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SYNTHESIS OF 11-HYDROXYMETHYLPROSTAGLANDINS[1]

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The total synthesis of some 9,11-bishydroxymethylprostaglandin F_1 derivatives has recently been described[2,3]. In connection with our interest in this area, we now report a remarkably simple synthesis of the 11α- and 11β-hydroxymethylprostaglandin E_2 derivatives (2a) and (2b). These compounds not only are of interest *per se*, but also provide a useful point of embarkation for the synthesis of other modified prostaglandins[4].

The benzophenone sensitized photoaddition[5] of methanol to PGA_2 methyl ester (1)[6] resulted in the formation of the two epimeric 11-hydroxymethyl compounds (2a) {oil; $\{\alpha\}_D$ -77.8; ν_{max} 3500, 3450, 1730 cm^{-1}; n.m.r. 3.69 p.p.m. (m, 11α-CH_2O)}[7] and (2b) {oil; $\{\alpha\}_D$ ±0; ν_{max} 3625, 3455, 1740 cm^{-1}; n.m.r. 3.68 (m, 11β-CH_2O)} in 22% and 10% yield, respectively. N.m.r. double resonance experiments, carried out in the presence of the shift reagent $Eu(fod)_3$, gave $J_{8,12} \simeq J_{11,12} \simeq$ 9.5 Hz for (2a), and $J_{8,12} = 11$, $J_{11,12} = 7$ Hz for (2b)[8], which established[9] the stereochemistry as *trans*, *trans* for (2a) and *trans*, *cis* for (2b). The stereochemistry about C-11 and C-12 was further supported by the following sequence of reactions. Reduction of (2a) with sodium borohydride gave a separable (t.l.c.), equimolar mixture of the 9α- (3a) {oil; $\{\alpha\}_D$ +21.6; n.m.r. 4.02 (m, H-9,15)} and 9β- (3b) {oil; $\{\alpha\}_D$ +8.3; n.m.r. 3.88 (m, H-9), 4.00 (m, H-15)} alcohols, which, upon oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene[10] at 50°, gave the stable, epimeric enones (4a) {oil; $\{\alpha\}_D$ +35.1; ν_{max} 3630, 3530 1730, 1693, 1665, 1622 cm^{-1}; λ_{max} 232.5 nm (log ε 4.10); n.m.r. 4.14 (m, H-9)} and (4b) {oil; $\{\alpha\}_D$ +23.1; ν_{max} 3630, 3460, 1730, 1693, 1665, 1624 cm^{-1}; λ_{max} 232.5 nm (log ε 4.07); n.m.r. 3.92 (m, H-9)}. On the other hand, the sodium borohydride reduction of (2b) gave, as expected[11], a single alcohol (5) {oil; $\{\alpha\}_D$ +23.2; n.m.r. 3.99 (m, H-9,15)} to which the 9β-configuration was assigned[12]. Oxidation of this triol with DDQ predictably[2] gave the bicyclic ether (6) {oil; $\{\alpha\}_D$ ± 0; ν_{max} 3625, 3460, 1735 cm^{-1}; n.m.r. 2.37 (d, J = 7.4 Hz; 14-CH$_2$), 2.54 (t, J = 6 Hz; 16-CH$_2$), 3.53, 392 (m, CH$_2$O and H-9), 4.27 (m, H-13)} derived from the conjugate addition of the *cis* disposed hydroxymethyl group to the intermediate enone.

The alcohols (3a) and (3b) were also prepared (in 40% combined overall yield) from the known[13] nitromethyl ketone (2c). This was accomplished by the borohydride reduction of (2c) to a 1:3 mixture of the alcohols (3c) {oil; $\{\alpha\}_D$ -36.6; n.m.r. 4.20 (m, H-9)} and (3d) {oil; $\{\alpha\}_D$ +2.3; n.m.r. 4.06 (m, H-9)}, the nitronate salts of which were converted, with buffered aqueous titanium trichloride[14], into the unstable aldehydes (3e) {oil; $\{\alpha\}_D$ +24.4; n.m.r. 9.61 (d, CHO)} and (3f) {oil; $\{\alpha\}_D$ +2.7; n.m.r. 9.63 (d, CHO)}. Sodium borohydride reduction of these aldehydes gave (3a) and (3b), respectively, identical to those derived from (2a).

The transformation of (2c) into the alcohols (3a) and (3b) proves that the nitromethyl group in (2c) does indeed occupy the α-position, an assignment which was previously[13] made, presumably on the basis of steric approach control considerations. This, to our knowledge, is the first reported instance of a rigorous proof of the stereochemistry of a product derived from a conjugate addition to PGA$_2$.

