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SYNTHESIS OF PROSTAGLANDIN E_1 AND RELATED COMPOUNDS FROM THE COMMON INTERMEDIATE II[1)]

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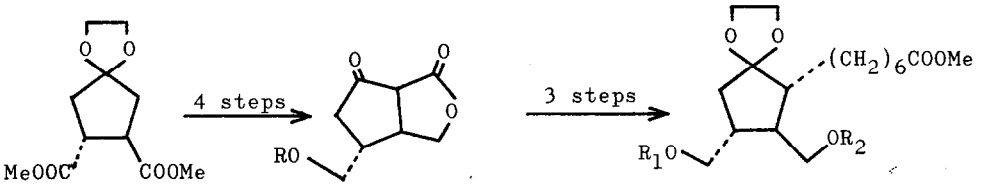
In connection with a scheme for the synthesis of 9 or 11-substituted prostaglandins which are of biological and medicinal interest to us, we have previously reported a stereo-controlled synthesis of 11α-hydroxymethyl prostaglandins[2a)] and their optically active forms[3)]. Now we describe the syntheses of prostaglandin E_1[4)], the intermediate XVII for 11-deoxy prostaglandin[5a,b)], and of 11α-hydroxymethyl prostaglandin E_2 XIII[2a,b)] by another route, starting from the common intermediate IIa, which is readily prepared.



I

IIa R=COOEt

IIb R=THP

III R_1=COOEt R_2=H

(-)III R_1=COOEt R_2=H $[\alpha]_D$-8.2°

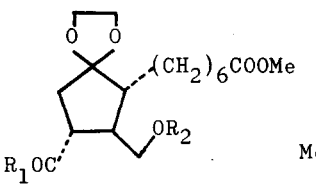
IV R_1=COOEt R_2=THP

V R_1=H R_2=THP

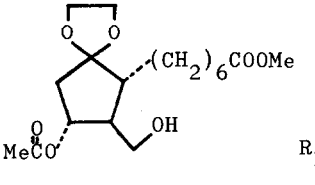
Synthesis of PGE_1

The hydroxy ketal III*[1)] which was involved in the synthesis of 11-deoxy 11α-hydroxymethyl prostaglandin E_1[2a)], was derived in 3 steps from the key intermediate IIa. Hydrolysis (aqueous MeOH-KOH) of the pyranyl ether IV obtained from III by treatment with dihydropyrane-p-TsOH in CH_2Cl_2, followed by re-esterification with CH_2N_2 in ether, afforded the alcohol V. V; ir 3450, 1741 nmr 3.90

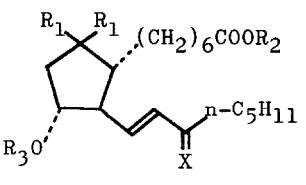
(4H, s, O-CH_2CH_2-O), 3.67 (3H, s, COOMe). The alcohol V was oxidized to the acid VI in 87% yield by Cornforth's reagent (CrO_3-H_2O-pyridine) at room temperature for 30 hrs: VI; ir 1735, 1710 nmr 8.00 (1H, broad, COOH). Conversion of the carboxyl group of the acid VI into the acetoxy group was effected as follows:

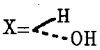


VI R_1=OH R_2=THP
VIIa R_1=Cl R_2=H
VIIb R_1=Cl R_2=COCOCl
VIIIa R_1=Me R_2=H
VIIIb R_1=Me R_2=COCOMe



IX



X R_1=R_1=O O R_2=Me R_3=Ac X=O
XI R_1=R_1=O O R_2=Me R_3=Ac X= 
XII R_1=R_1=O O R_2=R_3=H X= 
(dl)PGE_1 R_1=R_1=O R_2=R_3=H X= 

The potassium salt of VI was converted to the acyl chloride VII by chlorination with oxalyl chloride at room temperature for 1.5 hrs. Without purification, the reaction of VII with $(Me)_2CuLi$ at -60°C gave the methyl ketone VIIIa accompanied by a small amount of the keto diester VIIIb, which was easily hydrolyzed by K_2CO_3 in aqueous MeOH to afford VIIIa. VIIIa; 55% yield, ir 3500, 1735, 1705 nmr 3.93 (4H, s, OCH_2CH_2O) 3.61 (3H, s, COOMe) 2.15 (3H, s, COMe) mass spectrum M^+ (m/e) 342. VIIIb; ir 1730 nmr 3.83 (4H, s, OCH_2CH_2O) 3.60 (3H, s, COOMe) 2.40 (3H, s, COCOMe) 2.15 (3H, s, COMe) mass spectrum M^+ (m/e) 412.

The formation of VIIIb suggests that the acyl chloride VIIb arose from partial chloroglyoxalation after the cleavage of the tetrahydropyranyl group under the reaction conditions employed.

