Prostaglandin Synthesis: Design and Execution

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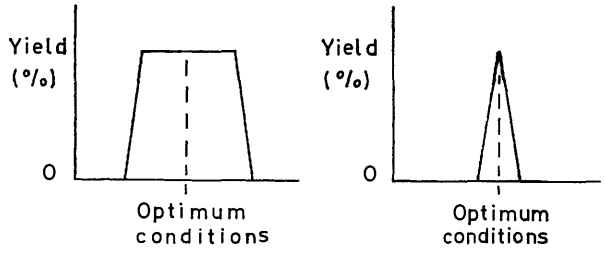
Application of the principles of synthesis design to the problem of prostaglandins led to many possible routes, including one commencing with *endo*-dicyclopentadiene. This starting material was then converted into racemic prostaglandin $F_{2\alpha}$ in a minimum of ten stages *via* bicyclo[3.3.0]octane intermediates.

PROSTAGLANDINS are a meeting place for many disciplines.[1] To the chemist they have represented a formidable synthetic challenge [2] partially motivated by the importance of these substances in biological systems and partially motivated by their poor availability from natural sources.[3] The probable commercial role of prostaglandins has also added momentum to the search for a good supply. In undertaking synthesis in the commercial environment there can frequently be factors quite different from those which are important in a university. The principles of synthesis design [4] must then undergo some modification and extension. For example, yield is an important yardstick for judging the merit of an academic synthesis, but in industry an expensive process A giving 80% yield may have to be abandoned in favour of the much cheaper process B giving only 50% yield. And whereas brevity in synthesis is the ideal, a longer process may have to be operated industrially because only the longer process will work on the large scale. Indeed largeness of scale imposes its own constraints, very often mechanical in nature; if a research synthesis depends on preparative g.l.c. for separation of a desired product it will almost certainly be useless at the ton level. Hence it is desirable that reactions should yield crude products suitable for the next process, or products which are relatively easy to purify, by direct crystallisation for instance.

We propose that two extremes of reaction type exist, namely the plateau type (I) and the point type (II). Plainly the conditions of point type reactions (II) are

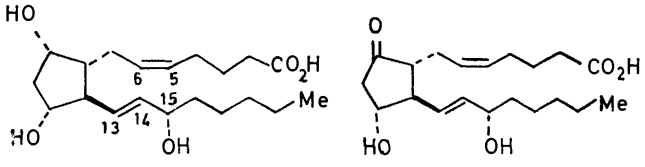


(I) Plateau type (II) Point type

critical, so that even slight deviations in conditions lead to zero yield. Many research operations are of this type, particularly those requiring exclusion of moisture. On the other hand an ideal industrial operation would prefer a plateau type reaction (I) where, if conditions deviate from the norm, the yield is essentially unaffected. This oversimplification has its exceptions; if an industrial operation is to be carried out repetitively over ten years there is considerable scope for optimising point type conditions on the large scale and keeping them under careful automatic control.

In the prostaglandin field it was of interest to attempt to apply these extended principles of synthesis in designing a route which would not only be aesthetically satisfying but also commercially acceptable.

The Target Molecule.—The prostaglandins (PGs) being a class of substances, do not offer a single target. Taking into account the desire of the medicinal chemist to prepare many analogues an even greater diversity of targets is established. Therefore the assumption was made that the synthesis should aim firstly at the natural prostaglandins, but have the in-built option for preparing a wide variety of analogues. Of the natural materials two are pre-eminent, namely $PGF_{2\alpha}$ (III) and PGE_2 (IV).



(III) (IV)

PGE_2 occupies a central position because it, or a close synthetic precursor, can be converted into all the major primary prostaglandins,[5] including $PGF_{2\alpha}$. On the other hand $PGF_{2\alpha}$ could not, at the time of commencing this work, be converted into PGE_2 and therefore represented a cul-de-sac. Nevertheless $PGF_{2\alpha}$ had at that time the most commercial promise and accordingly it became the primary objective. The choice was reinforced by the known comparative stability of $PGF_{2\alpha}$ when compared with the easy dehydration of PGE_2 and related β-hydroxy-ketones. The option to generate PGE_2 *via* a branch of the synthesis, or by discovering a method for the conversion of $F_{2\alpha}$ into E_2 was left as a secondary consideration.[6] Hence, in essence, the aim became a short simple synthesis of $PGF_{2\alpha}$ (III) wherein the assembly of fragments left scope for later variations.

[1] J. W. Hinman, *Ann. Rev. Biochem.*, 1972, **41**, 161; J. R. Weeks, *Ann. Rev. Pharmacol.*, 1972, **12**, 317.

[2] J. E. Pike, *Progr. Chem. Org. Natural Products*, 1970, **28**, 313; E. J. Corey, The Robert A. Welch Foundation Conferences on Chemical Research. XII. Organic Synthesis, Houston, Texas, 1968.

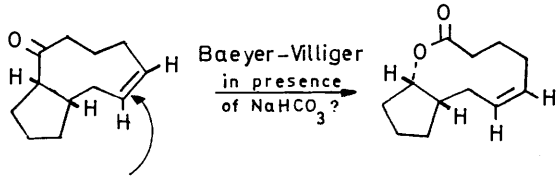
[3] But see W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, 1972, **94**, 2122 and following papers.

[4] E. J. Corey, *Quart. Rev.*, 1971, **25**, 455, and references therein.

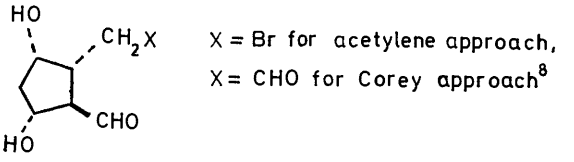
[5] E_2 to $F_{2\alpha}$ and E_2 to E_1, E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 7319. E_2 to A_2, J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, 1969, **34**, 3552.

[6] Subsequently the conversion of $F_{2\alpha}$ into E_2 was achieved, E. W. Yankee, C. H. Lin, and J. Fried, *J.C.S. Chem. Comm.*, 1972, 1120.

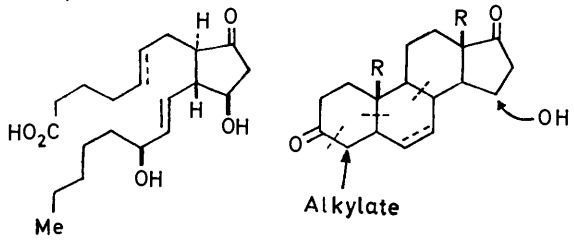
The Route.—At this stage literature input * revealed one excellent versatile method [8] for preparing prostaglandins. But this route manifested a number of disadvantages; [9] for example there were redundant operations, such as a deiodination and various oxidative and reductive adjustments, which were accessory to the overall plan and led to a lengthening of the synthesis. In an ideal synthesis every synthetic operation contributes concretely to the assembly of the target molecule so as to minimise the number of steps.



