Tetrahedron Letters No. 43, pp 3709 - 3712, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF OPTICALLY ACTIVE (-)11-DEOXY-11α-HYDROXYMETHYL PROSTAGLANDIN E_1[1)]

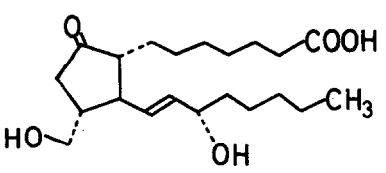
Osamu Oda, Koichi Kojima and Kiyoshi Sakai*

Central Research Laboratories, Sankyo Co., Ltd.

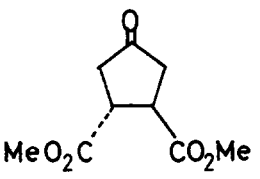
1-2-58 Hiromachi, Shinagawa-ku, Tokyo, Japan

(Received in Japan 28 August 1975; received in UK for publication 15 September 1975)

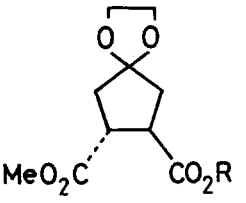
In a previous paper, we have reported on syntheses of (±)11-deoxy-11α-hydroxymethyl prostaglandin Es[1)]. In order to investigate in further detail on their biological activities[2)], in particular on uterus contraction, the optically active forms were required. Now, we wish to describe the synthesis of the optically active 11-deoxy-11α-hydroxymethyl PGE_1 (-)I.



(-)I $[\alpha]_D$ -72.3°
m.p 61~63°C



(-)II $[\alpha]_D$ -119°
(Sigg et al.)
-130°
(from (-)IV)

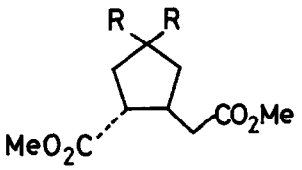


III R=Me, IV R=H
(-)IV R=H $[\alpha]_D$ -27.1°
(-)V R=Me $[\alpha]_D$ -30.3°

The absolute configuration of the diester (-)II which was obtained by H.P. Sigg et al.[3a,b)] as the degradation product of Brefeldin A is shown in above figure.

A partial hydrolysis (aqueous MeOH-K_2CO_3) of the ketal diester III*[1)] gave the mono acid IV which on optical resolution using d-ephedrine, afforded the optically active mono acid (-)IV $[\alpha]_D$ -27.1° in 60% of theoretical yield. By removal (p-TsOH-aqueous acetone) of the ketal group, followed by treatment with CH_2N_2 in ether, (-)IV yielded the diester (-)II $[\alpha]_D$ -130° (reported value $[\alpha]_D$ -119°[3)]). Furthermore, a chemical correlation of (-)IV with the compound, whose absolute configuration was already established, was accomplished as follows

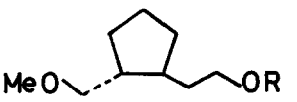
After chlorination of the carboxyl group with oxalyl chloride, (-)IV was submitted to Arndt-Eistert reaction (i. CH_2N_2, ii. AgOBz in MeOH). The ketal VI thus obtained was converted into the ethylene thioketal VII which on the desulfurization with Raney Ni afforded the deoxy VIII. Reduction of VIII with $LiAlH_4$, followed by treatment with NaH-MeI, yielded the dimethyl ether (-)IX $[\alpha]_D$ -58°.



VI R= R= O O

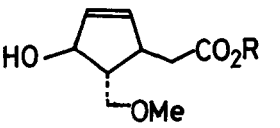
VII R= R= S S

VIII R= R= H



(-) IX R=Me $[\alpha]_D$ -58° (from (-)IV) -61.2° (from XI)

XII R= H



X R=H l-ephedrine salt $[\alpha]_D$ -36°(MeOH)

