A Total Synthesis of Prostaglandin E_1 and Related Substances *via* *endo*-Bicyclohexane Intermediates

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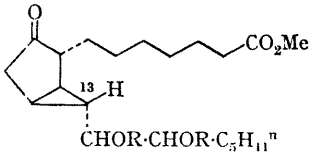
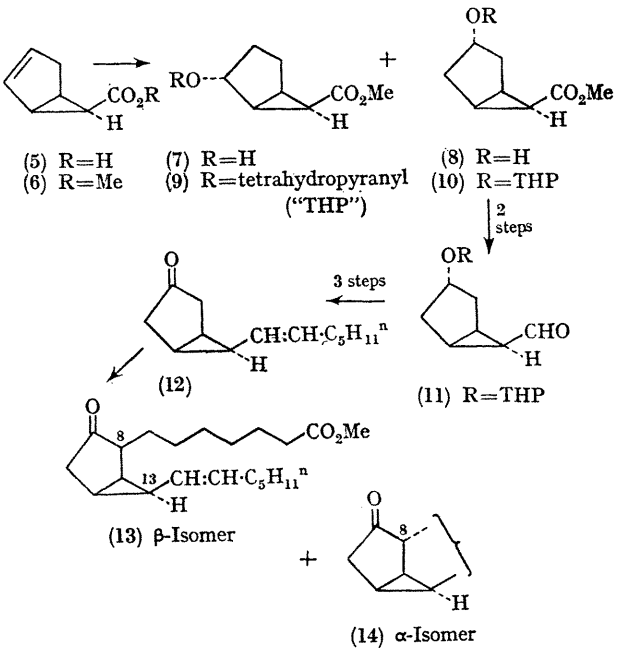
IN our studies concerning a prostaglandin synthesis *via* solvolysis of bismethanesulphonates (1)[1] we prepared all four possible glycols (2) (two racemates with *erythro*-configuration and two racemates with threo-configuration of the *vic*-glycol) in pure form. These glycols have *exo*-configuration at C-13. In addition, we isolated four minor products from our reaction mixtures with very similar chromatographic



(1) R=SO_2Me
(2) R=H

and spectral properties to those of the four major glycols. These minor by-products gave consistently 2—3 times higher yields of (±)-prostaglandin E_1 (PGE_1) methyl ester when converted into bismethanesulphonates and solvolysed under standard conditions. The origin and the properties of these by-products allowed only one conclusion about their structure: namely that these were the *endo*-isomers (at C-13) of glycols (2), formed in small amounts either during the carbene addition step[2] or by isomerization in later steps of the synthesis. To prove these structural assignments and to make use of the substantially higher yield in the solvolysis step, we devised a new synthesis which led stereospecifically to the *endo*-bicyclohexane glycols (3) and (4).

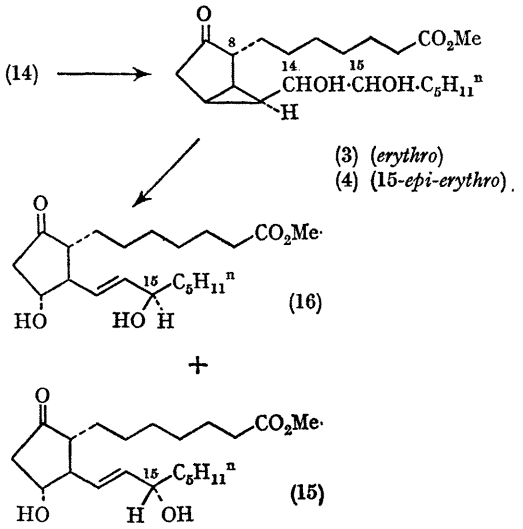


(5) R=H
(6) R=Me
(7) R=H
(9) R=tetrahydropyranyl ("THP")
(8) R=H
(10) R=THP
2 steps
3 steps
(12)
(11) R=THP
(13) β-Isomer
(14) α-Isomer

Bicyclo[3,1,0]hex-2-ene-6-*endo*-carboxylic acid (5), readily available from norbornadiene,[3] was converted into its methyl ester (6). Hydroboration followed by oxidation gave

alcohols (7) and (8),† which could be separated by column chromatography of their tetrahydropyranyl ethers (9) and (10). $LiAlH_4$ reduction of (10) and oxidation with Jones' reagent yielded aldehyde (11), which was converted into ketone (12) by Wittig reaction followed by removal of the protecting group and oxidation with Jones' reagent. Only the *cis*-isomer of (12) was formed in the Wittig reaction (J 11 Hz. for the olefinic protons in the n.m.r. spectrum). Alkylation of (12) with methyl ω-iodoheptanoate resulted in the formation of two alkylated ketones (13) and (14) isomeric at C-8, in a ratio of 1 : 4 in favour of the α-isomer (14). This ratio represents approximately the thermodynamic equilibrium, as equilibration studies (potassium t-butoxide) with pure (13) and pure (14) have shown, and is in contrast to the *exo*-series[1] (isomeric at C-13), where the thermodynamic equilibrium favours the β-isomer. Hydroxylation of (14) with OsO_4 yielded two glycols (3) and (4) in approximately equal amounts, which were identical with two of the four minor by-products isolated from the *exo*-series. Conversion of the less polar (silica gel chromatography) glycol (3) into the bismethanesulphonate followed by solvolysis in 2 : 1 acetone–water at room temperature gave 17—18% yield [based on glycol (3)] of (±)-PGE_1 methyl ester (15) [identical with (±)-PGE_1 methyl ester obtained earlier[1] in spectral properties, m.p. and mixed m.p.] and 19% of (±)-15-*epi*-PGE_1 methyl ester (16). The more polar glycol (4) gave 19% yield of (±)-PGE_1 methyl ester (15) and 16—17% yield of the 15-*epi*-isomer (16). Assuming that hydrolysis of the methanesulphonate group at C-15 proceeds predominantly with inversion at this centre, the less polar glycol (3) must have the same relative configuration at C-8 and C-15 as natural PGE_1 and the more polar glycol (4) the same relative configuration at these centres as 15-*epi*-PGE_1. The configuration at C-14 of (3) and (4) is determined by the *erythro*-relationship of the *vic*-glycol system.

The β-isomer (13) was converted into (±)-8-*iso*-PGE_1 methyl ester[4] and its 15-*epi*-isomer in a similar manner.



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† No attempt was made to determine the stereochemistry of the hydroxy-group relative to the three-membered ring, but it was assumed that the borane attack occurred from the less hindered side and no change in configuration took place during the peroxide oxidation.

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