The sensitized photoaddition of methanol to the 15-acetate or the 15-tetrahydropyranyl ether of PGA$_2$ methyl ester gave mixtures of the corresponding 11-hydroxymethyl compounds which were similar in composition to that obtained from (1).

REFERENCES

1. Contribution No. 452 from the Syntex Institute of Organic Chemistry.

2. I.T. Harrison, R. Grayshan, T. Williams, A. Semenovski, and J.H. Fried, Tetrahedron Letters 5151 (1972).

[3] J. Katsube, H. Shimomura, and M. Matsui, Agr. Biol. Chem., 36, 1997 (1972).

[4] After this work was completed, two syntheses of compounds (2a) and (3a), different from those described herein, were reported; D.P. Strike, W. Kao, and M. Rosenthale, Abstracts of Meeting of American Chemical Society, Mar. 30-Apr. 5, 1974, Medicinal Chemistry paper No. 30; D.P. Strike and W. Kao, U.S. Patent 3,845,042 (1974), and O. Oda, K. Sakai, T. Usa, H. Katano, Japan Kokai 74 43 948 (1974); Chem. Abstr., 81, 135538z (1974); Japan Kokai 74 43 947 (1974); Chem. Abstr., 81, 135539a (1974).

[5] B. Fraser-Ried, N.L. Holder, and M.B. Yunker, J.C.S. Chem. Comm., 1286 (1972).

[6] Natural PGA_2, isolated from Plexaura Homomalla (Esper.) by the method of A. Prince, F.S. Alvarez, and J. Young, Prostaglandins, 3, 531 (1973), was esterified with diazomethane.

[7] All new compounds had elemental analyses and/or mass spectra consistent with the assigned structures.

[8] For (2a) and (2b) $J_{12,13} = 8$ Hz. The authors thank MS. E. Dīaz, Facultad de Quimica, Universidad Nacional Autonoma de Mexico, for carrying out these experiments.

[9] R. Pappo and P.M. Collins, Tetrahedron Letters, 2627 (1974).

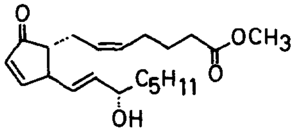
[10] E.J. Corey, I. Vlattas, N.H. Andersen, and K.Harding, J. Amer. Chem. Soc., 90, 3247 (1968).

[11] The sodium borohydride reduction of prostaglandin 9-ketones bearing a bulky 11β-substituent gives predominantly or exclusively the 9β-alcohol, J.M. Muchowski and E. Velarde, unpublished observations. See also W.P. Schneider, U.S. Patent 3,758,542 (1973).

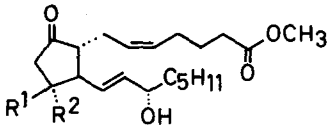
[12] J.F. Bagli and T. Bogri, Tetrahedron Letters, 5 (1967); 1639 (1969).

[13] C.V. Grudzinskas and M.J. Weiss, Tetrahedron Letters, 141 (1973).

[14] J.E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).



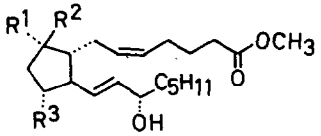
(1)



(2) a) $R^1 = H$, $R^2 = CH_2OH$

b) $R^1 = CH_2OH$, $R^2 = H$

c) $R^1 = H$, $R^2 = CH_2NO_2$



(3) a) $R^1 = OH$, $R^2 = H$, $R^3 = CH_2OH$

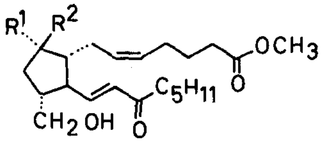
b) $R^1 = H$, $R^2 = OH$, $R^3 = CH_2OH$

c) $R^1 = OH$, $R^2 = H$, $R^3 = CH_2NO_2$

d) $R^1 = H$, $R^2 = OH$, $R^3 = CH_2NO_2$

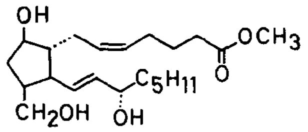
e) $R^1 = OH$, $R^2 = H$, $R^3 = CHO$

f) $R^1 = H$, $R^2 = OH$, $R^3 = CHO$



(4) a) $R^1 = OH$, $R^2 = H$

b) $R^1 = H$, $R^2 = OH$



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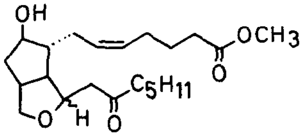

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