(V) Generate double bond in nine-membered ring (VI)



(VII)



(VIII) (IX)

But Corey's route did overcome one set of problems, namely the generation of the double bonds of $PGF_{2\alpha}$ (III) having the required 5,6-*cis*- and 13,14-*trans*-geometry. In general terms a limited number of options are available for generating the 5,6-*cis*-double bond of $PGF_{2\alpha}$ (III). Dominant amongst these options are the controlled Wittig process used by Corey, reduction of an acetylene link,[10] and constraint of a *cis*-double bond within a ring [*e.g.* part structures (V) to (VI)]. It was felt that the first two of these were viable so that the target for $PGF_{2\alpha}$ was reduced to the simpler fragment (VII) comprising the five-membered ring and four of the five stereocentres of $F_{2\alpha}$ (III). It was this fragment (VII) which was examined according to the simplified principles of synthesis design.[7]

Many theoretical routes were generated in this way. For example, the *symmetry* noted in fragment (VII) when the stereochemistry was ignored suggested a method commencing with the Diels–Alder reaction of cyclopentene-3,5-dione and butadiene.[11] It was not profitable to examine the relationship of fragment (VII) to known substances, but of interest is the resemblance between PGEs when written as (VIII) and certain steroids (IX). The development of some of the functionality followed logically, propylation at C(4) of the steroid and C(3)–C(4) cleavage, followed by a retro-diene reaction of a suitable Δ^6-steroid breaking both A/B and B/C ring junctions. Unfortunately the natural steroids possess the opposite absolute configuration to natural prostaglandins written in this way. Other relationships exist.[12] The recognition of *synthons* * in fragment (VII) was profitable, for the *cis*-hydroxy-groups suggested a cycloaddition involving O_2, and a similar reaction type was indicated by the linear C_4 unit containing the *trans*-substituents, in this case commencing with, say, 4-bromocrotonaldehyde and cyclopentadiene. Variations on the latter theme now exist,[13] but it was given low priority in our case, one reason being the need generally to separate *exo*- and *endo*-adducts in Diels–Alder processes. Nevertheless, when this type of approach was considered in conjunction with the *reconnection* * of the two aldehyde groups of fragment (VII; X = CHO) a fertile area evolved. The reconnection of the two aldehydes to form a cyclopentene generates a bicyclo[3.3.0]octane system (X) which is necessarily *cis*-fused at the ring junction, thereby inverting the desired configuration at the starred centre.

However it was envisaged that this could be corrected in the synthetic direction by epimerisation adjacent to the aldehyde group when developed.[7b] Now replacement of the oxygen atoms of (X) by carbon and reconnection, as in the Diels–Alder types above, generated a starting material, *endo*-dicyclopentadiene (XI). Further literature input revealed that this single adduct crystallises from inexpensive commercial dicyclopentadiene, so that the *exo*–*endo*-problem of the Diels–Alder approaches is overcome. Finally it is possible [14] to distinguish between the two double bonds of *endo*-dicyclopentadiene; very little other input is available.† Examination in the synthetic direction yielded a new approach (XII) ⟶ (XIII); cleavage of the less

* Terms are defined in refs. 4 and 7.

† Ozonolysis is claimed [15] to give a mixture of diacids. We were unable to repeat this work.

[7] (*a*) S. Turner, 'An Introduction to the Design of Organic Synthesis,' Koch–Light, Colnbrook, U.K., 1971; (*b*) a fuller discussion of the designing of this PG synthesis has been given, S. Turner, Prostaglandin Synthesis: Design, 3rd Internat. Symposium on Organic Synthesis, Oxford, 1973.

[8] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.

[9] E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, 1971, **93**, 1489.

[10] *E.g.* E. S. Ferdinandi and G. Just, *Canad. J. Chem.*, 1971, **49**, 1071.

[11] Upjohn Co., U.S.P. 3,505,386.

[12] B. E. Cross and G. R. B. Webster, *J. Chem. Soc.* (*C*), 1970, 1839. We thank Dr. P. L. Myers for bringing this to our attention. See also D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, *J. Chem. Soc.* (*C*), 1971, 1623.

[13] J. Katsube, H. Shimomura, and M. Matsui, *Agric. and Biol. Chem.* (*Japan*), 1971, **35**, 1828; G. Jones, R. A. Raphael, and S. Wright, *J.C.S. Chem. Comm.*, 1972, 609.

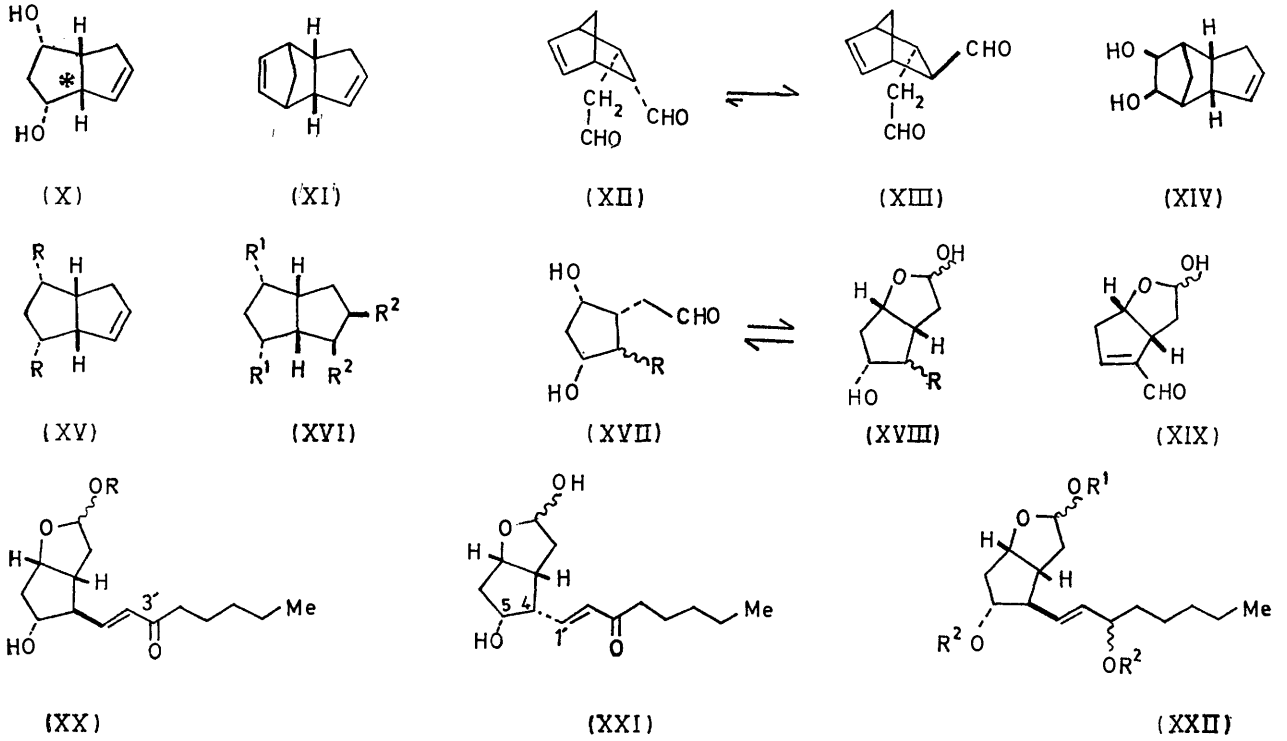
[14] 'Chemistry of Carbon Compounds,' ed. E. H. Rodd, Elsevier, Amsterdam 1953, vol. IIA, p. 343.