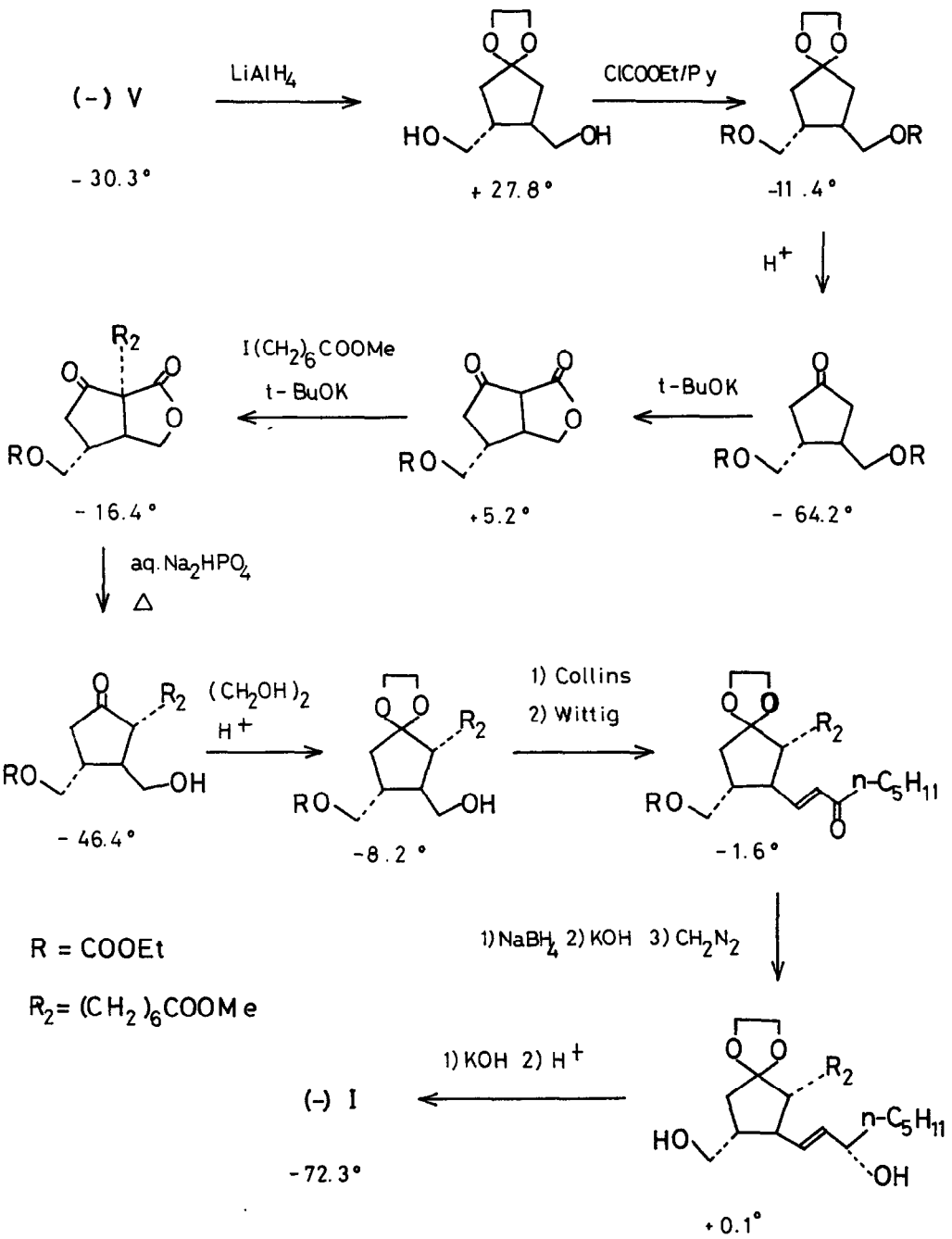
XI R=Me

On the other hand, the undesired enantiomer X in Corey's syntheses[4] on natural prostaglandins was converted into the ester XI by usual method. Catalytic reduction (5% Pd-C) of XI, followed by mesylation ($MeSO_2Cl$/Py) and reduction with $LiAlH_4$, afforded the mono ether XII. By methylation with NaH-MeI, XII gave the dimethylether $[\alpha]_D$ -61.2° identical with the dimethylether (-)IX.

Thus, by the application of the previously reported method,[1] the optically active 11-deoxy-11α-hydroxymethyl PG E_1 (-) I possessing the same absolute configuration as natural PG E was synthesized, starting from the diester (-) V $[\alpha]_D$ -30.3° obtained by treatment of (-) IV with CH_2N_2. Figure 1 shows the synthetic route and $[\alpha]_D$ values of main products.

The optically active form (-)I showed the same power as $PGF_{2\alpha}$ for uterus contraction (Rat), and the side effect as a diarrhea was remarkably reduced. More interestingly, the enantiomer $[\alpha]_D$ +30.1° of (-)V was racemized into $[\alpha]_D$ +1.5° by treatment with NaOMe in benzene at room temperature for 24 hrs. This fact suggests the possibility that the undesired enantiomer can be quantitatively recycled. This racemization may be caused by the cis-trans equilibrium.

Figure 1


(-) V
- 30.3°
LiAlH4
HO
OH
+ 27.8°
ClCOOEt/Py
RO
OR
-11.4°
H+
t-BuOK
RO
OR
- 64.2°
t-BuOK
I(CH2)6COOMe
t-BuOK
RO
+5.2°
R2
RO
- 16.4°
aq. Na2HPO4
Δ
(CH2OH)2
H+
RO
OH
- 46.4°
R2
RO
OH
-8.2°
1) Collins
2) Wittig
R2
RO
n-C5H11
-1.6°
1) NaBH4 2) KOH 3) CH2N2
R = COOEt
R2 = (CH2)6COOMe
1) KOH 2) H+
(-) I
-72.3°
R2
HO
n-C5H11
OH
+0.1°

Acknowledgement: The authors thank Director Dr. K. Arima, Assistant Director Dr. Y. Kishida and the former Assistant Director Dr. K. Tanabe of these laboratories for their valuable help and advice. We also acknowledge Mr. S. Amemiya, Mr. Y. Tajima and Miss T. Sugiura for their valuable assistance

References and Footnotes

*1) Specific rotations were measured in $CHCl_3$ at 20°C with P-141 Perkin-Elmer Polarimeter. The structures of all compounds obtained were supported by ir, nmr and mass spectrum.

1) Synthetic studies on prostanoids VII. Part VI. K. Sakai, J. Ide and O. Oda Tetrahedron Lett., 3021 (1975)

2) See Reviews. For example, Progress in Medicinal Chemistry Vol 8 (part II, chapter 7. The Prostaglandins (M.P. Caton) Butterworths 1971

3) a. H.P. Sigg Helv. Chim. Acta, 47 1401 (1964)
b. H.P. Weber, D. Hauser and H.P. Sigg ibid., 54 2763 (1971)

4) E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker and N.M. Weinshenker J. Amer. Chem. Soc., 92 397 (1970).