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# PROSTAGLANDINS II : 8,12-DIISO-PGE$_2$ (ent-11,15-EPI-PGE$_2$)

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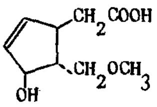
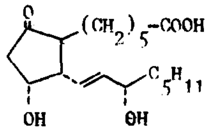
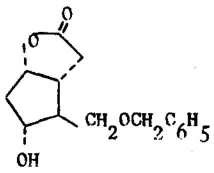
The inversion of configuration at C-4 (C-11 in prostaglandin numbering) performed either on the resolved (-)4β-hydroxy-5α-methoxymethyl-cyclopent-2-ene-1β-acetic acid (I), by-product of Corey synthesis of natural prostaglandins[1] or on its related derivatives makes them suitable intermediates for the total synthesis of optically active ent-11,15-epi-prostaglandins.



I



A ent-11,15-epi-PGE$_1$



B

Our interest in these unnatural compounds arose from the observations[2,3] that pure ent-11,15-epi-PGE$_1$ , A ,[4] [ent-PG(Eββ)$_1$][5] appears to be at least as potent as nat-PGE$_1$ on rat uterus and far more potent on other tissue preparations and its degradation rate should be only 15% of the rate of nat-PGE$_1$. In this way, two aims can be achieved : a) resistence to effect of dehydrogenase, b) modification of biological properties.

A recent paper[6] , regarding to inversion of configuration at C-4 in dl-5β-benzyloxymethyl--2α,4α-dihydroxy-cyclopentane-1α-acetic acid-(1'→2)γ-lactone , B , to obtain 11-epi-prostaglandins, prompts us to report our experimental results on the synthesis of optically pure 8,12-diiso-PGE$_2$ [ent-PG(Eββ)$_2$].

An aqueous solution of the l-ephedrine[7] salt[1] of the (-)5α-methoxymethyl-4β-hydroxy-cyclopent-2-ene-1β(2')acetic acid (I) was treated for 12 hr at r.t. with 2 equiv of aqueous potassium triiodide solution to form the iodolactone IIa in 96% yield, as a colorless oil, /α/$_D$= +45.5°[8].

Its acetate, IIb , m.p. 74.5-76° /α/$_D$ = +18.5°(c=0.97) was then converted with tributyl tin hydride[9] at 55° for 3 hr into the lactone acetate, IIc, a colorless oil, $/\alpha/_D$= +74.3°(c=1.51) in 90% yield after chromatographic purification. Selective cleavage of the acetate IIc by perchloric acid in methanol, for ca.3 hr, gave the hydroxylactone IId , oil , $/\alpha/_D$= +22.5°(c=1.35).

The same compound IId was directly obtained from IIa by reduction either with tributyl tin hydride or with chromous acetate in dimethylsulfoxide in the presence of ethanethiol[10,11]

Treatment of the (+)hydroxylactone, IId , in pyridine at 25° with p-toluensulfonylchloride (1.25 equiv) for 20 hr afforded the tosylate IIe, m.p. 102-103°, $/\alpha/_D$= +56.1°.

The reaction of this compound with potassium acetate and acetic acid (8 equiv) in dimethylformamide at reflux temperature yielded a mixture of the inverted acetate, IIIb, m.p. 86-88°(from hexane), $/\alpha/_D$= -12.9°, $/\alpha/_{365°}$=-18°(c=0.82) and of cyclopent-3-ene derivative, IVa, m.p.47-48°(from hexane), $/\alpha/_D$= -256°, $/\alpha/_{365°}$= -811.4°(c=0.5), N.M.R. : 5.99 $\delta$ (2H, m, $C_3$ and $C_4$ vinylic protons), 5.15 $\delta$ (1H, m, $C_2$ proton near to oxygen), resulting from elimination reaction in a ratio of 84 : 16.

