Tetrahedron Letters No. 43, pp 3667 - 3670, 1975. Pergamon Press. Printed in Great Britain.

A STEREOSELECTIVE TOTAL SYNTHESIS OF 7α-HYDROXY-5,11-DIKETOTETRANOR-PROSTANE-1,16-DIOIC ACID, THE MAJOR HUMAN URINARY METABOLITE OF PGE_1 AND PGE_2

By D. Taub*, Z. S. Zelawski and N. L. Wendler

Merck Sharp & Dohme Research Laboratories, Division of Merck and Co., Inc., Rahway, New Jersey 07065

(Received in USA 23rd July 1975; received in UK for publication 15th September 1975)

We have previously reported a stereoselective synthesis of (±) PGE_1 based on the Diels-Alder condensation of β-angelica lactone and methyl 8,10-undecadienoate.[1] We now report an adaptation of this approach to a stereoselective synthesis of crystalline (±)-7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid 1, the major urinary metabolite of PGE_1 and PGE_2 in man.[2,3] Assay of metabolite 1 is of importance in estimating physiological levels and rates of biosynthesis of PGE_1 and PGE_2.[2,4]

Condensation of butadiene and β-angelica lactone in xylene (200°, 24 hr) yielded bicyclic lactone 2[5,6] (65-70%) bp 75°/0.1mm (Found: C, 70.69; H, 7.79); ir 5.65μ; nmr δ 1.38 (3H, d, J=6), 4.25 (1H, q of d, J=6,2), 5.80 (2H, broad s); ms M^+ 152. Ozonolysis of 2 (CH_2Cl_2, -78°; CH_3COOH-H_2O_2, 65°) led to diacid 3a (88%) mp 162-165° converted (CH_3OH-H_2SO_4, 65°) to dimethyl ester 3b (97%) mp 56-57.5° (Found: C, 53.96; H, 6.68) ir 5.65, 5.78μ; ms M^+ 244.

Dieckmann condensation (Na t-amylate-C_6H_6, 60°) preferentially produced the desired β-ketoester regioisomer 4a (57%)[7,8] mp 87-90° (Found: C, 56.89; H, 5.74). Allylation of 4a (K t-butoxide-C_6H_6-allyl Br, 60°, 2 hr) smoothly gave 4b (96%) mp 88-90° (Found: C, 62.20; H, 6.44) ir 5.65, 5.75, 5.80, 6.10μ; nmr δ 1.45 (3H, d, J=6), 3.67 (3H, s), 4.46 (1H, m), 4.9-6.0 (3H, m). Decarbomethoxylation was effected by reverse Dieckmann reaction on 4b (CH_3ONa-CH_3OH, 65°, 2 hr), followed by treatment of 4c thus formed with NaCl in DMF:H_2O-10:1, 120°, 3 hr[9] to yield the desired allyl species 4d[10] (94%), mp 27-29° (Found: C, 67.87; H, 7.30) ir 5.68, 5.75, 6.15μ; nmr δ 1.45 (3H, d, J=7), 4.43 (1H, q of d, J=7,3), 5.0-5.4 (2H, m), 5.45-6.1 (1H, m); 2,4-dinitrophenylhydrazone, mp 185-

187° (Found: C, 54.21; H, 4.99; N, 14.83).

Conversion of allylketolactone 4d to its ethylene acetal derivative (mp 31-33°), followed by ozonolysis (O_3-CH_3OH, -78°; $(CH_3)_2S$) yielded aldehyde 5 which was homologated [$(Ø_3PCH_2OCH_3)^+Cl^-$-LiNCHMe$_2$]-50% excess-C_6H_6-25°-3 hr] with ensuing acetalization [$(CH_2OH)_2$-C_6H_6-pTSA, 80°] to afford bis-acetal 6[11] (70% from 4d) nmr δ 1.43 (3H, d, J=6), 4.05 (8H, broad s), 4.58 (1H, q of d, J=6,2), 5.05 (1H, t, J=4); ms M^+ 298. Oxidation of 6 at pH 8-9 ($NaHCO_3$-RuO_2-$NaIO_4$) with ensuing ester exchange and acetyl epimerization (CH_3ONa-CH_3OH)[1] produced crystalline acetyl monoester 7 possessing the required all trans stereochemistry (60-65%) mp 66-68° (Found: C, 55.85; H, 6.73) nmr δ 2.20 (3H, s), 3.70 (3H, s), 3.93 (4H, s), 10.7 (1H, s); ms M^+ 300.* Baeyer-Villiger oxidation (CF_3CO_3H-Na_2HPO_4-CH_2Cl_2) led smoothly to acetoxy monoester 8 (75-80%) mp 116-118° (Found: C, 53.02; H, 6.43) nmr δ 2.03 (3H, s), 3.62 (3H, s), 3.92 (4H, s), 5.20 (1H, m), 10.3 (1H, s); ms M^+ 316.

Reduction of 8 (carbonyldiimidazole-THF, 25°; LiAlH$(OBu^t)_3$-THF, 25°) yielded the corresponding aldehyde which was submitted to Wittig coupling with the ylid derived from dimethyl 2-keto-6-carbomethoxy-n-hexylphosphonate[12] (NaH-THF, 0-25°) to produce enone 9 (75% from 8) as a colorless oil (Found: C, 60.30; H, 7.28) $\lambda_{max}^{CH_3OH}$ 225nm (ε_m 12,900); ir 5.72-5.80, 5.90, 6.00, 6.15, 8.1, 10.20, 10.55μ; nmr δ 2.02 (3H, s), 3.68 (6H, s), 3.93 (4H, s), 4.92 (1H, broad q), 6.13 (1H, d, J=16), 6.75 (1H, d of d, J=16,8); ms M^+ 440. Hydrogenation (10% Pd/C-EtOAc, 1 Atm, 25°) of 9 followed by saponification (KOH-aq. CH_3OH, 25°) led to ethylene acetal 10, mp 103-104° (Found: C, 58.00; H, 7.58); ms M^+ of TMS derivative 588. Finally, removal of the acetal function (1:1 CH_3COOH-H_2O, 3 hr, 25°) afforded metabolite 1 (70-75% from 9) mp 102-103° (Found: C, 58.33; H, 7.22) nmr (acetone d_6) δ 4.06 (1H, broad s C_7-H), 6.80 (3H, broad s active H); GCMS of dimethyl ester trimethyl silyl ether bis O-methyloxime essentially identical with that of the corresponding derivative of the natural product.[2,14]