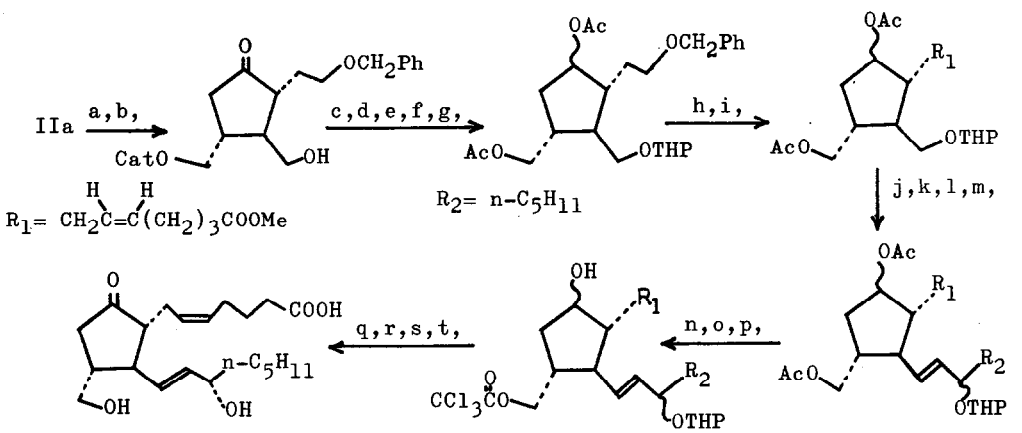
Baeyer-Villiger oxidation of the methyl ketone VIIIa with CF_3CO_3H-Na_2HPO_4 in CH_2Cl_2 at 0°C for 4 hrs. gave the acetate IX in 85% yield. IX; ir 3500, 1740, 1720 nmr 2.00 (3H, s, OCOMe).

(dl)-PGE_1 was synthesized from the acetate IX by an established method[6]. Collins oxidation of the acetate IX, followed by a Wittig reaction, afforded the enone X, which on reduction with $NaBH_4$ yielded an epimeric mixture XI at C_{15}.

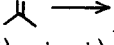
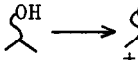
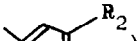
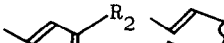
By silica gel column chromatography after hydrolysis of the ester group, the more polar 15α-OH epimer XII was obtained. Removal of the ketal group of XII by aqueous AcOH afforded (dl)-PGE_1 which was identical with an authentic sample. Application of the above synthetic route to the easily prepared optically active diester $[\alpha]_D$ -8.2° (-)III will clearly afford natural PGE_1.

Synthesis of (dl)-11-deoxy-11α-hydroxymethyl PGE_2 XIII

(dl)-XIII was synthesized in the following way.



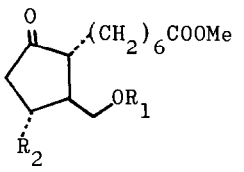
(dl) XIII

a, $PhCH_2OCH_2CH_2I$ /t-BuOK-DMSO. b, aq. Na_2HPO_4 Δ. c, dihydropyrane/H^+ (OH→OTHP). d, KOH (CatO→OH). e, Ac_2O/Py (OH→OAc). f, $NaBH_4$ (). g, Ac_2O/Py (). h, Pd-C ($-OCH_2Ph$→OH). i, i) oxidation ii) Wittig iii) CH_2N_2. j, H^+ (OTHP→OH). k, i) oxidation ii) Wittig (CH_2OH → ). l, $NaBH_4$ (). m, dihydropyrane/H^+ (C_{15}~OH → C_{15}~OTHP). n, K_2CO_3 (OAc→OH, COOMe→COOH). o, CH_2N_2 (COOH→COOMe). p, CCl_3COCl/Et_3N. q, Collins oxidation (C_9~OH→C_9=O). r, H^+ (OTHP→OH). s, KOH. t, preparative TLC (isolation of C_{15}-epimer).

(dl)-XIII showed two times the activity of (dl)-11-deoxy-11α-hydroxymethyl PGE_1 [2a] for the uterus contraction in pregnant rats.

Intermediate XVII for the synthesis of 11-deoxy prostaglandins

Acetylation of the hydroxy ketone XIV derived from the pyranyl lactone IIb, followed by removal of the tetrahydropyranyl group with aqueous AcOH,



XIV	R_1=H	R_2=CH_2OTHP
XV	R_1=Ac	R_2=CH_2OH
XVI	R_1=Ac	R_2=CHO
XVII	R_1=Ac	R_2=H

yielded the acetate XV in 73% yield. The aldehyde XVI obtained by Collins oxidation was submitted to deformylation[7] by treatment with Wilkinson-complex in $CHCl_3$. Thus, the acetate XVII, which was obtained in 60% yield, will serve as an intermediate in the synthesis of the 11-deoxy prostaglandin E_1[5a,b].

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References and Footnotes

*1) ir (cm^{-1}) spectra were taken in neat liquids and nmr (δ) spectra in $CDCl_3$ solutions containing tetramethylsilane as internal standard. All compounds exhibited ir, nmr and mass spectra consistent with the structures assigned.

1) Synthetic Studies on Prostanoids VIII. See reference 3 for Part VII.

2) a. K. Sakai, J. Ide and O. Oda Tetrahedron Lett., 3021 (1975)
b. For the partial synthesis from PGA_2. G.L. Bundy Tetrahedron Lett., 1957 (1975); A. Guzman and J.M. Muchowski Tetrahedron Lett., 2053 (1975).

3) O. Oda, K. Kojima and K. Sakai Tetrahedron Lett.,

4) K. Kojima and K. Sakai Tetrahedron Lett., 2837 (1975)
reference cited there.

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6) H.L. Slates, Z.S. Zelawski, D. Taub and N.L. Wendler Tetrahedron 819 (1974).

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