Tetrahedron Letters No. 29, pp 2479 - 2482, 1977. Pergamon Press. Printed in Great Britain.

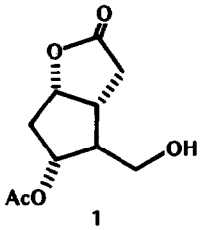
SYNTHESIS OF OPTICALLY ACTIVE 14-HYDROXYPROSTAGLANDINS

J. J. Plattner* and A. H. Gager
Pfizer Inc., Medical Research Laboratories
Groton, Connecticut 06340, USA

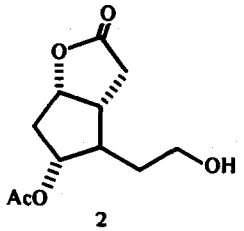
(Received in USA 11 April 1977; received in UK for publication 8 June 1977)

In the search for pharmacologically specific and metabolically stable prostaglandins, considerable effort has recently been directed towards the preparation of prostaglandin analogs in which the 15-hydroxyl functionality has been transposed to adjacent positions in the ω-chain. Thus, prostaglandin E analogs wherein the 15-hydroxyl group has been shifted to C-13[1], C-16[2,3], C-17[2,3] and C-20[3] have been described. No 14-hydroxyprostaglandin E analogs have been disclosed in the literature.[4] We now wish to report the synthesis of optically active 14-hydroxyprostaglandins.

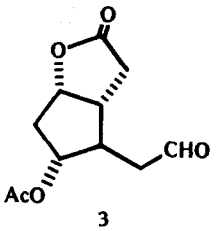
In a previous communication[5] we have described a homologation sequence on optically active Corey-intermediate 1 leading to alcohol 2. Pfitzner-Moffatt[6] oxidation of homolog 2 afforded the stable aldehyde 3 in 80% yield[7] [nmr ($CDCl_3$) δ 2.01 (3H, s, $C\underline{H}_3CO_2$), 4.96 (2H, m, $C\underline{H}OCOCH_3$ and $C\underline{H}OCO$)]. Reaction of 3 with the Grignard reagent derived from n-hexyl bromide in ether at -18° for 0.5 hr led to carbinol 4 as a mixture of diastereomers at C-14 [nmr ($CDCl_3$) δ 0.90 (3H, t, J = 4 Hz, $CH_2C\underline{H}_3$), 1.31 (12H, broad s, $-C\underline{H}_2-$), 2.01 and 2.05 (total 3H, both s, $C\underline{H}_3CO_2$), 3.76 (1H, m, $C\underline{H}OH$), 4.95 (2H, m, $C\underline{H}OCOCH_3$ and $C\underline{H}OCO$)]. The C-14 diastereomeric mixture was clearly discernable on TLC (1:1 ethyl acetate



