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SYNTHETIC STUDIES ON PROSTAGLANDINS*

K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock,
M. Harman, and J. A. Weisbach

Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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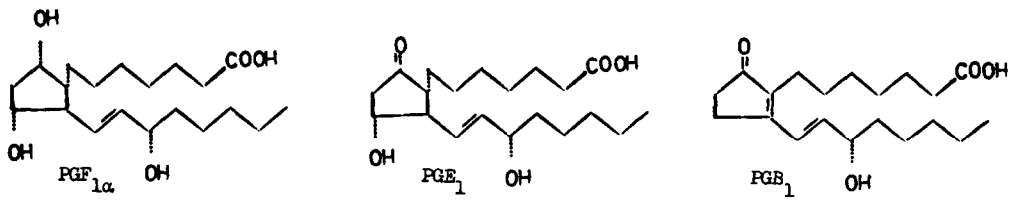
Recently, a total synthesis of prostaglandins $F_{1\alpha}$ ($PGF_{1\alpha}$) and E_1 (PGE_1) by a unique sequence was reported.[1] The well documented biological activities of these compounds[2,3] and the potential utility of synthetic variants motivated a thorough study of the sequence to assess its practical utility in our laboratory. To date, our results differ from the published report[1] in important respects, namely: (a) no detectable amount of PGE_1 is formed in the synthesis described, and (b) only a low yield of a separable mixture of $PGF_{1\alpha}$ isomers was obtained even under improved conditions. None of these correspond to authentic $PGF_{1\alpha}$.[4] The experimental basis for these conclusions as well as a direct route to PGB_1 (PGE_{278})[5] are described below.

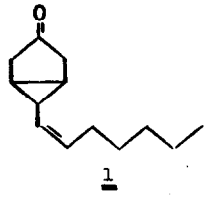


Bicyclic ketone 1 (cis-trans, 3:1), prepared essentially as described,[1,6] was alkylated with ethyl 7-bromoheptanoate via its pyrrolidine enamine in the absence of solvent. Pure 2 (25%) was obtained after chromatography followed by molecular distillation.

Attempted oxidation-rearrangement of 2, as previously described[1] (HCO_2H/buffered HCO_2H), gave the same product under a variety of experimental conditions. In every instance, it failed to show ultraviolet absorption at 278 mμ after treatment with alkali, showing that no PGE_1 was formed. This is a sensitive and specific[7] test for PGE_1 as it is readily converted to PGB_1 (λ_{max} 278 mμ, ε 26,800) under these conditions.[5] Mild alkaline hydrolysis ($NaHCO_3$) of formate esters present in the crude product followed by cleavage ($NaIO_4$) resulted in

*All of the structures in this communication (with the exception of 2a, b, and 17) were typed on the Smith Kline and French chemical typewriter [M. Gordon, U.S. Pat. 3,267,852, Aug. 23, 1966, Pharm. Ind. 28, (1966)]. Experiments are underway to adapt the typewriter tapes (Friden) to photocomposition with the Photon 90.

complete oxidation within 3 min. These data strongly suggest that generation of PGE_1 ethyl ester from 2 does not occur under these conditions, but instead that epoxidation and subsequent opening without rearrangement occur to give vicinal glycol 3.



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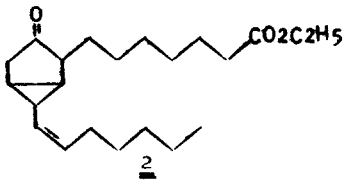

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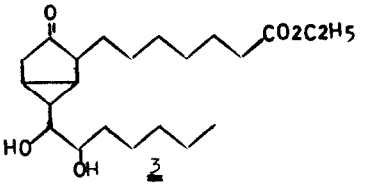
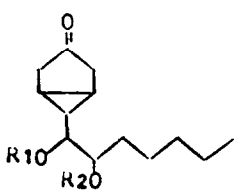


3

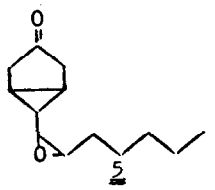
In order to study the rearrangement step in detail, we examined reactions of the less complicated, more easily available precursor ketone 1. After exposure to the same "oxidation-rearrangement" conditions used for 2, no rearranged materials could be detected. One major product was formed, and this was readily identified as 4a after ester hydrolysis. When 4a was subjected to acidic reagents (CF_3CO_2H or H_2SO_4/CH_3CO_2H), no PGE-type products were formed.

