Tetrahedron Letters No. 34, pp 3021 - 3024, 1975. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESES OF 11-DEOXY-11α-HYDROXYMETHYL PROSTAGLANDIN Es[1)]

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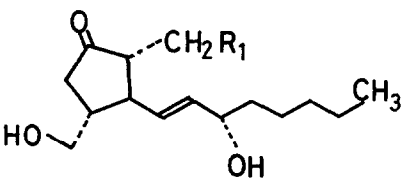
(Received in Japan 30 June 1975; received in UK for publication 14 July 1975)

As a part of the program to clarify the relationship between the pharmacological activities and the structures, we undertook the total syntheses of 11α-hydroxymethyl prostaglandins, in the hope that those compounds will exhibit higher and more selective biological activities than naturally occuring prostaglandins.[2)]

In this communication, we describe stereospecific syntheses of 11-deoxy-11α-hydroxymethyl prostaglandin Es (Ia, Ib, Ic).



Ia, $R_1 = (CH_2)_5COOH$

Ib, $R_1 = C\equiv C-(CH_2)_3COOH$

Ic, $R_1 = \overset{H}{\underset{}{}}C=C\overset{H}{\underset{}{}}-(CH_2)_3COOH$

The starting material, 3,4-dimethoxycarbonylcyclopentanone II obtained as a mixture of cis and trans isomers by Dolby's method[3)], was isomerized after usual ketalization, to the trans isomer III by treatment with NaOMe in MeOH-benzene at 50°C for 3 hrs. By $LiAlH_4$ reduction of III in ether, followed by cathylation with 2 eq. of ethylchloroformate-pyridine and treatment with aqueous p-TsOH, the ketone dicathylate IV was obtained in 65% yield. IV; nmr*[1)] 4.22 (4H, q, J=7) 4.30 (4H, broad s).

Treatment of IV with 1 eq. of t-BuOK in THF for 1 hr at -60°C afforded the crystalline lactone V in 80% yield, accompanied by a small amount of the hydroxy ester VI which was quantitatively converted to the lactone V on reflux with

p-TsOH in benzene. V; m.p. 65~66°C, ir (nujol) 1772, 1747 nmr 3.54 (Ha, d, J=9) 3.33 (Hb, m). Alkylation of the cis lactone V with Ra, b CH_2I[4a,b] in the presence of t-BuOK in DMSO at 5~15°C proceeded smoothly to afford the lactones VIIa, b alkylated stereospecifically at the α-side. VIIa; 80% yield, ir 1785 nmr 3.62 (COOMe). VIIb; 72% yield, ir 1786 nmr 3.67 (COOMe).

The selective hydrolysis and the spontaneous decarboxylation of the lactone moiety of VIIa, b by refluxing in aqueous dioxane-Na_2HPO_4 (or $AcONH_4$) yielded the ketones VIIIa, b. VIIIa; 67.3% yield, ir 3540, 1740 nmr 4.20~3.50 (6H, m). VIIIb; 70~75% yield, ir 3470, 1740. However, treatment of the lactones VIIa, b with comparatively strong base such as K_2CO_3 or NaOMe in MeOH resulted in the undesired cleavage of the five membered ring ketone to yield IXa, b.

Thus, the stereochemical configulations on the five membered ring in the ketones VIIIa, b should be the same as those of prostaglandin E.

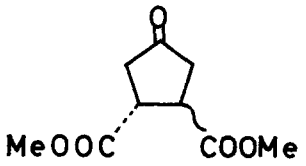
Ketalization of VIIIa, b by the usual method (ethylene glycol-p-TsOH) gave the corresponding ketals Xa, b. Xa; 70% yield, ir 3520, 1740 nmr 3.90 (4H, s, $-OCH_2CH_2O-$). Xb; 70% yield, ir 3470, 1740.

On catalytic reduction with Lindlar catalyst in benzene, the alcohol Xb afforded the cis olefin Xc in a quantitative yield. Xc; nmr 5.4 (2H, m, $\overset{H}{\diagdown}C=C\overset{H}{\diagup}$).

Collins oxidation[5] of Xa, b, c, followed by Wittig reaction with tri-n-butyl-2-oxo-heptylidene phosphorane in ether at room temperature, yielded the enones XIa, b, c, which on reduction with $NaBH_4$ in MeOH at 0°C gave the mixture of 15-epimeric alcohols XIIa, b, c. XIa; 85.5% yield, ir 1700, 1677, 1630 nmr 6.10 (C_{14}-H, d, J=15) 6.65 (C_{13}-H, dd, J=7,15). XIb; 86% yield, ir 1697, 1676, 1630 nmr 6.08 (C_{14}-H, d, J=16) 6.72 (C_{13}-H, dd, J=6,16). XIc; 85.5% yield, ir 1695, 1673, 1630.

