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PROSTAGLANDINS III : A MODIFIED ROUTE TO dl-PG_1-SERIES FROM A COREY'S INTERMEDIATE

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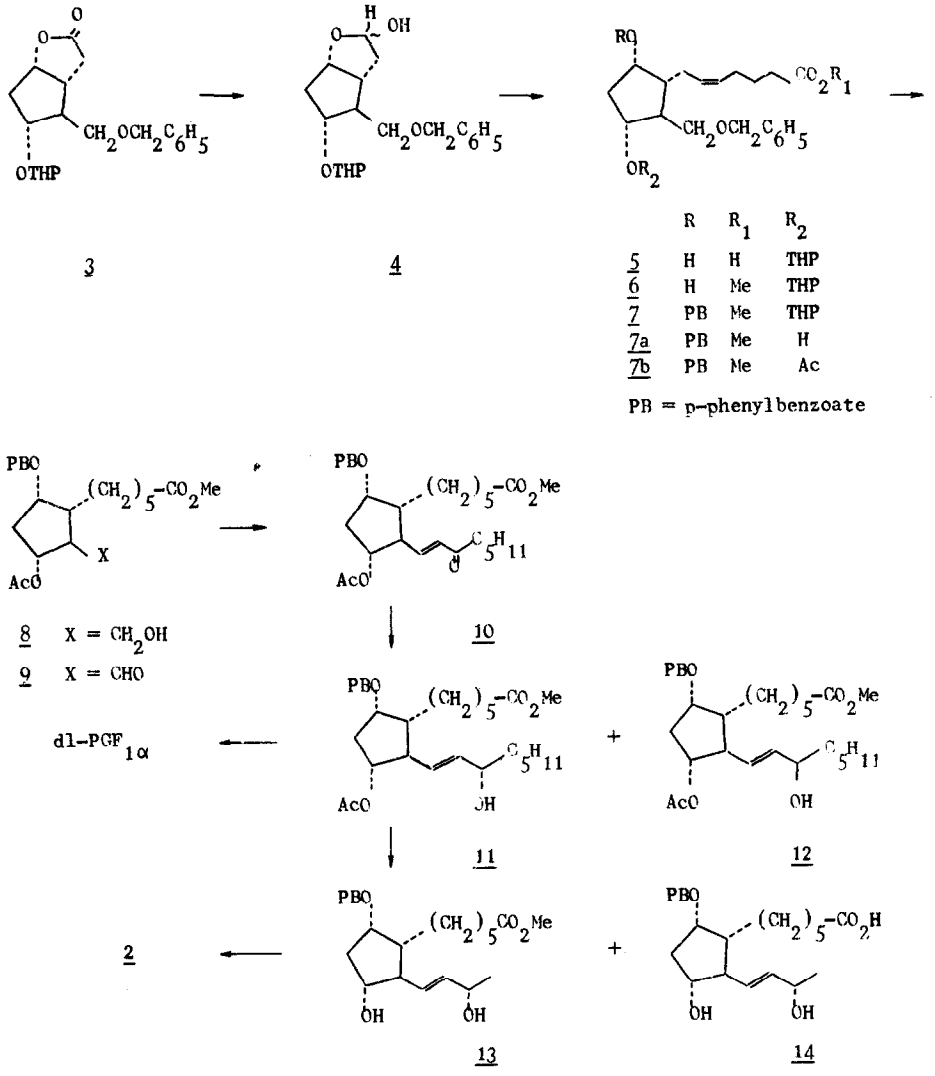
The selective hydrogenation of the cis-Δ^5 bond of $PGF_{2\alpha}$-11α,15S-bis-tetrahydropyranylether 1 carried out in methanol at -15° to -20° under 1 atm of hydrogen with 5% Pd-on-carbon as catalyst using a t.l.c. analytical tecnique to follow the progress of the reaction, was proposed by Corey[1] to obtain prostaglandins $PGF_{1\alpha}$ and PGE_1 from a common synthetic intermediate.