Further modifications of the published rearrangement sequence were also tried. Thus, ketone 1 reacts with m-chloroperbenzoic acid to give epoxide 5. Solvolysis of 5 under a variety of acidic conditions gave predominantly 4a after ester hydrolysis. Once again, no PGE-type products could be detected. Compound 5 smoothly incorporates one equivalent of p-toluenesulfonic acid to form a mixture of unstable hydroxy tosylates (4b) which was solvolyzed in 97-100% formic acid (0.1M) buffered with 0, 1, 3, 5, 7 and 10 equivalents of sodium formate. The major product after ester hydrolysis again was 4a in every case. However, small amounts (10-15%) of 6 were detected (tlc and absorption at 220 mμ) in the crude product when buffer was used. When buffer was omitted, less polar products showing long wavelength absorption were obtained instead of 6. Ketone 6 was readily converted to the fully conjugated dienone 7 (λ_{max} 270 mμ, ε 26,000) with alkali. No evidence was obtained for the presence of dihydroxy ketone 8, related to PGE_1, in any instance. These data suggest that some 8 may have been formed in this modified sequence but was dehydrated to 6. Alternatively, 6 may have been formed directly from 4b by concerted rearrangement-elimination.

Treatment of epoxide 5 with alkali (Na_2CO_3) causes rapid opening to dienone 7 via 6. When this sequence was applied to the alkylated ketone 2, isomeric dienones 9a and 10a were each produced in ca. 20% yield. These were characterized as the corresponding methyl esters 9b



4a, $R_1 = R_2 = H$
4b, R_1 = Ts, R_2 = H and R_1 = H, R_2 = Ts



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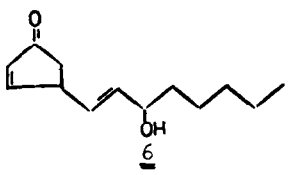

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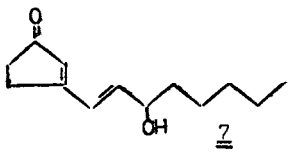

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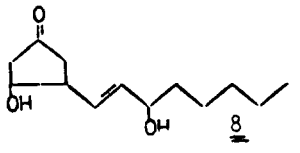

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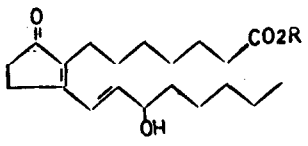
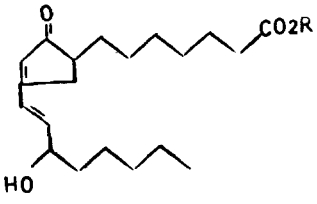
(λ_{max}278 mμ, ε 28,400) and 10b (λ_{max}271 mμ, ε 24,600). Synthetic dl-PGB_1 methyl ester (9b) was identical with naturally derived PGB_1 methyl ester (tlc, ultraviolet and mass spectra); alkaline hydrolysis of 9b gave 9a, identical with authentic PGB_1[4] in several tlc systems. Thus, this new series of reactions provides a facile total synthesis of dl-PGB_1.



