
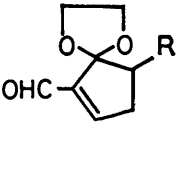
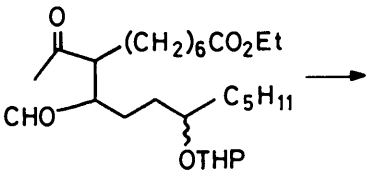


(42)

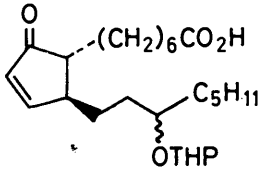


(43)

C. **C-10—C-11 Bond Formation.**—Strike and Smith[17] synthesized a stereoisomeric mixture (47), containing 13,14-dihydro-PGE_1, providing the only example in this section. Thus cyclization of the aldehyde (44) furnished the enone (45), which was epoxidized and hydrogenated to (46). Mild acid treatment gave (47).



(44)



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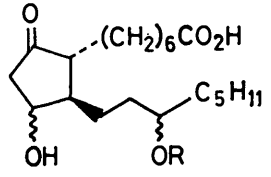
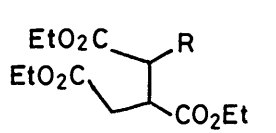


(46) R = THP
(47) R = H

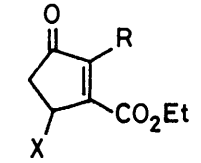
D. **C-9—C-10 Bond Formation.**—A route to PGE_1 methoxime by Finch and Fitt[18] will be only briefly discussed. Dieckmann cyclization of the tetraester (48) followed by five more steps afforded the enone (49). Introduction of the 11-hydroxy-group was achieved by allylic bromination to (50), treatment with silver acetate to (51), and methanolysis to (52). Following silylation, which gave (53), hydrogenation afforded the all-*cis* derivative (54), arising from *cis*-addition of hydrogen to the face opposite the bulky silyloxy-group. After protecting the 9-keto-group with methoxyamine and subsequent base treatment to place the side-chains in the more stable *trans*-orientation, eight further steps furnished PGE_1 methoxime. The protecting group was not successfully removed.

E. **C-8—C-9 Bond Formation.**—No examples in this section have appeared.

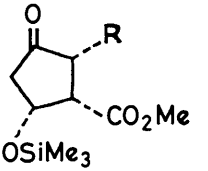
[17] D. P. Strike and H. Smith, *Tetrahedron Letters*, 1970, 4393.
[18] N. Finch and J. J. Fitt, *Tetrahedron Letters*, 1969, 4639.



(48) R = $(CH_2)_6CO_2H$ or ester



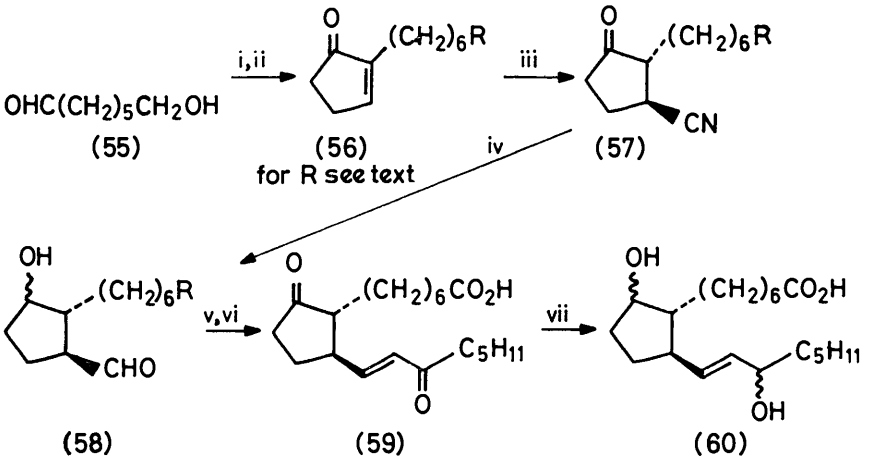
(49) X = H
(50) X = Br
(51) X = OAc
(52) X = OH
(53) X = $OSiMe_3$



(54)

5 Prostanoids from 'Simple' Cyclopentanes

A. Monocyclic Cyclopentanes.—The 11-deoxy-*E* and -*F* prostaglandins are currently of interest as possible substrates for microbiological oxidation at C-11 as well as for their intrinsic biological properties. A recent synthesis by Caton