[15] M. I. Fremery and E. K. Fields, *J. Org. Chem.*, 1963, **28**, 2537.

reactive double bond would yield an *endo*-aldehyde which might be epimerised without danger of elimination.

The full analysis produced many routes, and most were rejected when further constraints were considered. Bench work commenced on five of these routes and the final choice was dictated by experimental progress. Only the successful method is described in the following paragraphs.

Two olefin functionalising reactions were investigated for *endo*-dicyclopentadiene (XI), namely ozonolysis and hydroxylation, and the latter using $KMnO_4$ was immediately successful leading to the crystalline diol (XIV) (28% *). This diol was the product of partial oxidation, replaced with retention of configuration by oxygen atoms. Sadly, examination of the literature revealed [16] that aliphatic aldehydes undergo the Baeyer–Villiger reaction to give acids, rather than with insertion of the oxygen atom into the α-carbon–carbon bond. An adjustment was necessary, therefore, by transforming the aldehyde groups to ketones, and this was simply achieved by Grignard reaction with methylmagnesium iodide to give a mixture of diastereoisomeric alcohols (XV; R = MeCHOH) which were collectively oxidised to the crystalline diketone (XV; R = MeCO) (50% * over two steps). We rejected the one stage conversion of aldehydes into methyl ketones with diazomethane!



(X) (XI) (XII) (XIII) (XIV)

(XV) (XVI) (XVII) (XVIII) (XIX)

(XX) (XXI) (XXII)

for two olefinic protons remained in the n.m.r. spectrum and mass spectrometry confirmed the expected molecular weight. As it is known that the norbornene double bond of dicyclopentadiene (XI) is the more reactive of the two [14] we presumed the diol had structure (XIV) and this was confirmed in the n.m.r. spectrum; the protons adjacent to the norbornane oxygen functions appear as a broadened singlet (2H), whereas those of the alternative structure would be expected to show greater coupling. In any event the structure and stereochemistry were confirmed by subsequent transformations. For example, treatment with periodate ions, conveniently in a two-phase reaction, converted the diol (XIV) quantitatively into a crystalline dialdehyde (XV; R = CHO).

In the overall plan two carbon atoms of dicyclopentadiene (XI) now functionalised within the aldehyde groups of compound (XV; R = CHO) were to be

Having in hand the pure dialdehyde (XV; R = CHO) we were able to demonstrate by t.l.c. that partial ozonolysis of starting material (XI) followed by treatment [17] with dimethyl sulphide gave a mixture containing only a little of the dialdehyde (XV; R = CHO). Now we noted that the diacid (XV; R = CO_2H), which might also be available by direct oxidation [15] of dicyclopentadiene (XI) should, in one further step with methyllithium yield the diketone (XV; R = COMe) already prepared.

Before investigation of the ozonolysis the dialdehyde (XV; R = CHO) was oxidised in high yield to the required diacid (XV; R = CO_2H), thereby establishing that this new substance crystallised well from ethyl acetate and had a particular t.l.c. mobility. It thus became a simple matter to ozonise dicyclopentadiene (XI) and complete the reaction by an oxidation with

* Yields are quoted after recrystallisation.

[16] C. H. Hassall, *Org. Reactions*, 1957, **9**, 74; J. B. Lee and B. C. Uff, *Quart. Rev.*, 1967, **21**, 429.

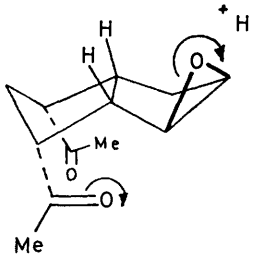
[17] J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 1966, 4273.

8N-chromic–sulphuric acid.[18] The diacid (XV; R = CO_2H) was obtained directly in 18% yield after crystallisation, and the identity of the two samples established in the usual fashion.

A tetrahydrofuran solution of the diacid (XV; R = CO_2H) treated with an excess of ethereal methyl-lithium gave the diketone (XV; R = COMe) (48% *), identical with material prepared by the longer method.

The diketone prepared by these routes was expected to maintain the stereochemistry shown in the formula (XV; R = COMe) and confirmatory evidence was obtained when an ethereal solution of the diketone (XV; R = COMe) was left in contact with 2N-HCl; it was substantially converted into a mixture of diketones having chromatographic behaviour different from that of the starting diketone. The *endo,endo*-diketone (XV; R = COMe) is the least stable of the four possible epimerised forms.[19]

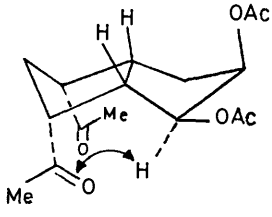
In thinking of the Baeyer–Villiger reaction for effecting the stereospecific replacement of the carbonyl carbon atoms of diketone (XV; R = COMe) by oxygen atoms, we were also aware that the peracid reagent could attack the olfinic link of the adjacent ring, giving an epoxide, thereby setting us on the way to the projected cleavage of this linkage. In the event the reaction of the diketone (XV; R = COMe) with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature appeared complex when examined by t.l.c. Our interpretation [(XXIII)] is that the epoxide is formed very rapidly on the ' top ' face, and that the adjacent carbonyl group is perfectly placed for speedy intramolecular opening of the oxiran. In an effort to suppress epoxide formation and promote the desired Baeyer–Villiger change, the reaction was also attempted in the presence of $NaHCO_3$.[20] This made little difference; unfortunately, even by retrospective examination, we have been unable to resolve the difficulties of this straightforward process.



(XXIII)

It was therefore necessary to protect the olefinic link of diketone (XV; R = COMe) while the Baeyer–Villiger reaction was carried out and we decided to use for protection groups that contributed directly to our aims.[21] Treatment of the diketone (XV; R = COMe) with one equivalent of OsO_4 gave in 85% yield the *cis*-diol (XVI; R^1 = COMe, R^2 = OH). Subsequently the process was carried out on the large scale with only a catalytic amount of OsO_4, using $KClO_3$ as consumed oxidant.[22] This cheap method gave a slightly lower yield and some by-products. However, the desired diol (XVI; R^1 = COMe, R^2 = OH) is almost totally insoluble in ether and was easy to purify by washing. The stereochemistry of the diol (XVI; R^1 = COMe, R^2 = OH) was predicted from top-face attack by the bulky osmium reagent and was proved in the sequel. Note that in protecting the olefinic linkage we had also gone part of the way to eventual formation of a dialdehyde.

Before the Baeyer–Villiger oxidation, the diol (XVI; R^1 = COMe, R^2 = OH) was converted in high yield into the crystalline diacetate (XVI; R^1 = COMe, R^2 = OAc). This also served the purpose of improving the solubility of the material. Examination of the n.m.r. spectrum of this substance gave confirmation of the total stereochemistry, for the less coupled of the two protons adjacent to the acetoxy-groups was moved 0·7 p.p.m. downfield relative to the other, clearly deshielded by the adjacent *endo*-carbonyl group [(XXIV)].