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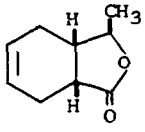
*Resolution of 7 with (-) and (+) ephedrine provided (+) 7 α_D^{chf} +12.3° (nat series) and (-) 7 α_D^{chf} -12.0°, respectively, thereby permitting synthesis of the nat and ent enantiomers of 1.



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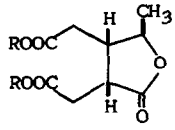
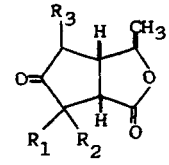
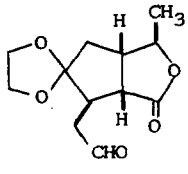


3a, R=H
3b, R=CH_3



4a, R_1=$COOCH_3$, R_2=R_3=H
4b, R_1=α-$COOCH_3$, R_2=β-allyl, R_3=H
4c, R_1=H, R_2=β-allyl, R_3=$COOCH_3$
4d, R_1=R_3=H, R_2=β-allyl
4e, R_1=R_2=H, R_3=$COOCH_3$



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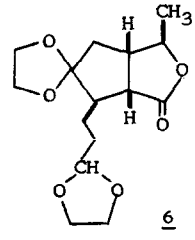

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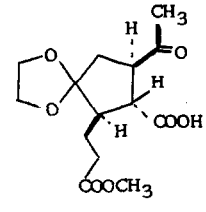

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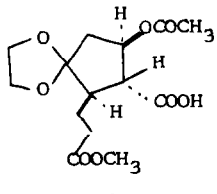

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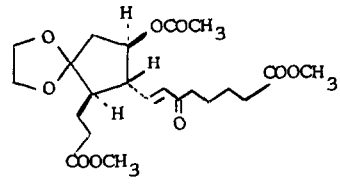

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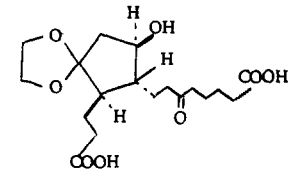

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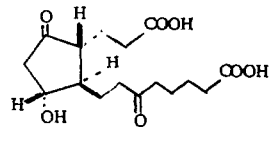

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References

1. C. H. Kuo, D. Taub and N. L. Wendler, Tetrahedron Lett., 5317 (1972).

2. M. Hamberg and B. Samuelsson, J. Am. Chem. Soc., 91, 2177 (1969); J. Biol. Chem., 246, 6713 (1971); M. Hamberg, Biochem. Biophys. Res. Comm., 49, 720 (1972).

3. A synthesis of 1 has been reported with a paucity of chemical detail by J. R. Boot, M. J. Foulis, N. J. A. Gutteridge and C. W. Smith, Prostaglandins, 8, 439 (1974). See E. G. Nidy and R. A. Johnson, J. Org. Chem., 40, 1415 (1975) for synthesis of $PGF_{2\alpha}$ metabolites.

4. Private communication from Drs. F. J. Wolf and W. J. A. VandenHeuvel of these laboratories. Metabolite 1 suitably labelled for GCMS isotope dilution assay is readily obtainable by our route.

5. Ca 1-2% of the methyl isomer of 2 is also formed. Its presence was demonstrated by GCMS - M^+ 152 with a similar fragmentation pattern as 2.

6. The "natural" series enantiomer of each racemate is formulated. IR spectra were taken in $CHCl_3$ and nmr spectra in $CDCl_3$ unless specified otherwise.

7. β-Keto ester 4a was obtained directly in ~50% yield, raised to 57% by conversion of the mother liquors to enol methyl ether (CH_2N_2-CH_3OH-Et_2O), mp 130-132° (Found: C, 58.18; H, 6.22) and reversal to 4a (acetone-1N HCl).

8. The depicted mode of Dieckmann ring closure to give predominantly 4a [rather than the alternative possibility 4e], and thereby determining the site of the 3-carbon side chain was substantiated by subsequent conversion of 5 to PGE_1 as well as by nmr studies on the ethylene acetal derived from 4d and its regioisomer derived from 4e.

9. Procedure of A. P. Krapcho and A. J. Lowey, Tetrahedron Lett., 957 (1973).

10. The side chain in 4d and all subsequent intermediates is in the thermodynamically preferred exo configuration.

11. The analogous bis-acetal derived from 5 is a key intermediate in a general route to PG-1 and PG-2 type prostaglandins to be reported later.

12. This phosphonate was prepared by reaction of lithio dimethyl methylphosphonate with monomeric adipic anhydride[13] in THF at -78° followed by conversion to the methyl ester with diazomethane, bp 100-105°/0.04mm (Found: C, 44.50; H, 7.30) nmr δ 1.67 (4H, m), 2.37 (2H, m), 2.70 (2H, m), 3.15 (2H, d, J=22), 3.72 (6H, s), 3.92 (3H, s).

13. J. W. Hill, J. Am. Chem. Soc., 52, 4110 (1930).

14. We thank Dr. W. J. A. VandenHeuvel for this comparison.