The epimeric alcohols XIIa, b, c were hydrolyzed with aqueous MeOH-KOH at room temperature, and the acids thus obtained were re-esterified with diazomethane to facilitate the separation by the subsequent column chromatography. The more polar fraction on thin layer chromatography[6] was tentatively assigned to the desired 15α-epimer.

Hydrolysis of the 15α-epimer with aqueous MeOH-KOH, followed by removal of



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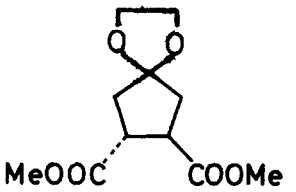

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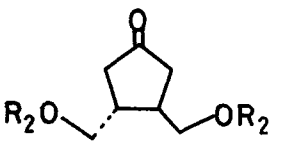

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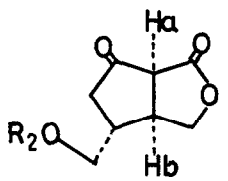

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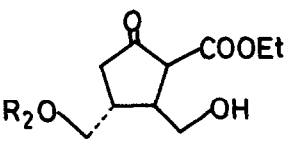

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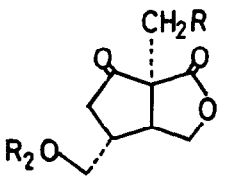
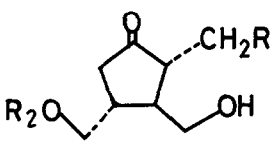
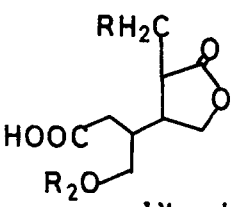


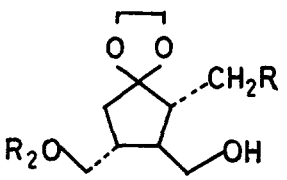
VII a, b



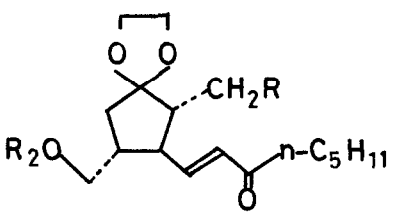
VIII a, b



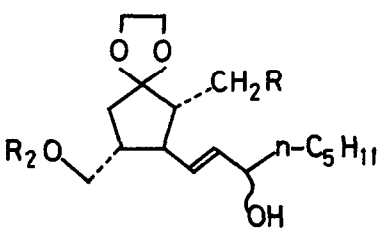
IX a, b



X a, b, c



XI a, b, c



XII a, b, c

R_2 = COOEt

(a) R = $(CH_2)_5COOMe$

(b) R = $C\equiv C-(CH_2)_3COOMe$

(c) R =  $(CH_2)_3COOMe$

the ethylene ketal with p-TsOH in aqueous acetone, gave 11-deoxy-11α-hydroxymethyl prostaglandin Es(Ia, b, c) in good yield. Ia; m.p. 65~66°C, ir 3400, 1730, 1705 nmr (CD_3COCD_3) 5.65 (2H, m). Ib; oily, ir 3400, 1737, 1705 nmr (CD_3COCD_3) 5.65 (2H, m). Ic; m.p. 62~63.5°C, ir (KBr) 3420, 1730, 1712 nmr (CD_3COCD_3) 5.43 (2H, m) 5.66 (2H, m). A synthesis of the optically active form will be described elsewhere.

Acknowledgement: The authors thank Director Dr. K. Arima, Assistant Director Dr. Y. Kishida and the former Assistant Director Dr. K. Tanabe of this laboratories for their encouragement through the course of this work. We also acknowledge Mr. S. Amemiya, Mr. Y. Tajima and Miss M. Sugiura for their valuable assistance.

References and Footnotes

*1) ir (cm^{-1}) spectrum was taken in neat liquids and nmr (δ) spectrum in $CDCl_3$ solution containing tetramethylsilane as internal standard unless otherwise stated.

1) Synthetic studies on prostanoids VI. Part V. K. Kojima and K. Sakai, Tetrahedron Lett., in press.

2) See review. For example, The Prostaglandins Volume 1. (P. Ramwell) Plenum Press, 1973.

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