Bull. Soc. Chim. Belg. vol. 84/n° 3/1975

CYCLOPENTANONES. XII[x]. AN ALTERNATIVE SYNTHESIS OF PROSTAGLANDINS INVOLVING CATALYTIC HYDROGENATION OF 2,3-DIALKYL-4-DIHYDROXY-2-CYCLOPENTENONES.

R. Coen[+], P. De Clercq[≠], D. Van Haver and M. Vandewalle

State University of Ghent, Department of Organic Chemistry,
Laboratory of Organic Synthesis,
Krijgslaan, 271 (S.4), B-9000 Ghent, Belgium.

Received 17/1/75 - Accepted 14/2/75.

ABSTRACT

A novel approach to Corey's aldehyde is described. A suitable substituted all cis 2,3-dialkyl-1,4-cyclopentanediol system is obtained by catalytic reduction of 2,3-dialkyl-4-hydroxy-2-cyclopentenones. Epimerisation to the prostaglandin configuration occurs spontaneously when later on the Horner reaction is carried out.

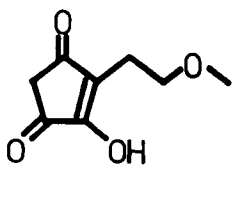
Suitable substituted 2,3-dialkyl-4-hydroxy-2-cyclopentenones, such as IV and IV', are important intermediates in our general approach[1,2,3] to prostaglandin synthesis. Their lithium-liquid ammonia-alcohol reduction and the subsequent steps to PG's have already been dealt with in previous papers.
The present communication describes a synthesis involving the catalytic hydrogenation of IV and IV' as an alternative reduction method. It has been shown by Corey and coworkers[4] that a versatile prostaglandin synthesis involves two Wittig type reactions for introducing the 5,6 and 13,14 double bonds. The side chains of a, for our purpose, suitable 4-hydroxy-2-cyclopentenone must therefore carry latent aldehyde functions which can survive catalytic reduction; a (2'-methoxy)-ethyl and a (2'-phenyl)-ethyl group respectively as the future C_8 and C_{12} side chains fulfil these requirements.

Compounds IV and IV' were obtained starting from 3-(2'-methoxy)-ethyl-1,2,4-cyclopentanetrione (enol form I) by a general and already described method[5]. Protecting the 1- and 4-carbonyl functions with triethyl orthoformate gave II [m.p. 53°C; 80 % yield after recrystallization from n.pentane]. Subsequent Grignard reaction with 2-phenyl-ethyl bromide in THF followed by acid hydrolysis (1 N HCl; 1 hr) afforded (95 % yield after recrystallization from ether) III [m.p. 102°C; $M^{+\cdot}$ at m/e 258; I.R. : 1745, 1705, 1640 cm^{-1}; Rf - 0.55 in ether-benzene 3.7]. Reduction with zinc-acetic acid in methylene chloride at -20°C

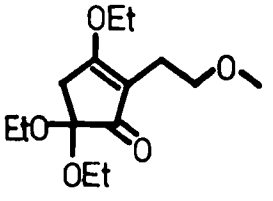
[x] Part XI : ref. 3.

[+] Bursary of the I.W.O.N.L.

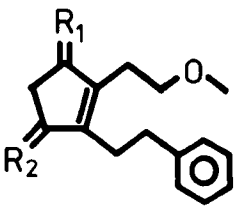
[≠] Aangesteld navorser N.F.W.O.



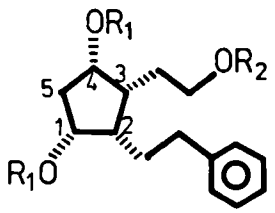
I



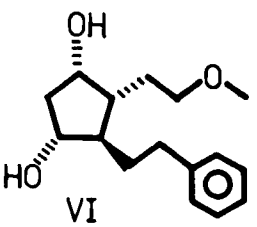
II



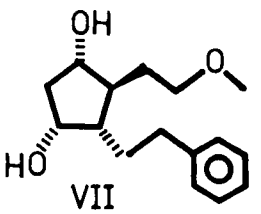
III, $R_1 = R_2 = O$
IV, $R_1 = \overset{H}{\underset{OH}{<}}$, $R_2 = O$
IV', $R_1 = O$, $R_2 = \overset{H}{\underset{OH}{<}}$