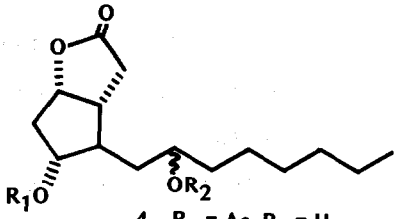
1



2

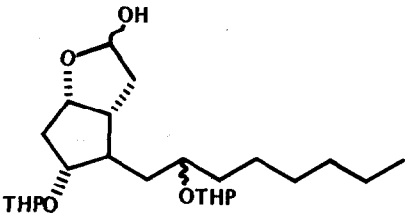


3

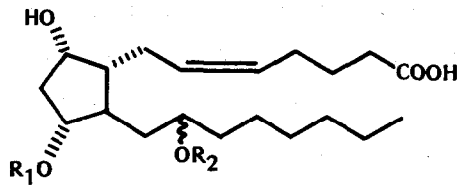


4 R_1 = Ac, R_2 = H

5 R_1 = R_2 = H

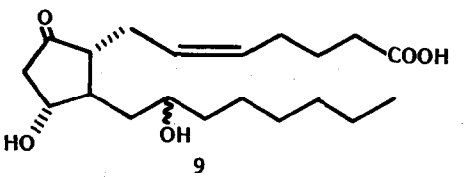


6



7 R_1 = R_2 = THP

8 R_1 = R_2 = H



9

in benzene) and in the nmr spectrum where the acetoxy methyl appeared as two sharp singlets of equal intensity. Deacetylation of 4 proceeded smoothly with potassium carbonate in anhydrous methanol to give diol 5 [40% from 3; nmr ($CDCl_3$) δ 0.86 (3H, t, J = 5 Hz, $CH_2\underline{CH_3}$), 2.53 (2H, m, $\underline{CH_2}CO$), 3.83 (2H, m, $\underline{CH}OH$), 4.83 (1H, m, $\underline{CH}OCO$)].

The remainder of the synthesis paralleled that described by Corey[8] in his synthesis of the natural prostaglandins. Thus, protection of the secondary alcohols in 5 as tetrahydropyranyl ethers (dihydropyran/p-toluenesulfonic acid) was followed by reduction of the lactone functionality with diisobutylaluminum hydride in toluene at -78° to give hemiacetal 6 (73% from 5). Wittig reaction of 6 with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide in dimethylsulfoxide[9] afforded hydroxyacid 7 from which the 13,14-dihydro-14-hydroxy-$PGF_{2\alpha}$ analog 8 was obtained by acetic acid/water (65/35) hydrolysis of the tetrahydropyranyl groups [61% from 6; nmr ($CDCl_3$) δ 0.88 (3H, t, J = 4 Hz, $CH_2\underline{CH_3}$), 3.53-4.26 (3H, m, $\underline{CH}OH$), 5.36 (2H, m, $\underline{CH}=\underline{CH}$)]. Oxidation of 7 with Jones reagent[10] at 0° for 10 min followed by hydrolysis of the tetrahydropyranyl groups (acetic acid/water, 25°, 18 hr) afforded the 13,14-dihydro-14-hydroxy-PGE_2 analog 9 [56% from 5; nmr ($CDCl_3$) δ 0.86 (3H, t, J = 4 Hz, $CH_2\underline{CH_3}$), 3.43-4.30 (2H, m, $\underline{CH}OH$), 5.35 (2H, m, $\underline{CH}=\underline{CH}$)].[11]

Acknowledgement

We wish to thank Dr. E. B. Whipple and Mr. R. S. Ware for high resolution mass spectra. Discussions with Dr. T. K. Schaaf are gratefully acknowledged.

References

1. A. Wissner, J. Org. Chem., 42, 356 (1977).
2. a) P. W. Collins, E. Z. Dajani, M. S. Bruhn, C. H. Brown, J. R. Palmer and R. Pappo, Tetrahedron Letters, 4217 (1975).
   b) M. Bruhn, C. H. Brown, P. W. Collins, J. R. Palmer, E. Z. Dajani and R. Pappo, Tetrahedron Letters, 235 (1976).
3. M. B. Floyd, R. E. Schaub and M. J. Weiss, Prostaglandins, 10, 289 (1975).
4. An 11-desoxy-14-hydroxyprostaglandin F analog as a mixture of all possible epimers at C-9 and C-14 has been described by G. Traverso and D. Pirillo, Farmaco, Ed. Sci., 29, 883 (1975).
5. J. J. Plattner and A. H. Gager, Tetrahedron Letters, in press.
6. K. E. Pfitzner and J. G. Moffatt, J. Am. Chem. Soc., 87, 5661, 5670 (1965).
7. Final products were homogeneous on TLC and gave correct nuclear magnetic resonance and high resolution mass spectra. Key intermediates possessed spectral data in agreement with the assigned structures.
8. E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969).
9. R. Greenwald, M. Chaykovsky and E. J. Corey, J. Org. Chem., 28, 1128 (1963).
10. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).
11. In the uterus contraction of guinea pigs, compounds 8 and 9 showed an activity less than 1/50 as potent as PGE_2.