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PROSTAGLANDIN VI* - AN EFFICIENT SYNTHESIS OF 11-DESOXYPROSTAGLANDINS

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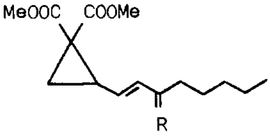
Kierstead and coworkers[1] reported that the condensation of diethyl 1-vinylcyclopropane-2,2-dicarboxylate I with diethyl malonate in the presence of sodium ethoxide yielded cyclopentanone II. We have used this reaction in a general and simple synthesis of 11-desoxyprostaglandins[2]. This is exemplified by the synthesis of dl-11-desoxy PGE_2 and its C-15 epimer (VII & VIII).

I

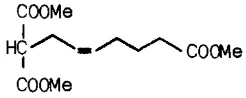
II

Reaction of dimethyl 2-formylcyclopropane-1,1-dicarboxylate (prepared in 72% yield by the same procedure as described by Warner[3] except that NaOMe was added in 2 hrs and the final product was chromatographed) with dimethyl 2-oxoheptylphosphonate[4] gave 70% yield of the α,β-unsaturated ketone III [ν_{max} 1725, 1695, 1672, 1624 cm^{-1}, λ_{max}^{MeOH} 238 mμ (ε=17,400), n.m.r. 0.88 δ (t, J = 5, terminal CH_3), 1.77 (m, ring $-CH_2-$), 2.50 (m, $-CO-CH_2$ and > CH-C=), 3.77 (s, 2 $COOCH_3$), 6.31 and 6.40 (m, -HC=CH-)]. $NaBH_4$ reduction of III gave 63% yield of a mixture of epimers of alcohol IV [ν_{max} 3400, 1725 cm^{-1}, n.m.r. 0.90 δ (t, J = 5, terminal CH_3), 2.33 (b, OH), 3.75 (s, 2 $COOCH_3$), 4.05 (m, > CH-O-), 5.26 and 5.80 (m, -HC=CH-). Equimolar quantities of IV, trimethyl cis-3-heptene-1,1,7-tricarboxylate V[5] [$b_{0.7}$ 144-150°, n.m.r. 3.35 δ (m, -HC <), 3.68 and 3.75 (2s, 3 $COOCH_3$), 5.41 (m, -HC=CH-)] and NaOMe heated 1 hr at 130° gave 40% yield of the cyclopentanone derivative VI, as a mixture of C-15 epimers [λ_{max}^{NaOH} 290 mμ (ε=15,000), n.m.r. 0.9 δ (t, J = 5, terminal CH_3), 3.68, 3.74 and 3.78 (3 $COOCH_3$), 4.5 (-O-CH <), 5.1 to 5.8 (m, 2 -HC-CH-)]. The yield of VI was increased to 68% if the condensation was effected via the tetrahydropyranyl ether of IV and the resulting product hydrolysed to VI using p-toluenesulfonic acid in MeOH. Alkaline treatment of VI (1 hr reflux with 7% NaOH in MeOH:

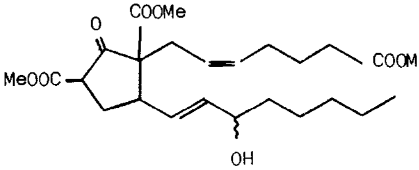


III , R = O

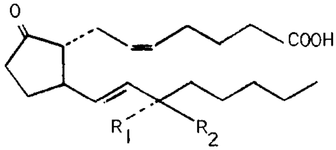
IV , R = $\genfrac{}{}{0pt}{}{\sim OH}{\sim H}$



V



VI



VII , R_1 = H, R_2 = OH

VIII , R_1 = OH, R_2 = H

H_2O=3:2) gave 60% yield of a mixture of C-15 epimers of dl-11-desoxy PGE_2 VII[6] and VIII[6] which were separated by column chromatography [less polar compound, oil, $\nu_{max}^{CHCl_3}$ 3600, 2400-2700, 1725, 1700 cm^{-1}; n.m.r. 0.89 δ (t, J = 5, CH_3), 4.2 (-O-CH <), 5.35-5.78 (m, 2-HC=CH-), 6.38 (s, COOH and OH): more polar compound, m. 46-49°, $\nu_{max}^{CHCl_3}$ 3600, 2400, 1725, 1700 cm^{-1}, n.m.r. 0.89 δ (t, J = 5, CH_3), 4.18 (-O-CH <), 5.3-5.77 (m, 2-HC=CH-), 6.74 (s, COOH and OH)]. VII (more polar compound) and VIII were identical (i.r., n.m.r. and t.l.c. in different systems) with the C-15 epimers of 11-desoxy PGE_2 prepared by a different route in these laboratories.

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References

* For paper V, see J.F. Bagli and T. Bogri, Tetrahedron Letters, 3815 (1972).

1. R.W. Kierstead et al, J. Chem. Soc., 3616 (1952).

2. For earlier work see J.F. Bagli, T. Bogri, R. Deghenghi and K. Wiesner, Tetrahedron Letters 465(1966), J.F. Bagli and T. Bogri, J. Org. Chem. 37, 2132(1972) and references therein, P. Crabbe and A. Guzman, Tetrahedron Letters 115(1972), M.P.L. Caton et al, ibid., 773(1972), C.J. Sih et al, ibid., 2435(1972).

3. D.T. Warner, J. Org. Chem., 24, 1536(1959).

4. E.J. Corey et al, J. Amer. Chem. Soc., 90, 3247(1968).

5. Prepared by condensation of dimethylmalonate and methyl 7-bromo-5-heptynoate (J. Martel and E. Toromanoff, Ger. Pat. 2, 121, 361; C.A. 1972, 76, 24712d) followed by hydrogenation of the resulting ester, $HC(COOMe)_2CH_2-C{\equiv}C-(CH_2)_3-COOMe$, $b_{0.4}$ 153° in presence of Lindlar catalyst.

6. These compounds gave satisfactory C, H microanalysis.