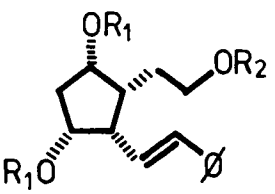
V, $R_1 = H$, $R_2 = CH_3$
VIII, $R_1 = Ac$, $R_2 = CH_3$



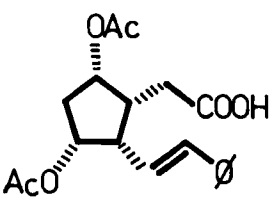
VI



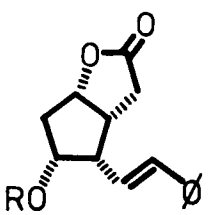
VII



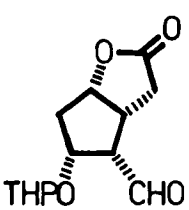
IX, $R_1 = Ac$, $R_2 = CH_3$
X, $R_1 = Ac$, $R_2 = H$



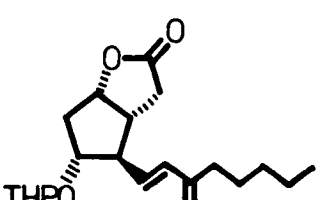
XI



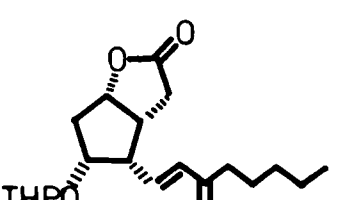
XII, R = H
XIII, R = THP



XIV



XV



XV'

-gave a mixture (yield 65 %) of isomeric cyclopentenolones IV and IV' [$M^{+\cdot}$ at m/e 260; I.R. : 3420, 1710, 1650cm^{-1}; Rf = 0.44 with ethyl acetate-isooctane 8:2] sufficiently pure after alkaline extraction of the corresponding 1,3-cyclopentanedione (formed by competing reduction of the double bond). Catalytic hydrogenation (Raney-Ni W7 dioxane) of the trimethylsilylethers of IV and IV'

and subsequent acid hydrolysis led to a mixture of diastereoisomers* V (75 %), VI (10 %) and VII (15 %). The formation of TMS ether was necessary in order to avoid hydrogenolysis of the hydroxyl group with this catalyst; furthermore the size of the TMS group must enhance the stereoselectivity[6]. The hydrogenolysis could however be avoided by the reduction of IV and IV' with a Raney-Ni modification W2 in ethanol; the isomer distribution being V (63 %), VI (11 %), VII (22 %) and 4 % of an unknown. After column chromatographic separation (silica-gel : ethyl acetate-isooctane 8:2) the yield of the all cis isomer V is 50 % [$M^{+\cdot}$ at m/e 264; I.R. : 3420, 1200, 1120 cm^{-1}; Rf = 0.39 same eluent]; VI and VII gave identical Rf values (0.32). As can be deduced from the reaction sequence the separation of the isomers is not necessary; both V and VI are usable for further synthesis while VII can be removed by alkaline extraction at the moment of the generation of carboxylic acid from the methoxy group (no lactone formation). As however an easy inversion at C_2 of V (C_{12} in PG) could be anticipated[9,10] the further steps were carried out on the pure isomer V in order to evaluate the magnitude of this phenomenon. The di-acetate VIII [$(M-HOAc)^{+\cdot}$ at m/e 288; I.R. : 1745, 1250, 1120 cm^{-1}; Rf = 0.60 in ethyl-acetate-isooctane 8:2] was formed (acetic anhydride-pyridine) in an almost quantitative yield. Benzylic bromination with NBS in refluxing carbon tetrachloride followed by treatment with lithium carbonate in DMF yielded (75 %) IX [$(M-HOAc)^{+\cdot}$ at m/e 286; I.R. 1745, 1250, 1120, 970 cm^{-1}; Rf = 0.59 in ethyl acetate-isooctane 8:2]. The methyl ether was cleaved with boron tribromide (4 eq) in methylene chloride (-20° for 5 days) to the alcohol X [I.R. : 3440, 1745, 1240, 100; Rf = 0.40 in ethyl acetate-isooctane 8:2]. Oxidation of the primary alcohol X with Jones reagent (0°C for 1 hr) have the carboxylic acid XI [$\bar{R}f$ = 0.27 in ethyl acetate] and subsequent hydrolysis of the acetate functions (1.2 N HCl; 80°C for 3 hrs) gave the crystalline γ-lactone XII [m.p. 133°C; $M^{+\cdot}$ at m/e 244; I.R. : 3460, 1770, 1180, 970 cm^{-1}; Rf = 0.44 in chloroform-ethyl acetate 6:4]. The overall yield of XI starting from IX was 60 % after recrystallization from ethyl acetate-isooctane. The tetrahydropyranyl ether XIII [Rf = 0.63 in chloroform-ethyl acetate 6:4; yield 90 %], prepared in the usual way, was oxidised to the aldehyde XIV with osmium tetroxide (catalytic amount)-sodium periodate in water-dioxane (20°, 3 hrs). The unstable aldehyde [Rf = 0.18 in chloroform-ethyl acetate 6:4] XIII was, without purification, treated with the sodio derivative