9a, R = H (dl-PGB_1)
9b, R = CH_3

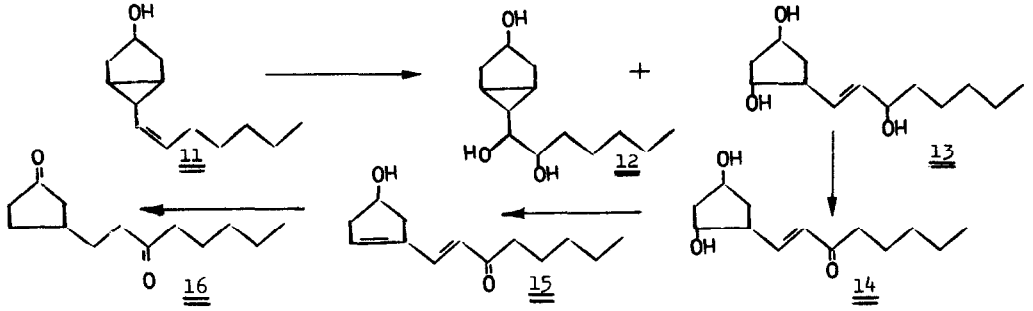


10a, R = H
10b, R = CH_3

Returning to the problem of the oxidation-rearrangement of 1 and 2 to PGE-type structures, we postulated that the cyclopentyl carbonyl might impede the rearrangement by inductive removal of electrons from the fused cyclopropyl moiety. To test this hypothesis, we investigated the oxidation-rearrangement of alcohol 11.[1] Initially, this was attempted essentially as previously described[1] (HCO_3H/buffered HCO_2H) for the analogous alkylated derivative. After hydrolysis of formate esters, the resulting material was essentially completely cleaved by sodium periodate, thus showing that the major product must be 12. However, on changing the conditions to formic acid without buffer, 13 was isolated in 33% yield. If the crude triol mixture (12 and 13) was allowed to remain in formic acid solution for 18 hr., the yield of 13 was raised to 54%.

The structure of 13 was confirmed as follows. Selective oxidation of the allylic alcohol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave α,β-unsaturated ketone 14 (λ_{max}230

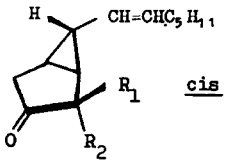
mμ, ε 13,500), which was dehydrated with alkali to dienone 15 (λ_{max} 282 mμ, ε 12,000). Catalytic reduction followed by Jones oxidation[9] gave 16. Compound 16 likewise was obtained when 7 was hydrogenated and oxidized.



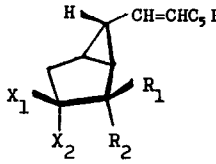
In view of our success with the rearrangement of 11, attention was focused on the synthesis of $PGF_{1\alpha}$. Reduction of 2 with LiAl $(t\text{-BuO})_3H$ gave a mixture of alcohols (17). The pre-existing 3:1 cis-trans double bond mixture of the starting ketone (1) is present in 2 and 17, but, in addition, a second point of isomerism was detected. Thus, after catalytic reduction to dihydro 2, a pair of isomers could be separated by tlc in approximately equal amount. Clearly, alkylation of 1 is not stereospecific, and 2 is therefore a mixture of four isomers (2a and 2b, cis and trans in both instances). This is of prime concern because it determines the stereochemistry of 17 and the final products.[10] Crude 17 was separated into four fractions (5:4:2:1) by column chromatography. All fractions gave satisfactory elemental analyses for 17 after molecular distillation, but the two minors were each mixtures of two components (glpc). Reoxidation of the two major isomers (Jones reagent) produced different cis ketones (2a and 2b). Assuming stereoselective reduction with a bulky hydride, it appears likely that the major products are cis-17a and cis-17b, and the minors are trans-17a,b and cis, trans-17c.

Oxidation-rearrangement of the total alcohol mixture (17) by the published method[1] gave mostly unrearranged glycol. However, under our modified conditions four crystalline products (A,B,C, and D) were formed in low yield (2.7, 2.4, 0.8 and 0.3% isolated, respectively). These were obtained as follows:

One equivalent of 30% hydrogen peroxide was added to 17 in cold, formic acid solution. After 18 hr at room temperature, the formic acid was evaporated at reduced pressure; formate esters of the residue were selectively hydrolyzed ($NaHCO_3$). 1,2-Glycolic materials were destroyed ($NaIO_4$) and the cleavage fragments, starting material, and dehydrated products were removed by column chromatography. Repeated chromatography and, finally, crystallization of the



cis and trans

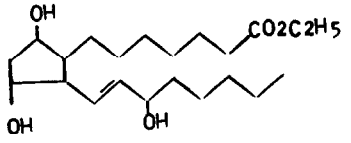


cis and trans

2a, R_1 = H, R_2 = $(CH_2)_6CO_2C_2H_5$
2b, R_1 = $(CH_2)_6CO_2C_2H_5$, R_2 = H

17a, R_1 = H, R_2 = $(CH_2)_6CO_2C_2H_5$
X_1 = H, X_2 = OH
17b, R_1 = $(CH_2)_6CO_2C_2H_5$, R_2 = H
X_1 = OH, X_2 = H
17c, R_1 = H, R_2 = $(CH_2)_6CO_2C_2H_5$
X_1 = OH, X_2 = H

fractions gave A, B, C, and D. A, B and C all gave correct elemental analyses and exhibited nmr and infrared spectra consistent with PGF_1 ethyl esters (18).[11] Insufficient D was obtained for analysis, and this sample was reserved for bioassay. Oxidation (DDQ) of A and B provided identical α,β-unsaturated ketones (19) (tlc, ultraviolet and infrared spectra). When 19 was treated with alkali, a bathochromic shift of its ultraviolet maximum was produced corresponding to that observed with the unalkylated derivative (14) and the related 11α-hydroxy-9,15-diketoprost-12-enoic acid.[12] Catalytic reduction of A and B produced different dihydro derivatives. These data indicate that the major products (A and B) are 15-hydroxy epimers.



