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THE SYNTHESIS OF (+)-11-EPI-$PGF_{2\alpha}$ AND (-)-11-EPI-PGE_2

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The Corey synthesis[1] is especially well suited for the preparation of prostaglandin stereoisomers and provides the opportunity to establish structure-activity correlations for this unique class of naturally occurring substances. By suitable modification of the synthetic scheme, we have developed a synthesis of the optically active 11-epi-$PGF_{2\alpha}$ (10) and 11-epi-PGE_2 (11) from the known[2] intermediate 1.

The bicyclic lactone 1[3] was protected as the mono-tetrahydropyranyl ether derivative 2 and then subjected to methanolysis (K_2CO_3, MeOH) to yield the hydroxylactone 3, $[\alpha]^{25}D$ -56.1° (c 7.0, THF), with the natural configuration at C_{11}[4]. Inversion[5] of alcohol 3 to the corresponding C_{11}-epimer 6 was accomplished in 59% overall yield as follows. Treatment of 0.197 mmoles of the tosylate 4 with 15 ml of a solution of dry acetone saturated with recrystallized tetraethylammonium formate (~20 equivalents) at reflux for 30 minutes gave a mixture of the inverted formate 5a and the elimination products 5b in a ratio of 63:37 (NMR analysis). Methanolysis of the crude product mixture with sodium bicarbonate followed by chromatography on silica gel (20X weight, 3:1 benzene-ethyl acetate) gave the pure 11-epi-alcohol 6 as an oil, $[\alpha]^{25}D$ -17.7° (c 4.3, THF).

A comparison of the NMR spectrum ($CDCl_3$) of the crude reaction mixture containing 5a and 5b with the spectrum ($CDCl_3$) of the formate derivative of alcohol 3 indicated complete stereoselectivity (within the limits of NMR measurement) of nucleophilic displacement based on the downfield shift of the C_9-proton in the inverted formate 5a. Essentially no difference in tlc R_f values was noticed for the isomeric alcohols 3 and 6 on silica gel using a wide variety of solvent systems.

Protection of the 11-epi-hydroxylactone 6 as the bis-tetrahydropyranyl ether 7 followed by reduction with diisobutylaluminumhydride[2] and subsequent condensation with the Wittig reagent[2] derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide gave 11-epi-$PGF_{2\alpha}$ bis-tetrahydropyranyl ether 9 (chromatographed) in 51% overall yield from lactone 6[6]. Hydrolysis in aqueous acetic acid[2] followed by chromatography on silica gel with 0.2% acetic acid in ethyl acetate produced crystalline (+)-11-epi-$PGF_{2\alpha}$. Two recrystallizations from acetonitrile gave pure material, mp 112-113.5°, $[\alpha]^{25}D$ +80.6° (c 1.0, THF). A mass spectrum was nearly identical with that of natural-$PGF_{2\alpha}$ and differed only in the relative intensity of various peaks. The NMR (CD_3COCD_3) spectrum displayed a small downfield shift of one of the O-C-H protons.

Moffatt oxidation of 9 followed by hydrolysis and chromatography on CC-4 silica gel (Mallinckrodt) with chloroform-ethanol mixtures (1.5 to 5%) then rechromatography with 0.2% acetic acid in ethyl acetate gave pure (-)-11-epi-PGE_2 as an oil[7]. The NMR spectrum ($CDCl_3$) was distinguished from PGE_2 by a downfield shift of the $C_{13,14}$ olefinic protons[8] and the C_{11} proton.

Bioassay[9] of (+)-11-epi-$PGF_{2\alpha}$ on an isolated rat uterus preparation (ovariectomized rat) exhibited 50% of the activity of natural-$PGF_{2\alpha}$. In addition, it was found possible to induce abortion in 3 out of 3 pregnant rats when given at a dosage level which was slightly less than twice the average dose at which $PGF_{2\alpha}$ was 100% effective. In contrast to these results (-)-11-epi-PGE_2 displayed only 12% of the activity of PGE_2 (isolated rat uterus). No inhibition of the standards was noted for either of these isomers.

It would thus appear that the absolute configuration of the hydroxyl group at C_{11} does not play an essential role in the biological activity examined in these systems.

This synthesis of 11-epimeric prostaglandins is adaptable to the 15-epi series and the results of that work will be reported elsewhere.

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References

(1) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, V. Koelliker and N. M. Weinshenker, ibid., 92, 397 (1970).

(2) E. J. Corey, M. Albonico, V. Koelliker, T. K. Schaaf, R. K. Varma, J. Am. Chem. Soc., 93, 1491 (1971).

(3) Prepared from the d-ephedrine salt of d-(4-hydroxy-5-methoxymethyl-2-cyclopentenyl)-acetic acid[1b], $[\alpha]^{25}D$ +37° (c 1.0, MeOH).