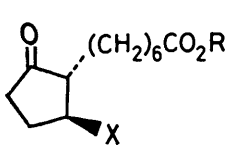
Reagents: i, cyclopentanone enamine; ii, HCl – BuOH; iii, $Me_2C(OH)CN - Na_2CO_3$; iv, Bu^i_2AlH; v, phosphorane (16); vi, CrO_3-H^+; vii, $NaBH_4$

Scheme 6

and co-workers[19] illustrates a relatively simple route to them (Scheme 6). The condensation product of cyclopentanone and the aldehyde (55) was dehydrated by acid to the enone (56; R = CH_2OH). Reaction of the latter with cyanide ion, provided by acetone cyanhydrin, afforded the nitrile (57; R = CH_2OH). The alkaline conditions of the reaction favour the formation of the more stable *trans*-isomer. Di-isobutylaluminium hydride reduced both the keto and nitrile functions of (57), and the product (58), after Wittig condensation, was oxidized at both alcohol groups and finally reduced to give a mixture (60), containing 11-deoxy-PG$F_{1\alpha}$.

The corresponding PG$F_{1\beta}$ derivative had been prepared earlier by Bagli and Bogri[20] using (56; R = CO_2H), which had been synthesized from 2-ethoxycarbonylcyclopentanone. Thus diacid (61; R = H), obtained by hydrolysis of the corresponding nitrile (57; R = CO_2H), was selectively esterified to the half-ester (61; R = Me). The elaboration of the C-12 side-chain was then achieved as follows: the acid chloride of (61; R = Me) reacted with hept-1-yne in the presence of aluminium chloride to provide (62); methanolic sodium hydroxide afforded the enol ether (63; R = Me), and hydrolysis, the acid (63; R = H); reduction of the latter by sodium borohydride followed by acid treatment led to the isolation of the enone (64); the configuration of the 9-hydroxy-group was established by other evidence; finally, a second borohydride reduction gave 11-deoxy-PG$F_{1\beta}$ (65) and its 15β-epimer.

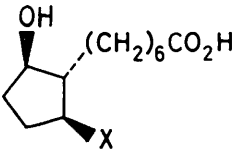
The enone (56; R = CO_2H) was also utilized in two similar syntheses of PGB_1 by Hardegger and co-workers,[21] and by Klok and associates.[22]



(61) X = CO_2H

(62) X = $CO{\cdot}CH{=}C(Cl)C_5H_{11}$; R = Me

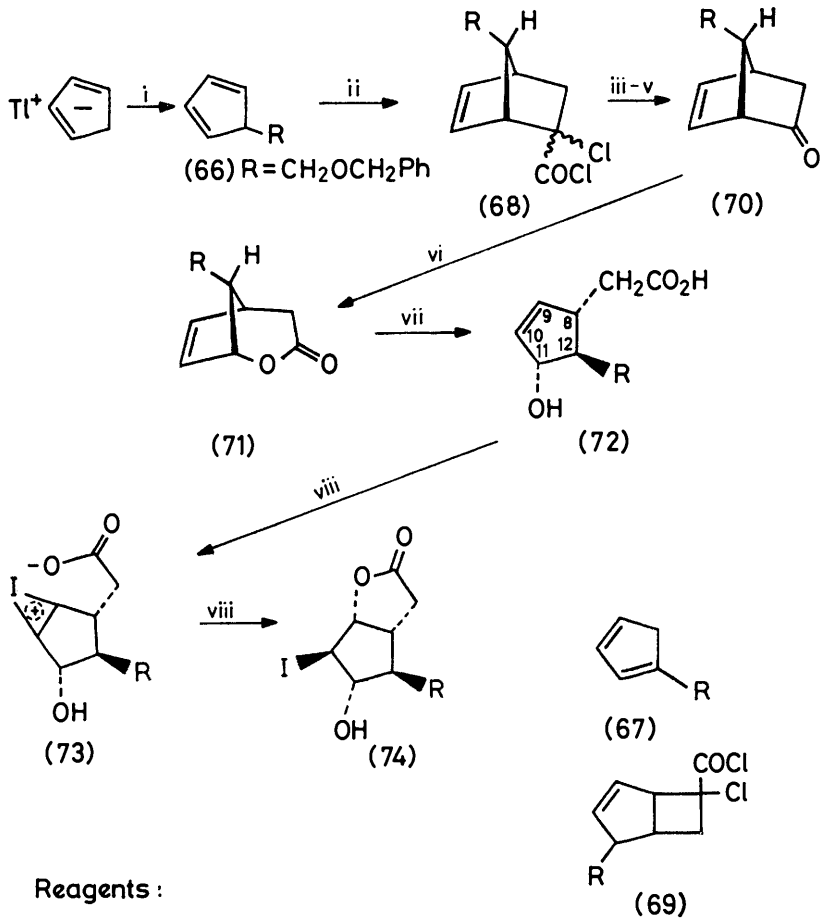
(63) X = $CO{\cdot}CH{=}C(OMe)C_5H_{11}$



