CYCLOPENTANONES. XVII[a] : PROSTAGLANDIN SYNTHESIS INVOLVING THE LITHIUM-LIQUID AMMONIA REDUCTION OF 3-ALKYL-4-HYDROXY-2-(1'-OCTYNYL)-2-CYCLOPENTENONES

P. De Clercq[b], M. De Smet, K. Legein, F. Vanhulle and M. Vandewalle[*]
Laboratory for Organic Synthesis
Department of Organic Chemistry, State University of Ghent
Krijgslaan, 271 (S.4), B-9000 GENT (Belgium)

Received 4/5/76 - Accepted 12/7/76.

ABSTRACT

The present paper describes the lithium-liquid ammonia reduction of 3-alkyl-4-hydroxy-2-(1'-octynyl)-2-cyclopentenones; depending on the nature of the 3-alkyl side chain prostaglandins of the F_1-series or primary prostaglandins of the 2-series are synthesised.

INTRODUCTION

The 4-hydroxy-3-alkyl-2-(1'-octynyl)-2-cyclopentenones (1) are readily available intermediates for the synthesis of prostaglandins. The eight carbon atoms of the C-12 side chain (prostaglandin numbering) are built in at an early stage; the triple bond is a potential trans double bond. Depending on the ultimate aim of the synthesis - prostaglandins of the 2- or 1-series - the 3-alkyl group must be a suitable 2-carbon unit or a saturated 7-carbon unit with a terminal carboxylic function. The present approach is based on the presumption that, due to cross-conjugation, the acetylenic bond can be reduced without interfering with the reduction of the cyclopentenone system; thus a lithium-liquid ammonia reduction with an alcohol as proton donor should yield a trans double bond next to the complete saturation of the cyclopentenone part in the molecule.

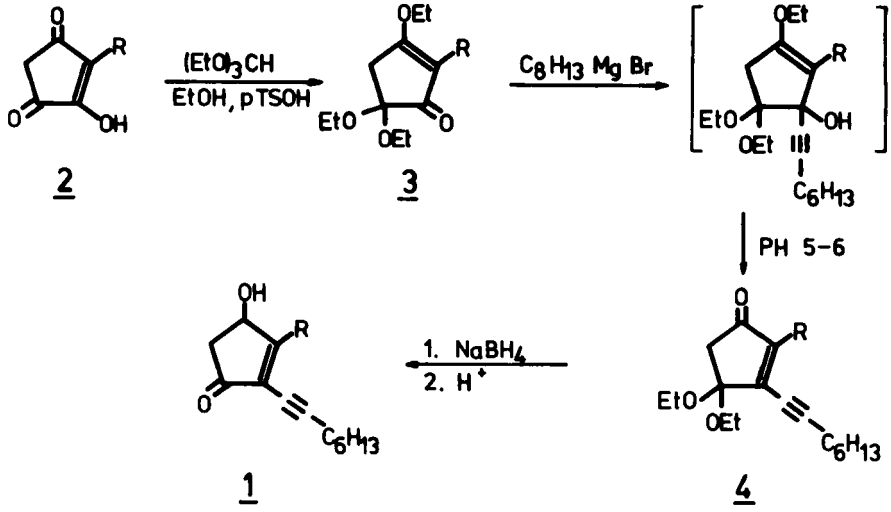
We have already given ample evidence of the stereochemical outcome[1,2] of the lithium-liquid ammonia reduction of 4-hydroxy-2,3-dialkyl-2-cyclopentenones and its use in prostaglandin synthesis[3-6]. We now want to describe the results of this reduction on the more complicated system present in compound 1. Preliminary results based on the reduction of 1a have already been published[6].

---

[a] Cyclopentanones XVI; in press.
Cyclopentanones XV ; Synthesis 39 (1976).

[b] Aangesteld Navorser N.F.W.O.

[*] To whom all correspondence should be addressed.



a ; R = $(CH_2)_6$ COOH
b ; R = $(CH_2)_2$ OCH_3
c ; R = $(CH_2)_2$ $OCH_2\phi$
d ; R = CH_2 COOH
e ; R = $(CH_2)_6$ COOEt
f ; R = CH_2 COOEt