(XXIV)

Eventually the Baeyer–Villiger oxidation of the diacetate (XVI; R^1 = COMe, R^2 = OAc) was successfully carried out; the tetra-acetate (XVI; R^1 = R^2 = OAc) was obtained (53%*) using *m*-chloroperbenzoic acid and a 13 day reflux in CH_2Cl_2.

In its i.r. spectrum, the tetra-acetate (XVI; R^1 = R^2 = OAc) showed only ester carbonyl absorption and no ketone; in the n.m.r. spectrum there was a broad resonance equivalent to four protons next to the acetoxy-groups; fragmentation in the mass spectrometer also accorded with the desired structure. The retention of configuration by the two acetoxy-groups derived from the acetyl functions was firmly based on past experience,[16] and was confirmed by later transformations. Subsequently the relatively expensive *m*-chloroperbenzoic acid used in this preparation could be replaced by the reusable peroxymaleic acid.[23]

The tetra-acetate (XVI; R^1 = R^2 = OAc) was a key intermediate, obtained in only five steps from dicyclopentadiene (XI) (seven steps by the longer route). Of these five operations, two are totally redundant in the sense that they do not contribute concretely to elaboration of the end product. The first of these, the addition

* Same note as on page 2798.

[18] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

[19] *Cf.* A. C. Cope and M. Brown, *J. Amer. Chem. Soc.*, 1958, **80**, 2859 and references therein.

[20] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.

[21] S. Turner, *Chem. in Britain*, 1971, **7**, 191.

[22] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 759 and references therein.

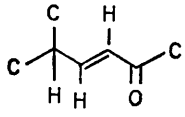
[23] E. G. E. Hawkins, *J. Chem. Soc.* (*C*), 1969, 2691.

of two methyl groups in going from diacid (XV; R = CO_2H) to diketone (XV; R = COMe) is necessitated by the limitations of the Baeyer–Villiger reaction. Industrial constraints did not allow us to create totally novel one-step alternatives (CO_2H to OH with retention of configuration [24]) to this difficulty. The second redundant step occurs purely as protection in the conversion of diol (XVI; R^1 = COMe, R^2 = OH) into diacetate (XVI; R^1 = COMe, R^2 = OAc). That only three fundamental operations are involved in converting dicyclopentadiene (XI) into tetra-acetate (XVI; R^1 = R^2 = OAc) points up the intrinsic aptness of this route; it is interesting that all three operations are oxidations.

The redundancy of the two stages just discussed was accentuated in the next step, when ester cleavage of tetra-acetate (XVI; R^1 = R^2 = OAc) gave the tetrol (XVI; R^1 = R^2 = OH). The two acetoxy-groups protecting the *cis*-1,2-glycol are lost at this point, but commercially more important, two further acetoxy-groups whose methyl group had originated as relatively expensive methyl iodide are lost.

A practical difficulty arose here because the tetrol (XVI; R^1 = R^2 = OH) was soluble in water but insoluble in solvents such as chloroform. This difficulty was overcome by cleaving the tetra-acetate (XVI; R^1 = R^2 = OAc) in methanol in the presence of a relatively small amount of K_2CO_3. Potassium ions were absorbed on an acidic resin, when filtration and evaporation gave quantitatively the pure oily tetrol (XVI; R^1 = R^2 = OH). This substance separated from methanol–acetonitrile as an amorphous solid, and the i.r. spectrum showed the absence of carbonyl absorption.

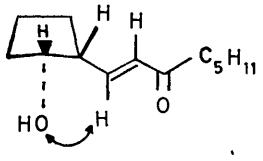
By cleavage with periodate ions the tetrol (XVI; R^1 = R^2 = OH) was converted into aldehydic material which moved largely as a single component on t.l.c.; it was accompanied by small amounts (*ca.* 10%) of a less polar component tentatively identified as the dehydrated aldehyde (XIX) by virtue of its u.v.-quenching behaviour on 'fluorescent' plates. The practical difficulties occasioned by the instability and water solubility of this aldehyde material (XVII ⇌ XVIII; R = α-CHO?) [25] were eventually overcome, and when a freshly prepared sample was reacted with the necessary phosphonate anion, t.l.c. examination of the total product revealed only three u.v.-quenching materials. The n.m.r. spectrum of the fastest-moving component (yield 10—20%) accorded with its being an impure sample of the unsaturated aldehyde (XIX). Surprisingly, however, the n.m.r. features of the remaining two crystalline materials accorded with both having the gross structure of the expected enone product (XXI). N.m.r. features clearly present in each were the end-of-chain methyl group, three protons adjacent to oxygens (well separated because of the different environments), and two olefinic resonances on a polarised *trans*-double bond. Since each enone was a mixture of isomeric hemiacetals the olefinic region of the spectrum was complicated by closely spaced signals. However, for all components the upfield olefinic resonance was a doublet and the low field resonance a quartet. Clearly, therefore, none of these products resulted from joining of the side-chain to the aldehyde group masked as hemiacetal in structure (XVIII; R = α-CHO), for in this case the low field olefinic resonance (now next to CH_2) would show greater coupling. On the contrary, each enone contained the part structure (XXV).



(XXV)

We dismissed the possibility that these two enones were simply epimeric at the hemiacetal position; such isomers interconvert *via* a low concentration of open-chain aldehyde. Two major differences existed in the n.m.r. spectra; in the faster moving enone the low field olefinic proton [*i.e.* at C(1′)] was 0·35 p.p.m. downfield compared to the same resonance in the slower enone, although the up-field olefinic protons were in approximately the same positions. Secondly, the highest field proton next to oxygen (*i.e.* 5-H) formed a broader resonance in the slower moving enone than in the faster. These differences, lying either side of the C(4), led us to the conclusion that the two enones were epimeric at that position, *i.e.* the epimerisation we desired to effect in converting dicyclopentadiene (XI) into $PGF_{2\alpha}$ (III) had already taken place in one of the enones!

From this working hypothesis we subsequently assigned to the faster moving enone the structure (XXI) for it was converted [26] into a prostaglandin chromatographically and biologically different from $PGF_{2\alpha}$ (III); furthermore the downfield shift of the olefinic 1′-H is consistent with deshielding by the *cis*-5-hydroxy-group



(XXVI)

[(XXVI)]. The slower moving enone was assigned the epimerised 'natural' structure (XX; R = H).* In later preparations of these two enones we observed that their ratio varied. We established that in recycling each pure enone through the conditions of its formation it was *not* converted into the other. Hence the proposed

* Considerable subsequent n.m.r. work by Dr. I. A. Selby with these compounds and derivatives has confirmed the structural and stereochemical assignments (to be published). Mass spectrometry also suggested that enones (XX; R = H) and (XXI) are stereoisomers.

[24] *Cf.* D. B. Denney, and N. Sherman, *J. Org. Chem.*, 1965, **30**, 3760.

[25] Much evidence supports the idea that hydroxy-carbonyl compounds exist solely as five- or six-membered hemiacetals where possible, *e.g.* J. T. Edward, P. F. Morand, and I. Puskas, *Canad. J. Chem.*, 1961, **39**, 2069. The position here is probably further complicated by intermolecular bonding, *cf.* M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, 1972, **37**, 1810.