(64) X = $CH{=}CHCOC_5H_{11}$

(65) X = $CH{=}CHCHC_5H_{11}$ (OH)

[19] M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *Tetrahedron Letters*, 1972, 773.
[20] J. F. Bagli and T. Bogri, *Tetrahedron Letters*, 1967, 5.
[21] E. Hardegger, H. P. Schenk, and E. Broger, *Helv. Chim. Acta*, 1967, **50**, 2501.
[22] R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Rec. Trav. chim.*, 1968, **87**, 813, and for extension to E_1 series: *ibid.*, 1970, **89**, 1043.



Scheme 7

B. Bicyclic Cyclopentanes.—This section includes three syntheses[23–25] using bicyclic intermediates. The Harvard synthesis[23] has provided intermediates from

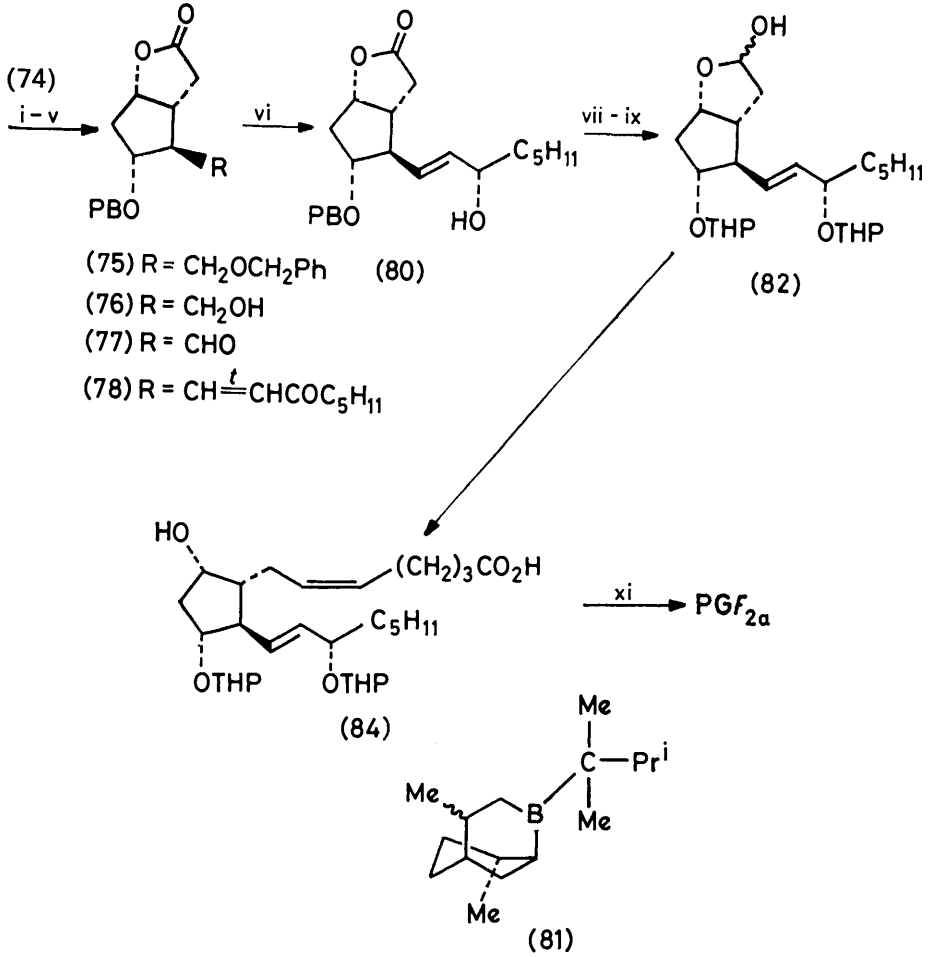
[23] See references 26—30 inclusive.
[24] H. L. Slates, Z. S. Zelawski, D. Taub, and N. L. Wendler, *J.C.S. Chem. Comm.*, 1972, 304.
[25] U. Axen, J. L. Thompson, and J. E. Pike, *Chem. Comm.*, 1970, 602, and earlier references cited.