(4) The numbering refers to that used for the prostanoic acid ring system; see U. S. von Euler and R. Eliasson, "Prostaglandins," Academic Press, New York, 1967, p. 14.

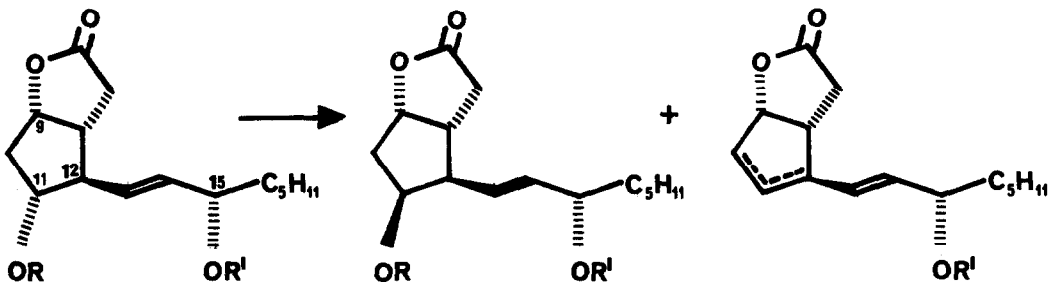
(5) For a full discussion of the inversion reaction for several intermediates in the Corey synthesis[1] see the accompanying paper.

(6) Of the four epimeric intermediates 6 through 9 only 11-epi-$PGF_{2\alpha}$ bis-tetrahydropyranyl ether (9) displayed any measureable difference (more polar) in the R_f values relative to the natural series when eluted twice in 2% acetic acid in ethyl acetate.

(7) $[\alpha]^{25}D$ -26° (0.000076 g/ml, 95% EtOH) was calculated from the optical rotatory dispursion curve (negative Cotton effect).

(8) G. L. Bundy, W. P. Schneider, F. H. Lincoln, J. E. Pike, J. Am. Chem. Soc., 94, 2123 (1972).

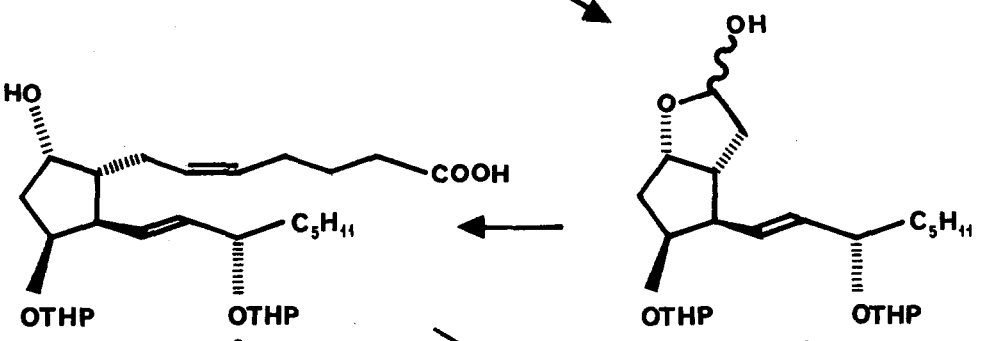
(9) Full bioassay details for these and other prostaglandin isomers will be presented in a subsequent paper.



1 R=COΦΦ R'=H
2 R=COΦΦ R'=THP
3 R=H R'=THP
4 R=Ts R'=THP

5a R=CHO R'=THP
6 R=H R'=THP
7 R= R'=THP

5b



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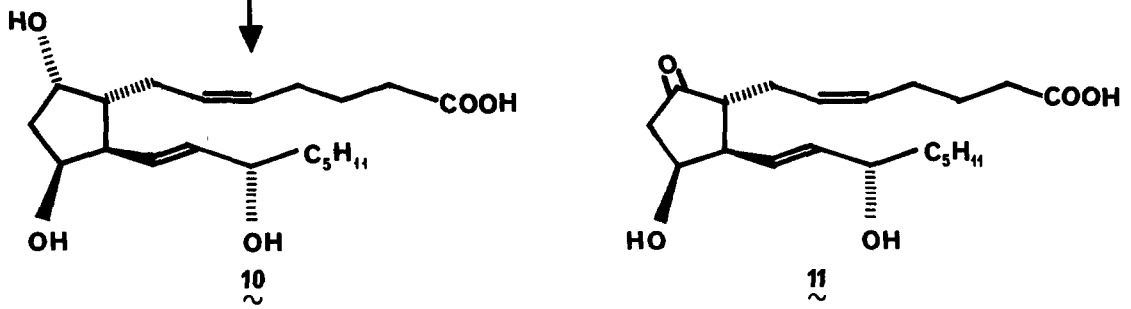

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