SCHEME 1

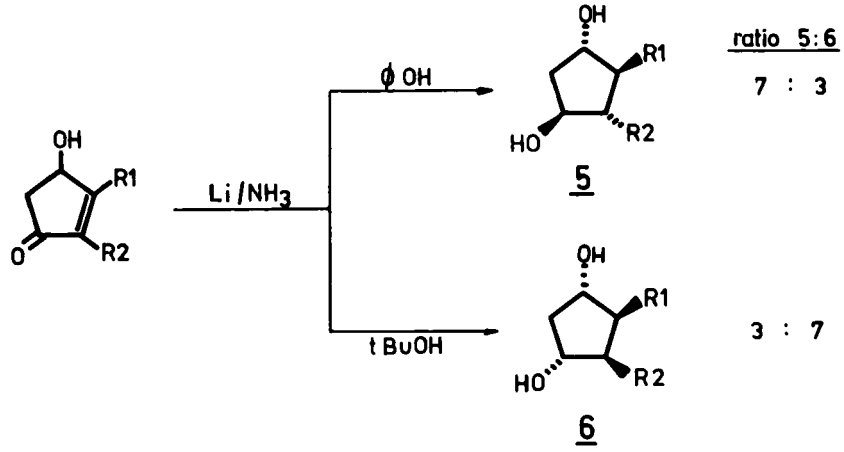
DISCUSSION

The hydroxy cyclopentenones 1a, b and c were obtained from 2a, b and c according to a general and already described method[7] (scheme 1). However, a few remarks on the synthesis of those particular compounds have to be made. Blooking of the 1- and 4-carbonyl functions in 2a and 2d occurred with the expected concomitant esterification of the carboxyl group, yielding respectively 3e and 3f. Whereas the selective hydrolysis of the ester function could be achieved in the case of product 3e, leading to the acid 3a in good yield, no efficient procedure could be found to hydrolise compound 3f to the acid 3d; in every case the hydrolysis of the vinylogous ester in the ring occurred. Since the octynyl-side chain has to be built in by means of a Grignard reaction the ester 3f is useless for further work; compounds 2b and 2c were therefore choosen as substitutes since a primary ether function can be considered as a latent carboxylic acid.

Reaction with octynyl magnesium bromide and subsequent hydrolysis in mild acid affords compounds 4a, b and c in high yield. The selective allylic rearrangement is brought about in buffer solution at pH 5-6; the presence of the triple bond allows an easy carbenium ion formation, thus enhancing the allylic rearrangement. When the side chain introduced by the Grignard reaction is linked to the ring by a sp^3-C atom the allylic rearrangement only occurs in a fairly acidic medium (pH = 4 or less), provoking at the same time the hydrolysis of the acetal function, thus yielding the corresponding cyclopentenediones, useless for further work. Indeed, only compounds 1 are suitable for the above mentioned dissolved metal reduction. The position isomer of 1 (a 4-hydroxy-3-(1'-octynyl)-2-alkyl-2-cyclopentenone) would afford a fully saturated cyclopentanediol, the triple bond being in conjugation with the enone system.

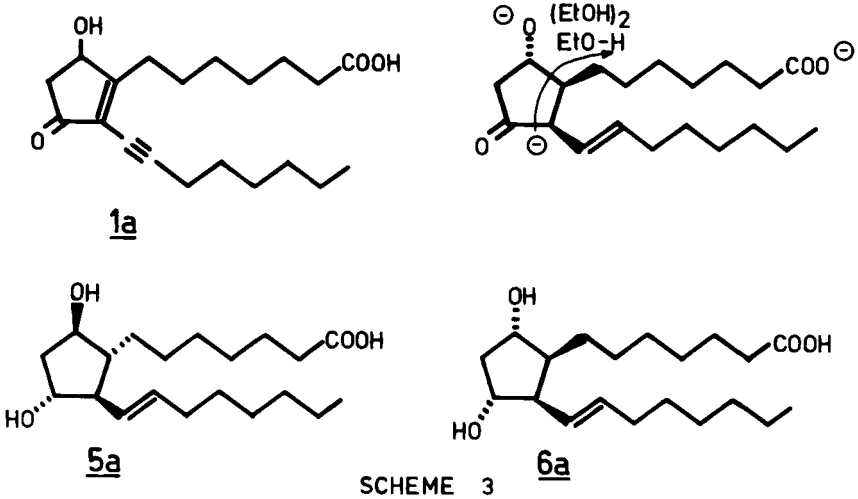
Reduction of the crude 4a, b and c with sodium borohydride leads to 1a, b and c in overall yields (from 3a and 3b, c) of respectively 47 % and 65 %.

The lithium-liquid ammonia alcohol reduction of 2,3-dialkyl-4-hydroxy-2-cyclopentenones has been studied in our laboratory. When the alkyl groups are attached to the ring through a methylene unit, the stereochemical outcome of the reduction is dependent on the acidity of the proton donor[2]. Whereas the use of phenol as proton-donor leads to the cyclopentanediols 5 as the major products, t.butanol yields mainly the cis isomers 6 by a mechanism involving internal protonation (scheme 2).