which all the primary prostaglandins in resolved form have been obtained. Prostaglandin E_1 is produced in twenty-one steps from cyclopentadiene, and yields are now such that the prostaglandins could soon be available on a substantial scale. Of the other two schemes, the one by Slates and co-workers[24] affords natural PGE_1 in twenty-nine steps from penta-1,3-diene, but yields, although probably not yet optimum, are less good. The Upjohn synthesis,[25] which has been discussed in the review by Pike,[4] has also led to most of the primary prostaglandins and their isomers. It has the advantage of being short, PGE_1 being produced in thirteen steps from norbornadiene. However, it suffers from poor yields at several stages. Only the Harvard scheme will be discussed in detail.

One important intermediate in Corey's route is the bicyclic iodolactone (74), the preferred synthesis[26] of which is shown in Scheme 7. The average yield per step is 85%. Because the alkylcyclopentadiene (66) is prone to isomerization to (67), it was found essential to carry out the alkylation and Diels–Alder reactions well below 0 °C and with as short an isolation time as possible. For large-scale operations the route shown had definite advantages over an earlier process.[27] The reaction of (66) with the dienophile led to (68), where the benzyloxymethyl substituent is exclusively *anti* to the carbon bearing the chloro and chloroformyl groups. In particular, no *syn* or 2+2 addition products [*e.g.* (69)] were formed. Replacement of the two groups by oxygen was achieved as shown without isolation of intermediates. The oxidation of the product (70) afforded (71) exclusively, no epoxide or isomeric lactone being produced. The hydrolysis product (72) was purified as an ammonium salt and resolved[28] if required. Thus the (+)-salt formed with (+)-amphetamine provided the natural prostaglandins, whereas the enantiomeric series would be obtained from the corresponding (−)-salt. It is apparent from the numbering in (72) that the carboxymethyl group ultimately provides the C-8-substituent and the benzyloxymethyl group the C-12-substituent. Reaction of (72) with potassium tri-iodide in aqueous bicarbonate introduced the 9α-hydroxy-group at (74) *via* the intermediate (73). The iodolactone therefore contained the desired stereochemistry at all the nuclear centres. Its conversion into the various prostaglandins will now be described.

PG$F_{2\alpha}$.[28] Acylation of (74) and deiodination provided (75), which was transformed into (78) by the sequence: catalytic hydrogenation to (76), oxidation with chromic oxide–pyridine complex to the aldehyde (77), and Wittig condensation with phosphonate (79) (Scheme 8). In this sequence the *p*-phenylbenzoyl (PB) group was chosen over simple acetyl since it allowed for easier crystallization and chromatographic separation of the subsequent reduction product (80) from its 15β-epimer. This reduction of (78) was extensively studied. Zinc borohydride produced a 1 : 1 mixture of the epimers. Other reducing agents yielded lesser

[26] See ref. 1 and ref. 28.
[27] E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, 1971, **93**, 1489, and cited references to earlier work.
[28] E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491.



$Na^{+}(MeO)_2P(=O)\bar{C}HCOC_5H_{11}$ (79)

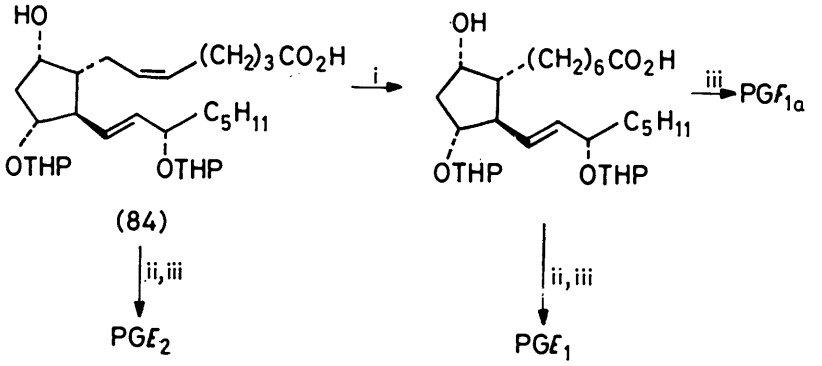
$Ph_3P=CH(CH_2)_3CO_2Na$ (83)