Several attempts to convert the 5α-methoxymethylether IIIb into the 5α-hydroxymethyl-4α-acetoxy-lactone IIId failed: in fact, $BBr_3$ cleavage of IIIb gave a diol derivative in poor yield, and the treatment of the same IIIb with iodine and sodium borohydride in carbon tetrachloride[12] afforded the iodomethyl derivative IIIc, m.p. 102-103°, $/\alpha/_D$= -28.3°, from which the following reaction with potassium acetate in dimethylformamide led to hexocyclic methylene compound, IIIe, oil, as the only product[13].

On the contrary, in methylene chloride at 0°, $BBr_3$-cleavage of the 5α-methoxymethylether-4β--p-toluenesulfonate, IIe,[14] easily afforded the 5α-hydroxymethyl-4β-p-toluenesulfonate, IIf, m.p.77-78°, $/\alpha/_D$= +54.8°, $/\alpha/_{365°}$= +177°, from which, by inversion at C-4 with potassium acetate in dimethylformamide, a mixture of the 5α-hydroxymethylcyclopent-3-ene derivative , IVb , oil, $/\alpha/_D$=-217°, $/\alpha/_{365°}$= -763°, IR : 1765 $cm^{-1}$( carbonyl lactone), 1600 $cm^{-1}$(double bond), and of the expected 5α-hydroxymethyl-4α-acetoxylactone, IIId, m.p. 165-166,5°, $/\alpha/_D$= +46.5°, $/\alpha/_{365°}$= +166°, was obtained.

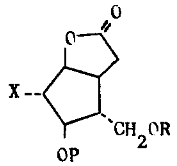
Unfortunately, it was impossible to obtain an aldehydic compound from IIId either with a modified Collins procedure[15] or with Moffatt's reagent[16].

However, the use of the p-phenylbenzoate esters allowed us to overcome all these difficulties.

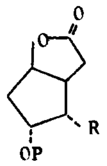
Selective cleavage of the acetate IIIb with $HClO_4$ in methanol at 25° for 4 hr gave the inverted (-)4α-hydroxy-5α-methoxymethyl ether-lactone IIIa, differing first of all, from the (+)-4β-hydroxy epimer IId for being a solid, m.p. 105-106°, $/\alpha/_D$= -3.6°, $/\alpha/_{365°}$= +12°(c=0.92).

Esterification of IIIa with p-phenylbenzoyl chloride (1.5 equiv) in pyridine for 2 days at r.t. afforded the p-phenylbenzoate IIIf, m.p.81-82°, $/\alpha/_D$= -76.5°, from which, by $BBr_3$-cleavage in methylene chloride for 15 min at 0°, the 5α-hydroxymethyl-lactone-4α-p-phenylbenzoate, IIIg, m.p. 145-146°, $/\alpha/_D$= -30.5° was obtained.

By oxidation of the alcohol IIIg with the Collins reagent[15] the p-phenylbenzoate aldehyde , IIIi, m.p. 148-149°(dec.), $/\alpha/_D$= -16.7° was obtained, which was treated with the sodium derivative

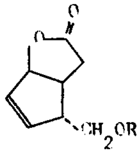


| II | X | P | R |
|---|---|---|---|
| a | I | H | Me |
| b | I | Ac | Me |
| c | H | Ac | Me |
| d | H | H | Me |
| e | H | Tosyl | Me |
| f | H | Tosyl | H |

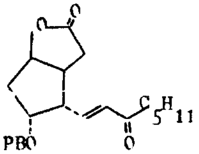


| III | P | R |
|---|---|---|
| a | H | $CH_2OMe$ |
| b | Ac | $CH_2OMe$ |
| c | Ac | $CH_2I$ |
| d | Ac | $CH_2OH$ |
| e | Ac | $=CH_2$ |
| f | PB | $CH_2OMe$ |
| g | PB | $CH_2OH$ |
| i | PB | CHO |
| l | PB | $=CH_2$ |