SCHEME 2

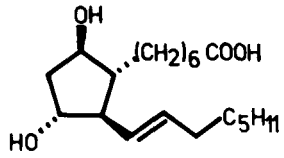
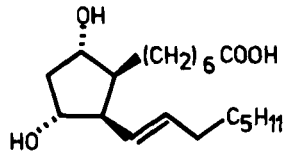
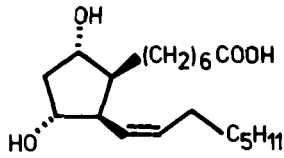
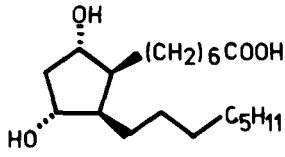
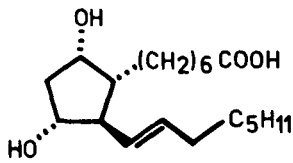
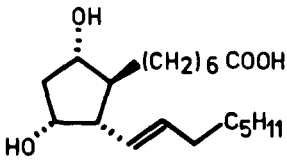
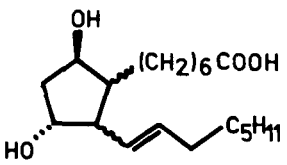
Reduction of 1a in the presence of t.butanol would thus directly afford 15-deoxy-8-epi-$PGF_{1\alpha}$ (6a). The straightforward results obtained on the model compounds could however not be reproduced; this seems to be due to solubility factors. For the particular reduction of 1a to 6a good reduction conditions were found using an observation made by Kelly and coworkers[8]; they showed in a kinetic study that alkoxy ions are rapidly solvated in liquid ammonia by three alcohol molecules. Thus solvation of the preformed dianion of 1a with ethanol could lead to the cis isomer 6a by a pseudo-internal protonation (scheme 3).



SCHEME 3

The total yield of the diol fraction was 56 % after column chromatography. Eight different cyclopentanediols were isolated after separation by Craig counter current distribution (CCD) on the free acids and by column chromatography on the corresponding methylesters. As can be seen from table 1, CCD allows an easy separation of the cyclopentanediols possessing a cis and trans relationship between the 1- and 4-hydroxylgroups (K value < 0.27 for trans and > 0.35 for cis compounds). The total percentage of products with a cis relationship between the 2- and 3-side chains (80 %) is even higher than for the model compounds in the presence of t.butanol. Structural determination and configurational assignment followed from spectroscopic data (mainly ^{1}H-NMR and mass spectroscopy). Cyclopentanediol 5a was converted to the fully saturated compound 11"a (diazomethane, catalytic hydrogenation and acetic anhydride-pyridine). In the same way both cyclopentanediols 6a and 6'a led separately to compound 12"a; the latter product was also obtained from 6"a (diazomethane and acetic anhydride-pyridine). The exact configuration of both 11"a and 12"a are

TABLE 1

	Compound	%	CCD : K	R_f* (silica gel ethyl acetate)
	5a	5	0.27	0.34
	6a	70	0.35	0.33
	6'a	10	0.43	0.38
	6"a	5	0.47	0.31
	7a	3	0.50	0.41
	8a	2	0.51	0.52
	9a, 10a	2.5 2.5	0.22 0.22	0.33 0.35

* for the corresponding methyl esters.

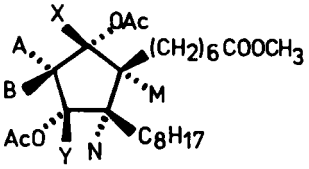
proven by comparison of their ^{1}H-NMR spectral data (Table 2) with the data of model compounds whose configurations were proven by us[1,3,5,9].

The configurations of the remaining cyclopentanediols 7a, 8a, 9a and 10a were assigned on basis of the mass spectra[10] of the corresponding trimethylsilyl ethers and n.butylboronates (for the cis-diols) of the corresponding methyl esters and on basis of ^{1}H-NMR spectral data[11] (for the methyl ester of 15-deoxy-$PGF_{2\alpha}$, 7a).

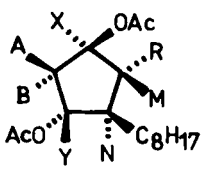
In order to synthesise $PGF_{1\beta}$, the reduction of 1a was carried out in the presence of phenol as proton donor. Practically the same ratio (77:23) of the two isomers 5a and 6a was found as for the model compounds. However the presence of the acetylenic bond badly influences the yield (20 % diol fraction, contamined with 34 % fully saturated diols).