[26] M. E. Spinner and S. Turner, unpublished work.

epimerisation takes place after cleavage of the tetrol (XVI; $R^1 = R^2 = OH$), but before attachment of the prostaglandin side chain. We know that the periodate cleavage of tetrol (XVI; $R^1 = R^2 = OH$) at neutral pH gave aldehydic material (XVII ⇌ XVIII; R = α-CHO?) moving essentially as a single component (t.l.c.). On the other hand, the ' Wittig ' reaction, attaching the side-chain, is carried out under basic conditions; it is, however, a rapid process, most enones being formed in the first ten minutes at room temperature. We propose therefore that the aldehyde material (XVII ⇌ XVIII; R = α-CHO) is epimerised to varying extents in the early phases of the ' Wittig ' reaction.*

Finally the periodate cleavage of tetrol (XVI; $R^1 = R^2 = OH$) was carried out in the presence of excess of K_2CO_3.† In this case the aldehyde material (XVII ⇌ XVIII; R = CHO) was clearly a mixture of two closely running components (t.l.c.), and in the subsequent ' Wittig ' step gave consistent results, the slower moving, epimerised enone (XX; R = H) predominating over the faster with a ratio of 3 or 4 : 1.

The enone (XX; R = H) had been obtained in eight steps from dicyclopentadiene (XI). Within the enone (XX; R = H) the three main functional groups are all different in character; for example, dissolution in alcohols in the presence of catalytic amounts of toluene *p*-sulphonic acid (TsOH) yielded quantitatively the ethers (XX; R = Me, $PhCH_2$, CCl_3CH_2, *etc.*) with no evidence of acetalisation at C(3′).‡ This observation was used in our preliminary synthesis [29] of $PGF_{2\alpha}$ (see Experimental section), but the need for protecting groups lengthened the overall conversion to 13 stages. A much simpler method resulted from direct reduction of the enone (XX; R = H) with sodium borohydride at −20°. Under these conditions reduction takes place primarily at the 3′-ketone group to give the trihydroxy-material (XXII; $R^1 = R^2 = H$); the main side-reaction, reduction of the masked aldehyde, gives some of the isomeric enone-primary alcohol. The same trihydroxy-compound was available from the methoxy-enone (XX; R = Me) by a slightly longer, but more reliable route (see Experimental section).

Following the method used by Fried and his co-workers [30] the trihydroxy-compound (XXII; $R^1 = R^2 = H$) was converted in one step into a mixture of racemic $PGF_{2\alpha}$ (III) and racemic 15-*epi*-$PGF_{2\alpha}$, separated by modifications of literature methods.[31] The synthetic racemic $PGF_{2\alpha}$ (III) was thus available in ten steps from dicyclopentadiene (XI) and was identified by means of spectroscopic, chromatographic, and biological comparisons with natural $PGF_{2\alpha}$.§ $PGF_{2\alpha}$ has recently been converted into PGE_2,[6] thereby establishing the versatility of our synthesis.

* *Cf.* ref. 27.

† We thank Professor G. W. Kirby for this suggestion.

‡ Although these ethers are written as structure (XX; R = *e.g.* CCl_3CH_2) some undoubtedly contain small amounts of isomeric products involving cyclisation of the aldehyde to the 5-hydroxy-group. For example, material carried to PGE_2 (M. Myers) also gave small amounts of by-products which appeared to be PGD_2 and 15-*epi*-PGD_2 (*cf.* ref. 28).

§ From Cambrian Chemicals Ltd., Croydon. We also thank Professor D. C. Chapman for providing samples of prostaglandins, and Professor E. J. Corey for i.r. and n.m.r. spectra of $PGF_{2\alpha}$.

EXPERIMENTAL

N.m.r. spectra were measured in $CDCl_3$ (unless stated otherwise) on a Varian Associates T60 spectrometer with tetramethylsilane as internal standard. T.l.c. plates were coated with silica F_{254}, and R_F values are quoted for plates of thickness 0·25 mm.

(±)-5-exo,6-exo-*Dihydroxy*-endo-3a,4,5,6,7,7a-*hexahydro*-4,7-*methanoindene* (XIV).—A vigorously stirred solution at 0° of *endo*-dicyclopentadiene (32 g) in ethanol (1800 ml) was treated in portions with a solution of $KMnO_4$ (39 g) in water (600 ml). After 2 h the mixture was filtered, the filtrate concentrated *in vacuo*, diluted with water, and the crude product extracted with ether (×4). Crystallisation of the crude product from light petroleum (b.p. 80—100°) gave the *methanoindene* (XIV) (11·3 g, 28%), m.p. 48—51°, δ 3·70br (2H, s, C*H*OH) and 5·55 (2H, s, CH=) [Found: C, 72·45; H, 8·5%; *M* (mass spectrum), 166. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%; *M*, 166].

(±)-1β,5β-*Bicyclo*[3.3.0]*oct*-6-*ene*-2α,4α-*dicarbaldehyde* (XV; R = CHO).—A mixture of the foregoing product (XIV) (30 g), water (50 ml), ether (100 ml), and KIO_4 (50 g) was stirred vigorously for 1 h with cooling in a water-bath. The ether layer was separated and the aqueous layer extracted with ether (×2). Evaporation of the combined ether layers gave the *dialdehyde* (XV; R = CHO) (28·6 g, 97%), m.p. 36—42°. A portion recrystallised from light petroleum (b.p. 60—80°) had m.p. 45·5—46°, $\nu_{max.}$ (CCl_4) 2810, 2720, and 1725 cm^{-1}, δ 5·66 (2H, m, CH=), 9·66 (d), and 9·75br (s) (2H in total, 2× CHO) (Found: C, 73·4; H, 7·6. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%).

(±)-1β,5β-*Bicyclo*[3.3.0]*oct*-6-*ene*-2α,4α-*dicarboxylic Acid* (XV; R = CO_2H).—(*a*) The preceding product (XV; R = CHO) (4·83 g) in acetone (250 ml) at 0° was oxidised by addition in portions of an excess of 8N-chromic–sulphuric acid [18] with stirring. Most acetone was removed *in vacuo*, some water added, and the product extracted with ether (×3). Evaporation of the ether gave crude material which crystallised from ethyl acetate to give the *diacid* (XV; R = CO_2H) (4·00 g, 69%), m.p. 201—205°, $\nu_{max.}$ (KBr) 2500—3400 and 1690 cm^{-1}, δ [$(CD_3)_2SO$] 5·45 (1H, m, CH=), 5·75 (1H, m, CH=), and 12br (2H, CO_2H, disappears with D_2O) (Found: C, 61·2; H, 6·15. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

(*b*) A solution of *endo*-dicyclopentadiene (30 g) in ethyl acetate (1 l) at 0° was treated with *ca.* 2% ozone–oxygen for 24 h. The reaction was flushed with oxygen, solvent removed *in vacuo*, and the residue redissolved in acetone (700 ml) with vigorous mechanical stirring at 0°. An excess of 8N-chromic–sulphuric acid [18] was added in portions, followed by a little water, and most acetone removed *in vacuo*. The residue was extracted with ether (×3), and combined ether layers extracted with 2N-NaOH (×2). Acidification of the basic extracts with concentrated HCl

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and extraction with ether (×3) yielded the crude acidic material. After one crystallisation from ethyl acetate there was obtained product (XV; R = CO_2H) (8·0 g, 18%), m.p. 199—204°, mixed m.p. with material prepared by the first route, 200—205°. Identity was confirmed by i.r. and n.m.r. spectroscopy.