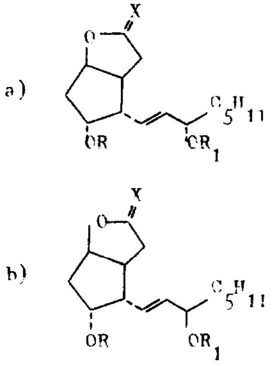
PB = p-phenylbenzoate



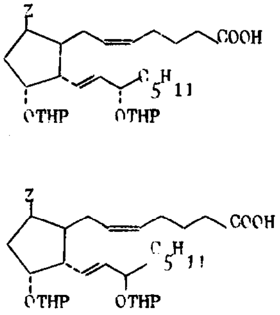
IVa R = Me
IVb R = H



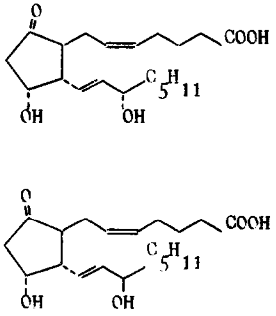
V



| | X | R | $R_1$ |
|---|---|---|---|
| VI | O | PB | H |
| VII | O | H | H |
| VIII | O | THP | THP |
| IX | <H, OH | THP | THP |



| | Z |
|---|---|
| X | <H, OH |
| XI | =O |



XII

of dimethyl-2-oxo-heptylphosphonate in benzene to form the trans-enone-lactone V , as a crystalline product, m.p. 112-113°(from ether), $/\alpha/_D$= -196°, $/\alpha/_{365°}$= -928°, with 60% yield from IVc.

The following step, $Zn(BH_4)_2$ reduction in ether-dimethoxyethane(5:1), afforded a mixture of 15R and 15S epimers, showing almost the same chromatographic mobility.

After several fractionated crystallizations from isopropyl ether,the less polar 15*R* epimer, VIb,could be obtained as a pure compound, m.p. 141-142°,$/\alpha/_D = -152°$;thereafter from the mother liquors, by chromatography on $SiO_2$ (ethyl ether-isopropyl ether 1:1 as eluent), the 15*S* epimer, VIa , m.p. 90-91°,$/\alpha/_D = -154°$ was recovered.

Using a well known procedure[17]: i) saponification to the diol-lactones VIIa (m.p. 79-81°, $/\alpha/_D = -36°$) and VIIb (m.p. 78-79°,$/\alpha/_D = -57°$); ii) conversion to the related THP-ethers VIIIa (oil,$/\alpha/ = -86°$) and VIIIb (oil,$/\alpha/_D = -3.5°$); iii) diisobutylaluminum hydride reduction to the lactols IXa (oil,$/\alpha/_D = -75°$) and IXb (oil,$/\alpha/_D = +15.5°$) were performed.

Condensation of IXa with the Wittig reagent derived from triphenylphosphoniopentanoic acid and NaH in DMSO afforded the 5-*cis*-13-*trans*-8,12-diiso-9β,11α,15*S*-trihydroxy-prostadienoic acid 11,15-bis-THP-ether, Xa ,(oil,$/\alpha/_D = -101°$).Oxidation of Xa to XIa,followed by acetone-0.1N oxalic acid treatment provided pure 8,12-diiso-$PGE_2$ $\left[\text{ent-PG}(E\beta\beta)_2\right]$,XIIa,oil,$/\alpha/_D = +33.2°$,$/\alpha/_{365°} = +323°$ (c= 1% ethanol). In similar way from IXb we prepared the 8,12-diiso-15*R*-$PGE_2$, XIIb , oil,$/\alpha/_D = +22°$,$/\alpha/_{365°} = +270°$ (c=0.3% in ethanol).

*Experimental*:Unless otherwise stated, specific rotations were measured in $CHCl_3$ solution (c=1%) at 20°, with a P-141 Perkin-Elmer polarimeter. N.M.R.spectra were recorded on a Varian HA-100 (100 MHz) spectrometer in $CDCl_3$ with TMS as internal reference ($\delta = 0.0$).

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