Reagents: i, *p*-$C_6H_5C_6H_4COCl$; ii, Bu^{n}_3SnH; iii, H_2–Pd/C–H^+; iv, CrO_3–py; v, (79); vi, (81)–$Bu^{t}Li$–$OP(NMe_2)_3$–THF; vii, K_2CO_3; viii,  ; ix, Bu^{i}_2AlH; x, (83); xi, H^+

Scheme 8

amounts of (80) and products arising from a 1,4-reduction of the enone system. However, of several optically active borohydride ions ($Li^+{-}BR_3H$), the reagent derived from the borane (81) and t-butyl-lithium in hexamethylphosphoramide–tetrahydrofuran at $-120\,°C$, was shown to reduce (78) to (80) and the 15β-epimer in the ratio 4.5 : 1. Commercially it may be more convenient to effect this reaction with less sophisticated reagents since, following separation, the unwanted epimer can be reoxidized to (78) for recycling. An alternative approach to the stereoselective introduction of the 15-hydroxy-group is described later. The ester group of (80) was next hydrolysed and the two hydroxy-groups of the product reprotected as THP-ethers. Reduction to the lactol (82) and Wittig condensation with phosphorane (83) provided (84) with the desired 5,6-*cis*-double bond. Mild hydrolysis furnished PG$F_{2\alpha}$.

PG$F_{1\alpha}$, PGE_2, PGE_1. Scheme 9 shows how intermediate (84) was further

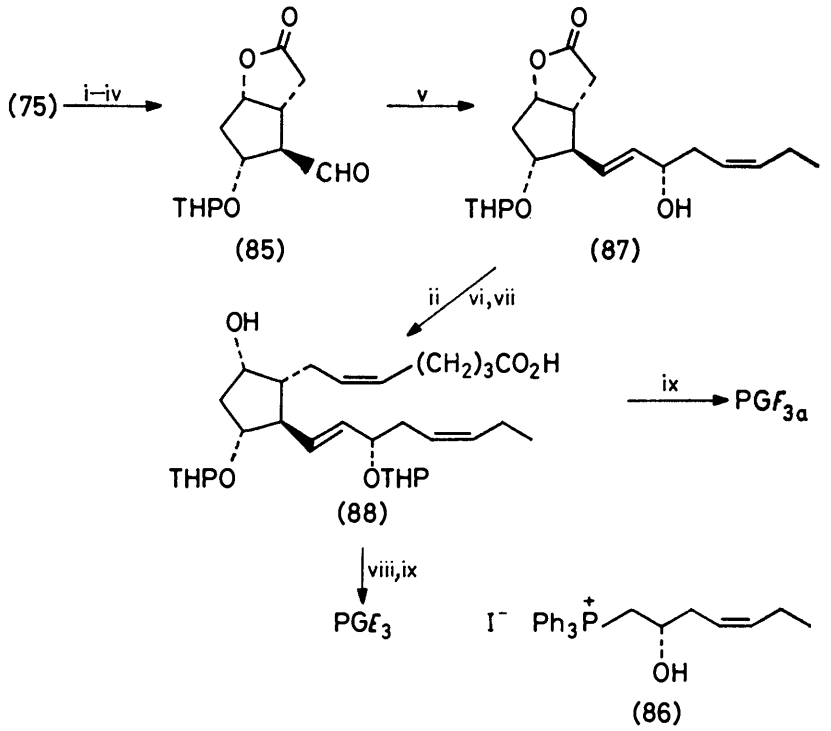


Scheme 9

transformed.[29] The selective reduction of the 5,6-double bond depended on the screening of the 13,14-double bond by the two tetrahydropyranyloxy-groups. More recent work[5] has shown that the dimethylisopropylsilyloxy-group is even more effective in this respect.

PG$F_{3\alpha}$, PGE_3. The desired C-12 side-chain of these prostaglandins was introduced stereospecifically[30] by condensation of optically active aldehyde (85) with the ylide derived from the phosphonium salt (86) (Scheme 10). The latter had been

[29] E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, 1970, **92**, 2586.
[30] E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, 1971, **93**, 1490.