(±)-6α,8α-*Diacetyl*-1β,5β-*bicyclo*[3.3.0]*oct*-2-*ene* (XV; R = COMe).—(*a*) A solution of methyl-lithium in ether, from methyl iodide (14·2 g) and lithium (1·05 g), was cooled and added under nitrogen to the diacid (XV; R = CO_2H) (0·50 g) in dry tetrahydrofuran (25 ml). After being stirred for 0·5 h at room temperature the solution was left for 65 h, poured into saturated NH_4Cl (150 ml), and extracted with ether (×4). Evaporation of the ether gave crude product (XV; R = COMe) (0·326 g, 65%), m.p. 110—121°. Recrystallisation from ether gave the *diketone* (XV; R = COMe) (48%), m.p. 121·5—122·5°, $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}, δ 2·20 (6H, s, MeCO), 5·40 (1H, m, CH=), and 5·70 (1H, m, CH=) [Found: C, 74·8; H, 8·4%; *M* (mass spectrum), 192. $C_{12}H_{16}O_2$ requires C, 74·9; H, 8·4%; *M*, 192].

(*b*) To a solution of methylmagnesium iodide at 0° in ether, from methyl iodide (26 g) and magnesium (4·3 g), was added in portions with vigorous stirring a solution of dialdehyde (XV; R = CHO) (10 g) in dry ether (100 ml). The reaction was heated under reflux for 3 h, cooled to 0°, and saturated NH_4Cl (50 ml) was added carefully with stirring. To the cold mixture was added 2N-HCl (150 ml), the ether layer separated, and the aqueous layer extracted with $CHCl_3$ (×4). Evaporation of the combined organic layers gave the crude intermediate alcohols (14·1 g). The alcohols (1·96 g) in CH_2Cl_2 (40 ml) were oxidised with chromium trioxide (6 g) and pyridine (9·49 g) in CH_2Cl_2 (150 ml). The reaction was washed with N-NaOH (3 × 100 ml), 2N-HCl (2 × 100 ml), and saturated $NaHCO_3$ (100 ml). From the organic layer was obtained, after recrystallisation, the diketone (XV; R = COMe) (50%), identified by t.l.c. and m.p. comparison with material prepared by route (*a*).

(±)-6α,8α-*Diacetyl*-2β,3β-*dihydroxy*-1β,5β-*bicyclo*[3.3.0]-*octane* (XVI; R^1 = COMe, R^2 = OH).—A stirred mixture of the foregoing diketone (XV; R = COMe) (10 g), pure dioxan (200 ml), water (80 ml), $KClO_3$ (7·9 g), and OsO_4 (*ca.* 15 mg) was heated on an oil-bath at 85° for 5 h. Solvents were removed *in vacuo* and the residue exhaustively extracted with $CHCl_3$ in the presence of anhydrous Na_2SO_4. Evaporation of the $CHCl_3$ extracts gave a crude product which was washed (ether, ×3), leaving, as a powder, the *bishydroxy-ketone* (XVI; R^1 = COMe, R^2 = OH) (8·7 g, 74%), m.p. 181—185°, $\nu_{max.}$ (KBr) 3200—3500 and 1700 cm^{-1}, δ [$(CD_3)_2SO$–D_2O] 2·08 (3H, s, MeCO), 2·22 (3H, s, MeCO), 3·45 (1H, m, C*H*OH), and 3·85 (1H, m, C*H*OH) [Found: *M* (mass spectrum), 226. $C_{12}H_{18}O_4$ requires *M*, 226].

The *diacetate* (XVI; R^1 = COMe, R^2 = OAc) crystallised from ether–CH_2Cl_2 in 53—58% yield from diketone (XV; R = COMe) with m.p. 123—125°, $\nu_{max.}$ ($CHCl_3$) 1710 and 1740 cm^{-1}, δ 1·93 (3H, s, OAc), 2·05 (3H, s, OAc), 2·15 and 2·18 (6H, 2s, MeCO), 4·70 (1H, m, $W_{\frac{1}{2}}$ 13 Hz, C*H*OAc), and 5·35 (1H, m, $W_{\frac{1}{2}}$ 10 Hz, C*H*OAc) (Found: C, 62·15; H, 7·2. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·15%).

(±)-2β,3β,6α,8α-*Tetra-acetoxy*-1β,5β-*bicyclo*[3.3.0]*octane* (XVI; R^1 = R^2 = OAc).—(*a*) The diacetate (XVI; R^1 = COMe, R^2 = OAc) (15 g) and *m*-chloroperbenzoic acid (39·2 g) were heated under reflux in CH_2Cl_2 (59 ml; alumina washed) for 13 days. The reaction mixture was diluted with CH_2Cl_2 and washed with a mixture of 10% Na_2SO_3 (100 ml) and saturated K_2CO_3 (100 ml) with vigorous shaking until all solid had dissolved. The organic layer was washed with aqueous K_2CO_3 (100 ml of saturated solution and 100 ml of H_2O), water, and dried (Na_2SO_4). Evaporation of solvent yielded crude product (16·7 g) which crystallised from aqueous methanol to give material (11·4 g), m.p. 118—127°. Recrystallisation from ether–CH_2Cl_2–light petroleum (b.p. 60—80°) gave the *tetra-acetate* (XVI; R^1 = R^2 = OAc) (8·86 g, 54%), m.p. 130—131°, $\nu_{max.}$ ($CHCl_3$) 1735 cm^{-1}, δ 2·02 (12H, 4s, OAc) and 4·9—5·5 (4H, 4m, C*H*OAc) (Found: C, 56·2; H, 6·5. $C_{16}H_{22}O_8$ requires C, 56·1; H, 6·5%).

(*b*) Crude peroxymaleic acid [23] (10·08 g; titrated at 0·003668 mol peracid g^{-1}) and the diacetate (XVI; R^1 = COMe, R^2 = OAc) (2·0 g) were heated under reflux with stirring in CH_2Cl_2 (15 ml; alumina washed) for 4 days, further crude peracid (5·12 g) being added after 2 days. At completion the reaction was diluted with CH_2Cl_2 (15 ml) and filtered, the residue being well washed with CH_2Cl_2. The combined CH_2Cl_2 was washed with aqueous $NaHCO_3$ (to pH 8), water, and dried. Evaporation gave the crude product (1·73 g) which after three crystallisations from methanol yielded the tetra-acetate (XVI; R^1 = R^2 = OAc) (33%), m.p. 129—130·5°, mixed m.p. with a sample prepared by route (*a*) 126—128°, and further shown to be identical by i.r. and n.m.r. spectroscopy.

