

TOTAL SYNTHESIS OF 15-DEHYDRO-PROSTAGLANDIN E₁

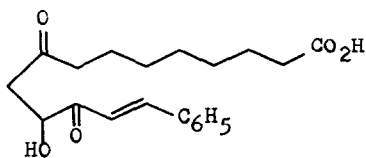
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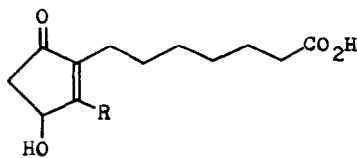
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A recent communication(1) from another laboratory outlined a possible pathway for the preparation of PGE₁(VII). However, efforts toward this goal by the above investigators have thus far been unsuccessful. Their synthetic scheme is, in part, similar to our own approach which has already resulted in the successful preparation of 15-dehydro-PGE₁.

The condensation of 3-keto-undecan-1,11-dioic acid(2) with styrylgyoxal, prepared easily by a selenous acid oxidation of benzalacetone, afforded a crystalline compound(I)(3), mp 81.5-83° ($\lambda_{\text{max}}^{\text{MeOH}}$ 294.5 μ , ϵ 22,300) in nearly quantitative yield. I was cyclized to II(3), mp 117-8° ($\lambda_{\text{max}}^{\text{MeOH}}$ 325 μ , ϵ 36,400) in 40-50% yield(4) by treatment with dilute alkali. The Pappo-



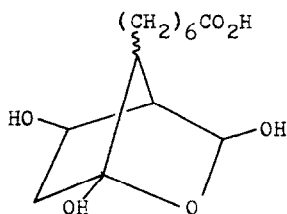
I



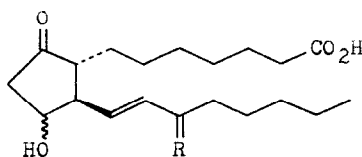
II R : CH=CHC₆H₅

III R : CHO

Allen oxidation(5) of II gave rise to the aldehyde(III)(3) ($\lambda_{\max}^{\text{MeOH}}$ 228 μ , ϵ 10,100) which was characterized as the aldoxime(3), mp 111-2° as well as the dioxime(3), mp 179.5-181.5°. The crude aldehyde(III) was reduced with zinc in aqueous acetic acid to give 8,12-dihydro-III which probably exists as a mixture of hydrated cyclic forms such as IV(tentative). Wittig condensation of the crude reduced acid aldehyde with n-hexanoylmethylene triphenylphosphorane(6) afforded a condensation product in 30% overall yield(4) from II. The



IV



V 11-OH dotted line, R : O

VI 11-OH solid line, R : O

VII 11-OH dotted line, R : $\begin{matrix} \text{OH} \\ \diagup \\ \text{H} \end{matrix}$

product was a mixture of two substances in ratios ranging from 5:1 to 2:1. The major component was an approximately 1:1 mixture of 15-dehydro-PGE₁(V)(7) and the 11-epi isomer(VI). Separation of the isomers was achieved by partition chromatography on silica gel.

The infrared spectrum(neat) of the totally synthetic 15-dehydro-PGE₁(V)(3) was in agreement with the optically active compound(7). The C-13, -14 and -12 protons, appearing as an ABX pattern(8) and the quasiaxial C-11 proton appearing as a quartet, were indistinguishable from that of authentic 15-dehydro-PGE₂ of natural origin(7). The ultraviolet spectrum($\lambda_{\max}^{\text{MeOH}}$ 228.5 μ , ϵ 10,700) was slightly different from the natural product($\lambda_{\max}^{\text{EtOH}}$ 230 μ , ϵ 8,450)(7), possibly due to the fact that the natural product was not a pure compound.

The totally synthetic 11-epi-15-dehydro-PGE₁(VI)(3) showed very similar infrared(neat) and ultraviolet($\lambda_{\max}^{\text{MeOH}}$ 228.5 μ , ϵ 11,400) spectra, but had a somewhat different nmr spectrum(8) compared with the 11-normal isomer. The

quasi-equatorial C-11 proton was, as expected, shifted to a lower field (5.46 τ , narrow multiplet, width of the half height 7 cps). The C-13 proton was shifted 12 cps to a lower field while the C-14 proton was displaced by 1.5 cps to a higher field.

The minor products of the Wittig reaction were dehydration products (9) of 15-dehydro-PGE₁ and could easily be removed by partition column chromatography during the separation of the stereoisomers V and VI.

Our scheme for the synthesis of 15-dehydro-PGE₁ involves only a few steps and only one chromatographic separation is necessary. This approach can readily be adapted for the large scale preparation of 15-dehydro-PGE₁.

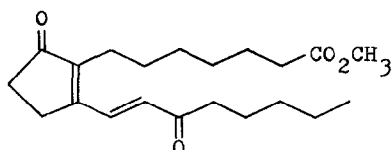
Although PGE₁ and 15-dehydro-PGE₁ are interconvertible by enzymatic transformation (10), the equilibrium appears to favor the latter. We are currently studying the chemical conversion of 15-dehydro-PGE₁ into PGE₁ (11).

References

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2. K. E. Arosenius, G. Ställberg, E. Stenhagen and B. Tägtström-Eketorp, Arkiv Kemi, Mineral. Geol., 26A, No 19, 20(1948).
3. A good elementary analysis was obtained. The nmr spectrum was in accordance with the proposed structure.
4. The optimum conditions have not yet been determined.
5. R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, J. Org. Chem., 21, 478(1956).
6. (a) S. Trippett and D. M. Walker, J. Chem. Soc., 1266(1961); (b) F. F. Beal, III, J. C. Babcock and F. H. Lincoln, J. Amer. Chem. Soc., 88, 3131(1966); (c) An efficient and novel large scale preparation for this compound has been developed in these laboratories.
7. (a) E. Anggård and B. Samuelsson, Arkiv För Kemi, 25, 293(1966); (b) É.

"Ånggård and B. Samuelsson, J. Biol. Chem., 239, 4097(1964).

8. Taken in deuteriochloroform.
9. One of the dehydration products exhibiting ultraviolet absorption at 282 μ was described in the literature(7b), but was incorrectly designated as the 8(12),13-dienoate(VIII). The same material was described again recently by another group(1) with the correct structural assignment(11(12),13-dienoate). The missing hypothetical compound(VIII) was prepared in our



VIII

laboratories by a total synthesis(not yet published) and exhibited different spectral properties($\lambda_{\max}^{\text{MeOH}}$ 296 μ , ϵ 22,800).

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11. For total synthesis of PGE₁ see (a) D. H. Nugteren, H. Vonkeman and D. A. van Dorp, Rec. Trav. Chim., 86, 1237(1967); (b) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas and R. E. K. Winter, J. Amer. Chem. Soc., 90, 3245(1968); (c) E. J. Corey, I. Vlattas, N. H. Andersen and K. Harding, J. Amer. Chem. Soc., 90, 3247(1968); (d) E. J. Corey, I. Vlattas and K. Harding, J. Amer. Chem. Soc., 91, 535(1969); (e) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike and J. L. Thompson, J. Amer. Chem. Soc., 90, 5895(1968).