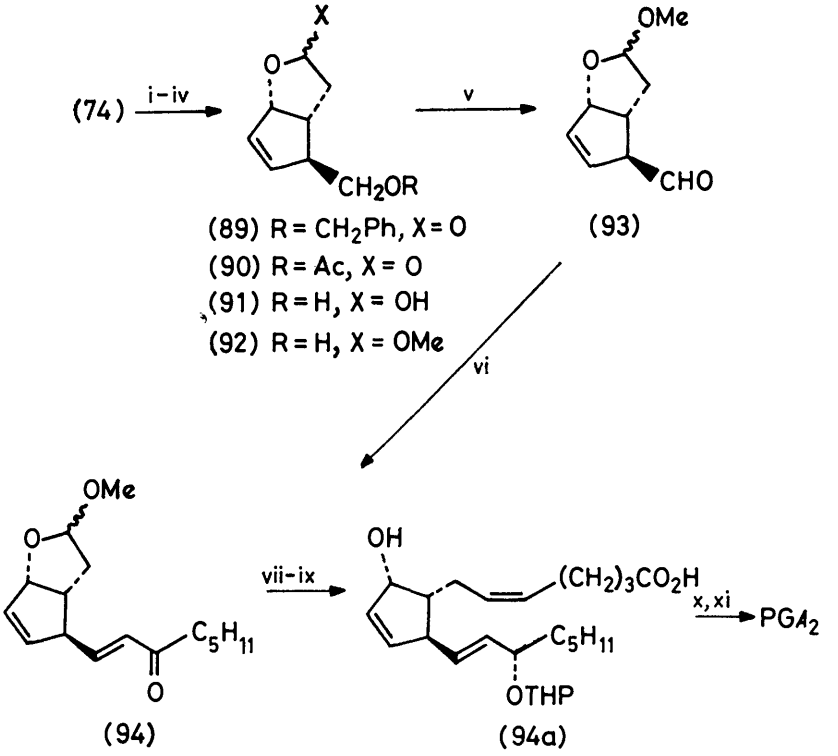


Scheme 10

prepared from *S*-(−)-malic acid. The product (87) was transformed as before to a bis-THP derivative (88) and thence to natural $PGF_{3\alpha}$ and PGE_3.

PGA_2. A novel elimination reaction of the iodolactone (74) provided the basis of a high-yielding synthesis[31] of the PG*A* intermediate (94) (Scheme 11). Although the *A* series is available from the *E* series (Scheme 1), this attractive synthesis is of considerable interest. The elimination to (89) was followed by a one-step ether-cleavage and esterification to (90), ester and lactone reduction to (91), methyl acetal formation to (92), and transformation of the latter to (93) and (94) as before. Further reactions of (94) were not described, but a conversion into (94a) would be envisaged, followed by oxidation and hydrolysis to PGA_2.

[31] E. J. Corey and P. A. Grieco, *Tetrahedron Letters*, 1972, 107.



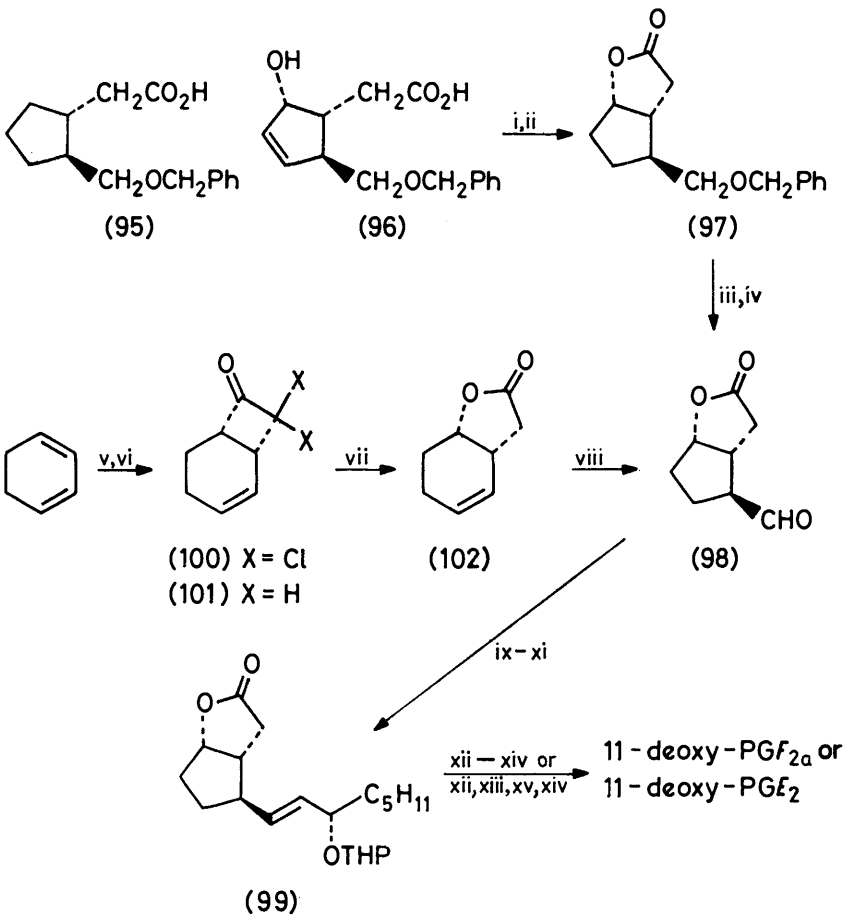
Reagents:

i, $MeSO_2Cl$; ii, Ac_2O-BF_3; iii, Bu^i_2AlH; iv, BF_3-MeOH;
v, CrO_3-py; vi, (79); vii, $ZnBH_4$; viii,  ; ix, (83); x, CrO_3; xi, H^+

Scheme 11

Other Prostanoids. Reference has already been made to the importance of the 11-deoxy-prostaglandins. An efficient route to them was developed by Crabbé and Guzmán[32] using racemic (89). Direct reduction of the double bond in (89) with Raney Nickel produced (95), through simultaneous hydrogenolysis of the allylic oxygen[33] (Scheme 12). However, the corresponding hydroxy-acid (96), after reduction and re-lactonization, furnished the desired lactone (97). The

[32] P. Crabbé and A. Guzmán, *Tetrahedron Letters*, 1972, 115.
[33] (95) was subsequently transformed to a 9,11-bisdeoxyprostaglandin (ref. 34).
[34] P. Crabbé, A. Cervantes, and A. Guzmán, *Tetrahedron Letters*, 1972, 1123.

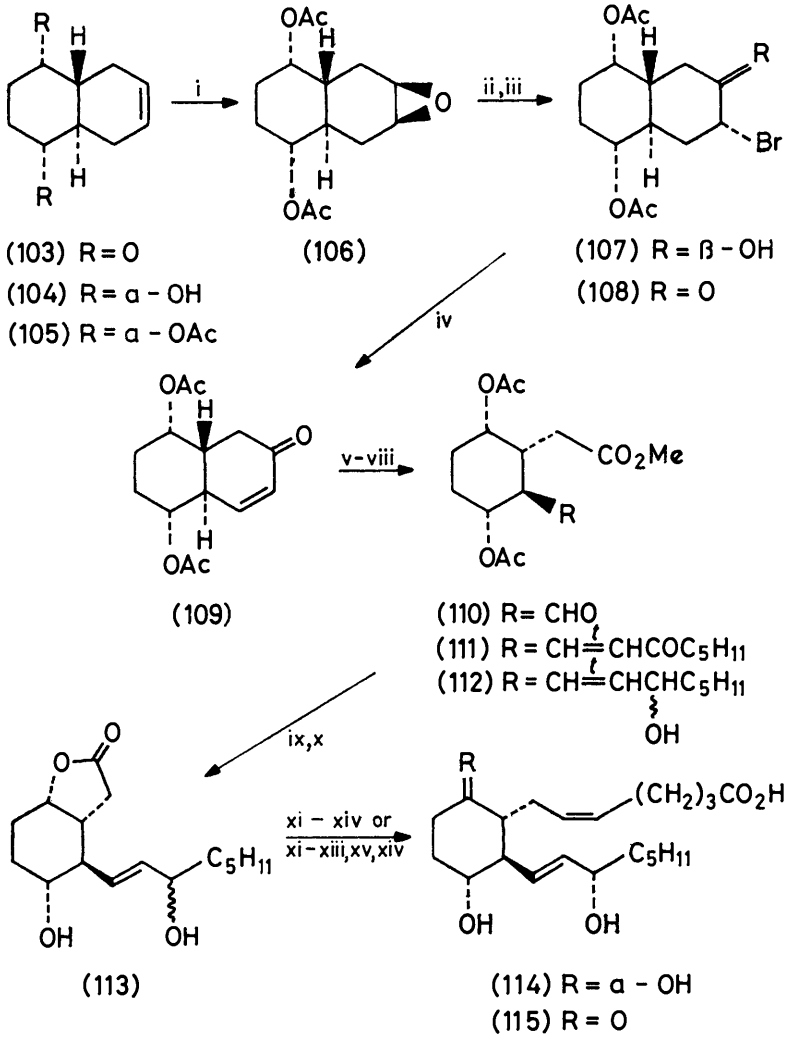


Reagents: i, Raney Ni; ii, H^+; iii, H_2–Pd/C–H^+; iv, CrO_3–py; v, $Cl_2CHCOCl$–Et_3N; vi, Zn–AcOH; vii, H_2O_2–OH^-; viii, $Tl(NO_3)_3$–H^+; ix, (79); x, $ZnBH_4$; xi, ; xii, Bu^i_2AlH; xiii, (83); xiv, H^+; xv, CrO_3