(±)-2β,3β,6α,8α-*Tetrahydroxy*-1β,5β-*bicyclo*[3.3.0]*octane* (XVI; R^1 = R^2 = OH).—The foregoing product (1 g) was stirred with anhydrous K_2CO_3 (50 mg) in methanol (25 ml) for 20 h at room temperature. Amberlite CG120 (H^+ form) (0·5 g) was added and stirring continued for 0·25 h. Filtration and evaporation gave the oily *tetrol* (XVI; R^1 = R^2 = OH) (0·5 g, 100%) suitable for the next stage. A sample separated as a solid with trituration from acetonitrile–methanol to give m.p. 110—114°, $\nu_{max.}$ (KBr) 3200—3500 cm^{-1}, δ (D_2O) 1·2—3·2 (6H) and 3·8—4·5 (4H, C*H*OH) (Found: C, 55·2; H, 8·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%).

3,3a,4,5,6,6a-*Hexahydro*-2,5-*dihydroxy*-4-(3-*oxo*-*oct*-1-*enyl*)-2H-*cyclopenta*[b]*furans* (XX; R = H) *and* (XXI).—The foregoing tetrol (XVI; R^1 = R^2 = OH) (900 mg) in 10% H_2O–t-butyl alcohol (16 ml) was stirred with K_2CO_3 (680 mg) and $NaIO_4$ (1·80 g) under nitrogen for 1·5 h at room temperature. $CHCl_3$ (8 ml; alumina washed) was added and the reaction filtered through a pre-washed column of silica gel (15 g), washing through with 33% $CHCl_3$–t-butyl alcohol under a pressure of nitrogen. Evaporation of the first eluate (*ca.* 30°) from the column gave the unstable oily aldehyde (XVIII; R = CHO) (880 mg, 100%) suitable for the next step. The material was characterised by t.l.c. on silica with 25% MeOH–$CHCl_3$, R_F *ca.* 0·6.

Dimethyl 2-oxoheptyl phosphonate (1·248 g; Aldrich) in dry dimethoxyethane (48 ml) at 5°, was treated in portions with a 50% sodium hydride dispersion (244 mg) with stirring. The mixture was allowed to warm to room temperature and shaken *very* vigorously during 1 h, by which time a white gel formed. The gel was transferred with swirling to a solution of the preceding freshly prepared aldehyde (XVIII; R = CHO) (880 mg) in dry dimethoxyethane (8 ml), and the resultant mixture stirred 0·5 h at room temperature. Solvent was removed *in vacuo* and the residue applied to one 20 × 20 cm, 2 mm thick silica t.l.c. plate. After developing by continuous elution for 18 h with $CHCl_3$–MeOH (40 : 1) the product bands were located

by u.v. light. Elution with ethyl acetate from separate regions gave the slower moving enone (XX; R = H) (444 mg; 32% from tetrol) and the faster moving enone (XXI) (110 mg; 8%).

The enone (XX; R = H) (an oil which slowly crystallised on refrigeration) had $\nu_{max.}$ ($CHCl_3$) 3200—3500, 1690, 1665, and 1625 cm^{-1}, λ (EtOH) 235 nm (ε 12,000), δ 4·05 (1H, m, 5-H), 4·70 (1H, m, 6a-H), 5·62 (1H, m, OCHO), 6·17 (1H, d, J 16 Hz, =CHCO), and 6·80 (1H, q, J 7·5 and 16 Hz, CH=) (some multiplicity suggesting an isomer ratio of 3 : 1) [Found: M (mass spectrum), 268. $C_{15}H_{24}O_4$ requires M, 268].

The crystalline enone (XXI) had $\nu_{max.}$ ($CHCl_3$) 3200—3500, 1690sh, 1660, and 1620 cm^{-1}, λ (EtOH) 235 nm (ε 11,000), δ 4·30 (1H, m, 5-H), 4·90 (1H, m, 6a-H), 5·60 (1H, m, OCHO), 6·25 (1H, d, J 16 Hz, =CHCO), and 7·15 (1H, complex q, CH=). A portion recrystallised from hexane–ethyl acetate had m.p. 93—95° [Found: M (mass spectrum), 268·1673. $C_{15}H_{24}O_4$ requires M, 268·1674].

(±)-*PGF*$_{2\alpha}$ (III) *and* 15-epi-*PGF*$_{2\alpha}$.[20,30]—(*a*, i) A solution of the enone (XX; R = H) (448 mg) in 10% H_2O–EtOH (11 ml) at −20° was treated with $NaBH_4$ (30 mg) for 3 h. A slight excess of acetic acid was added, followed, at room temperature, by saturated $NaHCO_3$ (5 ml). Extraction with CH_2Cl_2 (×3) gave crude product (438 mg) from which the trihydroxy-compound (XXII; $R^1 = R^2 = H$) (45%) was isolated by preparative t.l.c. on silica with DII [31] using continuous elution for 41 h. The identity of the trihydroxy-compound (XXII; $R^1 = R^2 = H$) was established by careful t.l.c. and n.m.r. comparison with material prepared below.

(*a*, ii) The enone (XX; R = H) (2·411 g) in methanol (50 ml) was shaken with TsOH (58 mg) at room temperature for 0·5 h. Saturated $NaHCO_3$ (18 ml) was added with shaking and the oily methoxy-product (XX; R = Me) (2·12 g, 84%), extracted with CH_2Cl_2, had $\nu_{max.}$ (film) 3200—3600, 1690sh, 1665, and 1625 cm^{-1}, δ 3·30 (3H, singlets, MeO), 5·10 (1H, m, OCHO), 6·18 (1H, 2d, J 16 Hz, =CHCO), and 6·75 (1H, m, CH=).

The methoxy-product (XX; R = Me) (2·12 g) in 30% H_2O–EtOH (31 ml) was reduced with $NaBH_4$ (0·310 g) at room temperature for 0·75 h. A slight excess of acetic acid was added, followed by aqueous $NaHCO_3$. The desired oily dihydroxy-compound (XXII; R^1 = Me, R^2 = H) (2·09 g, 97%), extracted with CH_2Cl_2 (×4), had $\nu_{max.}$ (film) 3200—3550 cm^{-1}, δ 3·32 (3H, singlets, MeO), 5·10 (1H, m, OCHO), and 5·58 (2H, m, CH=).

The dihydroxy-compound (XXII; R^1 = Me, R^2 = H) (2·09 g) was treated with TsOH (51 mg) in 50% aq. t-butyl alcohol (28 ml) for 5 days at room temperature. Saturated $NaHCO_3$ (40 ml) was added and the crude product (2·27 g) extracted with CH_2Cl_2 (×3). After fractionation on silica using continuous elution (18 h) with $CHCl_3$–MeOH (20 : 1) there was obtained the oily *trihydroxy-compound* (XXII; $R^1 = R^2 = H$) (1·094 g, 45% from starting enone) having $\nu_{max.}$ (film) 3100—3600 cm^{-1}, δ ($CDCl_3$–D_2O) 3·82 (2H, m, 3′- and 5-H), 4·50 (1H, m, 6a-H) and 5·50 (3H, m, OCHO and CH=). In the mass spectrum the highest peak was at m/e 252 ($M - H_2O$) (Found: C, 66·5; H, 9·7. $C_{15}H_{26}O_4$ requires C, 66·7; H, 9·7%).