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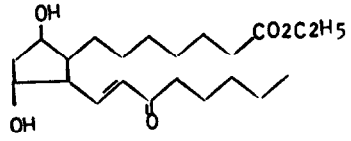

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A, B, C, and D, as well as some very minor products that were not isolated in crystalline form, were saponified (Na_2CO_3). None were identical with authentic $PGF_{1\alpha}$[4] (tlc on silica gel using solvent system AI[13]), nor were they identical with $PGF_{1\alpha}$ methyl ester after esterification with diazomethane (tlc, silica gel, solvent system MI[13]).

Bioassay[14] of the acids showed that most activity was associated with the major product, A, which exhibited ca. 20% of the result obtained from authentic $PGF_{1\alpha}$. The acids from B and C showed weak (< 10%) activity, and the acid from D was essentially inactive. In addition, the acids from some of the very minor products showed significant activity (< 20%).

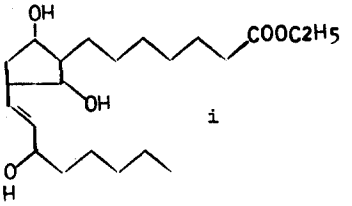
It now appears that the published PGE_1 and PGF_1 synthesis[1] is not a practical route to these compounds. However, by suitable modification of that scheme PGB_1 as well as some bio-

logically active PGF_1 isomers have been prepared. Our results do not preclude the possibility that exiguous amounts of $PGF_{1\alpha}$ were obtained or that further modification and refinement of the synthetic scheme might eventually lead to isolable amounts of $PGF_{1\alpha}$ and PGE_1.

Acknowledgements: We would like to thank Drs. W. Patton and D. Rivard for preparation of starting materials and A. Bachmann, A. Villani and R. Dunoff for technical assistance. A number of stimulating discussions with Prof. H. Rapoport (Berkeley) and Drs. J. F. Kerwin, B. Douglas, J. W. Wilson, H. E. Reiff and M. Gordon are also acknowledged at this time.

REFERENCES

1. G. Just and C. Simonovitch, Tetrahedron Letters, 2093 (1967). We thank Dr. Just for informing us of his results prior to publication.
2. S. Bergström, Science, 157, 382 (1967).
3. E. W. Horton, Experientia, 21, 113 (1965).
4. We thank Dr. J. E. Pike, Upjohn Company, for samples of PGB_1, PGE_1, and $PGF_{1\alpha}$ and Dr. D. A. van Dorp, Unilever N.U. for PGE_1 and PGE_2.
5. S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjovall, J. Biol. Chem., 238, 3555 (1963).
6. Satisfactory elemental analyses and spectroscopic data were obtained for all compounds unless otherwise noted.
7. This test would also have shown the presence of any PGA_1 which might have been formed as it is also converted to PGB_1 with alkali.
8. R. E. Parker and N. S. Isaacs, Chem. Rev., 59, 737 (1959).
9. K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 39 (1946).
10. In the F series 2b must eventually yield a prostaglandin with cis alkyl side chains. In the E series epimerization to the natural trans arrangement would be theoretically possible; however, conditions sufficient to accomplish this would almost certainly result in dehydration of the ring hydroxyl.
11. Our data do not preclude the possibility that some or all of the products have the isomeric structure (i), related to 10, which arises by cleavage of the cyclopropyl bond adjacent to the ester side chain.



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12. E. Anggård and B. Samuelsson, J. Biol. Chem., 239, 4097 (1964).
13. K. Green and B. Samuelsson, J. Lipid Res., 5, 117 (1964).
14. We are particularly indebted to Dr. S. J. Ehrreich, Smith Kline and French Laboratories, who performed these tests using a rabbit jejunum assay according to the method of E. W. Horton and I. H. M. Main, Brit. J. Pharmacol., 24, 470 (1965).