1 2

The troublesome procedure for this selective reduction, involving subsequent tedious chromatographic purifications, prompted us to investigate an alternative route to 2 and to prostaglandins of the PG_1-series, starting from the cyclopentane-lactone-benzylether 3[2].

A solution of sodium-(2-methoxyethoxy)aluminum hydride[3,4] (2.5 equiv) was added under stirring to a solution of 3 in toluene, cooled at -65° to -70°, over a period of 1 hr. The reaction mixture was again stirred for 4 hr at -70° and excess reative was decomposed by N isopropanol in toluene. The solution was then washed to neutrality with a saturated sodium dihydrogenphosphate solution to obtain the lactol 4, as colorless oil[5]. This compound was subjected to a Wittig reaction with the ylide salt prepared from 5-triphenylphosphoniopentanoic acid (2.5 equiv) and tert-BuOK (5 equiv) to form (84% overall yield) the cis-7-cyclopentan-hept-5-ene-1-oic acid 5, which was then converted to methylester 6 by diazomethane.

The esterification with p-phenylbenzoyl chloride (1.5 equiv) in pyridine for 4 hr at r.t. to give 7, the subsequent hydrolysis of the tetrahydropyranylether in acetone - 0.1 N oxalic acid (1:1) to 7a and the treatment with acetic anhydride in pyridine afforded the dl-2α,4α-dihydroxy-



cyclopentane-1α(hept-cis-5'-ene-1'-oic acid methylester)-5β-benzyloxymethyl-2-p-phenylbenzoate-4-acetate (7b), homogeneous by t.l.c., as colorless oil, in 88% yield.

Hydrogenation of cis-Δ^5-bond and removal of the benzylether protective group to give the saturated 5β-hydroxymethyl derivative 8, oil, were carried out in one step by treatment of a solution of 7b in ethyl acetate-methanol (2:1), under 1 atm of hydrogen, with 10% Pd-on-carbon in the presence of small amounts of conc. hydrocloric acid.

According to the modified Collins procedure[6], oxidation of 8 gave the aldehyde 9, which was directly transformed into 15-dehydro-$PGF_{1\alpha}$-methylester-9-p-phenylbenzoate-11-acetate (10) in 85%

yield by reaction with the sodium derivative of dimethyl-2-oxo-heptylphosphonate in dry dimethoxyethane at 15°.

The reduction of 10 with excess zinc borohydride in ethyl ether–dimethoxyethane (5:1) for 6 hours at r.t. afforded, in 92% yield, a mixture of the $PGF_{1\alpha}$-triester (11) and 15-R-epimer (12) in ca. 1.5 / 1 ratio. The separation of the 15-S isomer from the mixture was accomplished by column chromatography on SiO_2 using cyclohexane–ether (70:30) as well as isopropyl ether as eluent.

The saponification of 11 with 1% KOH in methanol for 1 hr at reflux temperature and the following chromatographic purification on acid-SiO_2, using ethyl acetate as eluent , afforded in 85% yield the dl-$PGF_{1\alpha}$, m.p. 73–74° ,reported[7] m.p. 81°.

Selective hydrolysis of the 11-acetate group of the dl-$PGF_{1\alpha}$ triester (11) by means of perchloric acid in methanol and with hydrochloric acid in aqueous dioxane was unsuccessful because of partial isomerisation of hydroxy function at C-15[8].

On the contrary,selective saponification of the 11-acetate group was made possible by treating 11 in methanol with 10% sodium hydrogen carbonate at r.t. for 7 days to give the dl-$PGF_{1\alpha}$-methylester-9-p-phenylbenzoate (13) in 80% yield, together with small amounts of dl-$PGF_{1\alpha}$-9-p-phenylbenzoate (14).

Starting from the diester 13, dl-PGE_1 can be obtained by means of the following well known procedures[9] : a) protection of the 11 ,15S-dihydroxy-functions by THP-derivatives,

b) saponification to 2 ,

c) oxidation with Jones reagent at -10° in acetone,

d) hydrolysis of bis-THP-ether protective groups.

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