A 50% sodium hydride dispersion (240 mg) in dry DMSO (dimethyl sulphoxide) (1·13 ml) was heated under nitrogen at 80° for 1 h. The reaction was frozen in ice and a solution of dried 5-triphenylphosphoniovaleric acid [20] (1·11 g) in dry DMSO (2·5 ml) added. The mixture was allowed to warm to room temperature for 10 min (red colour), refrozen, and a solution of the trihydroxy-compound (XXII; $R^1 = R^2 = H$) (110 mg) in dry DMSO (0·6 ml) added, washing in with further DMSO (0·6 ml). The reaction was left at room temperature for 18 h, diluted with H_2O (20 ml), and extracted with CH_2Cl_2 (×3). The aqueous layer was acidified with 2N-HCl (24 ml) and extracted with CH_2Cl_2 (×3) to give crude acids. Fractionation on silica with DII [31] using continuous elution for 40 h gave (±)-$PGF_{2\alpha}$ (32 mg, 23%) and (±)-15-*epi*-$PGF_{2\alpha}$ (50 mg; not fully purified). The racemic $PGF_{2\alpha}$ was identified by t.l.c., i.r. spectroscopy, and bioassay comparison with material prepared below.

(*b*) Enone (XX; R = H) (1·03 g) was treated with TsOH (9 mg) in trichloroethanol (25 ml) for 2 h at room temperature. Saturated $NaHCO_3$ (2 ml) was added and the mixture shaken vigorously for 20 min. Anhydrous Na_2SO_4 was added, the reaction filtered, and concentrated *in vacuo* to give the oily trichloroethoxy-derivative (XX; R = CCl_3CH_2) (1·63 g, 100%), $\nu_{max.}$ (film) 3250—3550, 1690sh, 1665, 1625, 810, and 720 cm^{-1}, λ (EtOH) 230 nm (ε 10,000), δ 6·20 (1H, complex d, =CHCO) and 6·75 (1H, m, CH=). The mass spectrum gave molecular ions, m/e 398—403, and major peaks at m/e 251 ($M - CCl_3CH_2O$) and 99 ($C_5H_{11}CO$).

The trichloroethoxy-compound (XX; R = CCl_3CH_2) (1·55 g) in 30% H_2O–EtOH (20 ml) was treated with $NaBH_4$ (0·2 g) for 0·75 h at room temperature. The usual isolation gave the oily diol (XXII; $R^1 = CCl_3CH_2$, R^2 = H) (1·38 g, 88%), $\nu_{max.}$ (film) 3150—3550, 807, and 720 cm^{-1}, δ 5·55 (3H, m, OCHO and CH=), and in the mass spectrum there was a major peak at m/e 253 ($M - CCl_3CH_2O$).

The derived diacetate (XXII; $R^1 = CCl_3CH_2$, R^2 = Ac) (1·49 g) had $\nu_{max.}$ (film) 1735, 805, and 720 cm^{-1}, δ 2·01 (6H, singlets, AcO) and 4·0—5·6 (8H, multiplets), R_F (silica; 7% MeOH–$CHCl_3$) *ca.* 0·75.

The diacetate (XXII; $R^1 = CCl_3CH_2$, R^2 = Ac) (1·92 g) in acetic acid (7 ml) and H_2O (4 ml) was stirred vigorously with zinc dust (0·5 g) for 35 min at room temperature. The reaction was diluted with CH_2Cl_2 (30 ml), filtered, and washed with saturated $NaHCO_3$ (175 ml). From the organic layer was obtained the crude product (1·64 g). Fractionation on silica, using continuous elution with 1% MeOH–$CHCl_3$ for 4 h gave separately unchanged starting material (0·61 g) and the oily hemiacetal (XXII; R^1 = H, R^2 = Ac) (0·56 g, total yield after retreating recovered starting material is 35—40%), $\nu_{max.}$ (film) 3300—3550, 1735, 1370, 1240, and 1015 cm^{-1}, δ 2·03 (6H, singlets, AcO) and 4·4—5·6 (6H, multiplets), R_F (silica; 4% MeOH–$CHCl_3$) 0·35 (silica; ethyl acetate) 0·5.

A 50% sodium hydride dispersion (0·362 g) and dry DMSO (1·85 ml) were heated under nitrogen at 80° for 1 h. The reaction was frozen in ice and a solution of 5-triphenylphosphoniovaleric acid (1·65 g) in dry DMSO (3·7 ml) added. The mixture was swirled 10 min at room temperature, refrozen, and a solution of foregoing hemiacetal (XXII; R^1 = H, R^2 = Ac) (0·436 g) in dry DMSO (2·4 ml) added, washing in with DMSO (2·4 ml). The reaction was thawed, swirled at room temperature for 0·5 h, diluted with water (30 ml), and extracted with CH_2Cl_2 (×3). The aqueous layer was acidified with 2N-HCl (36 ml) and extracted with CH_2Cl_2 (×3) to give crude acids. Treatment with methanolic KOH–benzene hydrolysed residual ester groupings giving, after acidification, material which was fractionated on silica by continuous elution with DII [31]

for 18 h. Thus was obtained substantially pure racemic 15-*epi*-$PGF_{2\alpha}$ (144 mg; faster band) and oily racemic $PGF_{2\alpha}$ (III) (62 mg, 14%), $\nu_{max.}$ (KBr) 2500—3600, 1710, and 970 cm^{-1} (identical with natural $PGF_{2\alpha}$), δ (CD_3OD) 5·50 (4H, m, CH=), 3·6—4·25 (3H, m, C*H*OH), and 0·90 (3H, t, MeR). Significant peaks in the mass spectrum were at *m/e* 318 ($M - 2H_2O$), 264 ($M - H_2O - C_5H_{12}$), 194, and 137 (identical with natural $PGF_{2\alpha}$).

Identity with natural $PGF_{2\alpha}$ was also established chromatographically by g.l.c. (trimethylsilyl ethers of methyl esters; CDMS 3%; 6 ft at 190°; carrier gas nitrogen at 50 ml min^{-1}), t_R (synthetic and natural) 33·5 min, t.l.c. (silica), R_F (synthetic and natural identical) (0·25% formic acid–ethyl acetate, continuous elution 18 h) 0·6, (DII,[31] continuous elution 24 h), 0·25 (PII [31]), 0·4, and t.l.c. (10% $AgNO_3$–silica), R_F (synthetic and natural) (PII, continuous elution 6 h) 0·5.

Finally identity was confirmed by bioassay * on rat fundus, and by radioimmunoassay.† Dose response curves were parallel for natural and synthetic racemic $PGF_{2\alpha}$.

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* We thank Mr. J. Doxey and Dr. C. F. C. Smith for bioassay results. Early synthetic samples had *ca.* 35% of the activity of natural $PGF_{2\alpha}$, but later samples approached 50%.

† Kindly carried out by Dr. K. Hillier, John Radcliffe Hospital, Oxford.