Scheme 12

synthesis was completed along now familiar lines as shown, *e.g.* (97) → (98) → (99) → 11-deoxy-PGE_2 or -PG$F_{2\alpha}$.

However, this route had probably already been superseded by a novel and



Reagents: i, On(105): *m*-*Cl*·$C_6H_4CO_3H$; ii, HBr; iii, oxidize; iv, $CaCO_3$; v, OsO_4; vi, $Pb(OAc)_4$; vii, (79); viii, $ZnBH_4$; ix, KOH; x, HCl – MeOH; xi,  ; xii, Bu^i_2AlH; xiii, (83); xiv, H^+; xv, CrO_3

Scheme 13

simple synthesis by the Harvard group,[35] who obtained (98) in four steps from cyclohexadiene with an average yield of >85%. Thus the adduct (100) from the diene and dichlorketen was dechlorinated to (101) (Scheme 12). Careful oxidation provided the desired lactone (102), which underwent oxidative ring-contraction with thallium trinitrate to furnish (98).

The later stages of the Harvard syntheses of PG$F_{2\alpha}$ and PGE_2 were also used by Crossley[36] to prepare the cyclohexane analogues (114) and (115) (Scheme 13). Thus the dione (103), available from a Diels–Alder addition of *p*-benzoquinone and butadiene, was reduced with sodium borohydride, and the isolated *cis*-diol (104) was acetylated to (105) and epoxidized. After removing the α-epoxide, the β-isomer (106) was treated with hydrogen bromide to give the bromohydrin (107), oxidized to the bromoketone (108), and dehydrobrominated to (109). Hydroxylation and cleavage of the double bond furnished the aldehyde (110), which underwent Wittig condensation to the enone (111). The latter was reduced to the diols (112), the three ester groups hydrolysed, and the product lactonized to (113). The remaining steps closely followed the Harvard syntheses and furnished the analogues (114) and (115) and their C-15-epimers.[37]

An unexpected source of the prostaglandins, which might compete with the syntheses discussed, is the coral *Plexaura homomalla*, which has been shown to contain PGA_2 and its C-15-epimer;[38] these have been converted into PGE_2 and PG$F_{2\alpha}$.[6]

Note added in proof: The rapid developments in prostanoid chemistry since April 1972 have seen the following innovations.

1. Conversion of PG*F*'s into PG*E*'s (E. W. Yankee, C. H. Lin, and J. Fried, *J.C.S. Chem. Comm.*, 1972, 1120).
2. Further stereoselective syntheses based on bicyclic intermediates (G. Jones, K. A. Raphael, and S. Wright, *J.C.S. Chem. Comm.*, 1972, 609; and D. Brewster, M. Myers, J. Ormerod, M. E. Spinner, S. Turner, and A. C. B. Smith, *ibid*, p. 1235).
3. Synthesis from (82), (74), and (96), respectively, of novel prostanoids containing:
   (i) a propadiene group at C-4,5 (P. Crabbé and H. Carpio, *J.C.S. Chem. Comm.*, 1972, 904).
   (ii) a 10α-hydroxy-group (P. Crabbé, A. Guzmán, and E. Velarde, *J.C.S. Chem. Comm.*, 1972, 1126).
   (iii) photoadducts at C-10,11 (P. Crabbé, G. A. Garcia, and C. Riùs, *Tetrahedron Letters*, 1972, 2951).

The author thanks colleagues at the Beecham and Wellcome Research Laboratories for helpful discussions.

[35] E. J. Corey and T. Ravindranathan, *Tetrahedron Letters*, 1971, 4753.
[36] N. S. Crossley, *Tetrahedron Letters*, 1971, 3327.
[37] Other true analogues include the 7-oxo-PG's. For these and others see: J. Fried, C. Lin, M. Mehra, K. Kao, and P. Dalven, *Ann. New York Acad. Sci.*, 1971, **180**, 38.
[38] W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, 1972, **94**, 2122.