* For configurational assignment see references 7 and 8.

of dimethyl-2-oxoheptylphosphonate, yielding the epimeric enones XV and XV' [$(M-THP)^{+\cdot}$ at m/e 265, $(M-OTHP)^{+\cdot}$ at m/e 249; I.R. : 1765, 1680, 1630; U.V. : λ_{max} = 226 nm; Rf = 0.71 in ethyl acetate] in a ratio of 2:1, the overall yield starting from XII being 55 %. The configurational assignment followed from the ^{1}H-NMR spectra in accordance with an observation made by Turner and coworkers[10] who showed that in an all cis isomer the olefinic H_{13} is downfield compared to the same resonance for natural PG configuration; H_{13} in XV has δ = 6.80 while for XV' the value is δ = 7.05. The remaining transformation for the synthesis of prostaglandins starting from XV are adequately described in the literature.

ACKNOWLEDGEMENT

We thank the "Nationaal Fonds voor Wetenschappelijk Onderzoek" for financial help to the laboratory.

REFERENCES

1) F. Vanhulle, V. Sipido, M. Vandewalle; Tetrahedron Letters, 24, 2213 (1973).

2) P. De Clercq, M. Vandewalle; Bull. Soc. Chim. Belges, 83, 305 (1974).

3) J. Van Hooland, P. De Clercq, M. Vandewalle; Tetrah. Lett., 4343 (1974)

4) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, W. Huber; J. Am. Chem. Soc., 91, 5675 (1969) and E.J. Corey, N. Shiraname, H. Yamamoto, S. Terashima, A. Vankateswarlu, T.K. Schaaf; J. Am. Chem. Soc., 93, 1490 (1971).

5) L. Van Wijnsberghe, M. Vandewalle; Bull. Soc. Chim. Belges 79, 699 (1970).

6) N. Finch, L. Della Vecchia, J.J. Fitt, R. Stephani, I. Vlattas; J. Org. Chem., 38, 4412 (1973).

7) P. De Clercq, D. Van Haver, D. Tavernier, M. Vandewalle; Tetrahedron, 30, 55 (1974).

8) D. Van Haver, D. Tavernier, M. Anteunis, M. Vandewalle; Tetrahedron, 30, 105 (1974).

9) P. Crabbé, A. Cervantes and M. Meana; J. Chem. Soc. Chem. Comm., 119 (1973).

10) D. Brewster, M. Myers, J. Ormerod, Ph. Otter, A. Smith, M.E. Spinner, S. Turner; J. Chem. Soc., Perkin Transactions I, p. 2796-2804 (1973).