TABLE 2

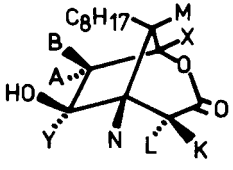
^{1}H-NMR data : 300 MHz, solvent $CDCl_3$



12"a



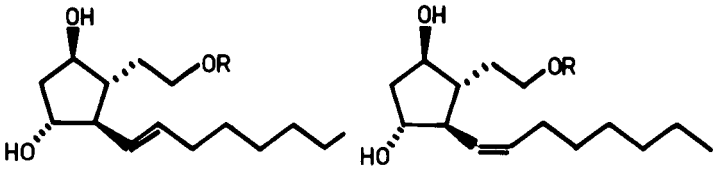
11"a; R=$(CH_2)_6COOCH_3$ 11"b; R=$(CH_2)_2OCH_3$



19

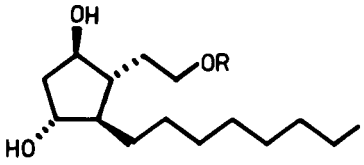
	12"a	11"a	11"b	19
δ_A	1.54	2.00	2.01	2.66
δ_B	2.67	2.00	2.01	b
δ_X	4.84	4.91	4.95	4.68
δ_Y	4.84	4.91	4.93	4.31
δ_M	2.12	1.41	b	b
δ_N	2.12	1.41	b	2.29
J_{AB}	-16.15	-	-	-16.0
J_{AX}	∿ 3.2	6.4	a	1.2
J_{AY}	∿ 3.2	6.4	a	7.5
J_{BX}	7.8	6.4	a	a
J_{BY}	7.8	6.4	a	3.5
J_{XM}	a	a	a	a
J_{YN}	a	a	a	1.2
J_{MN}	a	a	a	a

[a] Could not be measured. [b] Could not be located.



5b ; R = CH_3 5'b ; R = CH_3

5g ; R = H 5'g ; R = H



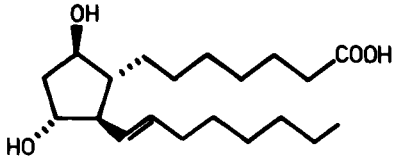
5"b ; R = CH_3

5"g ; R = H

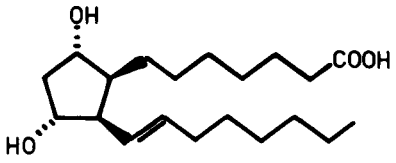
SCHEME 4

For the homologues 1b and 1c only the reduction in the presence of phenol was suitable for further works although the yield of the reduction was low (25 %). With less acidic proton donors a substantial amount of byproducts were formed which lacked the oxygen function in the side chain. With phenol as proton donor only products with the all trans configuration were formed; no isomers with configuration 6 could be detected. The diol fraction consists of 5b, 5'b and 5"b (for the reduction of 1b) in a ratio of 6:3:1. As shown by Stork[12] a 13,14-Z double bond in prostaglandins can be isomerised easily; separation of the Z and E isomers is therefore not necessary for preparative work. However in order to elucidate structures the three compounds were separated by column chromatography. Both 5b and 5'b gave 5"b on catalytic hydrogenation. Proof for the all trans configuration follows from comparison of the ^{1}H-NMR spectral data of the corresponding diacetate 11"b (obtained from 5"b) with model compounds[1,3,5,9] and with 11"a (table 2). The homologue 1c is an interesting starting material. Upon dissolved metal reduction, the formation of the all trans system (including the E double bond) will occur next to the cleavage of the benzyl ether. Best results for the reduction were found when a mixture of ethanol-phenol (9:1) was used as cosolvent and proton donor. The diols 5g, 5'g and 5"g were obtained in a total yield of 35 % (identical ratio as for the b series in Scheme 4). It was unnecessary to prove the configurations at this

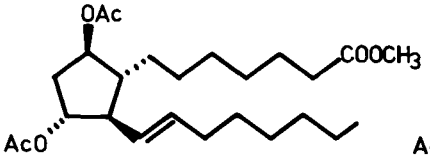
stage since the mixture eventually led to the same lactones 17 (Scheme 6) as starting from 1b.



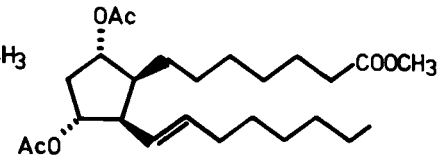
5a



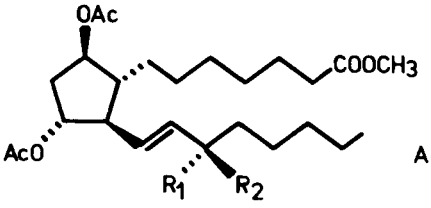
6a



11a

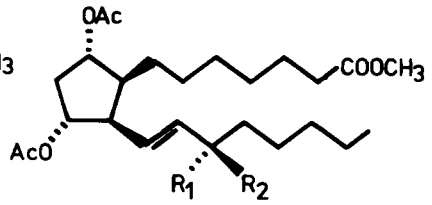


12a



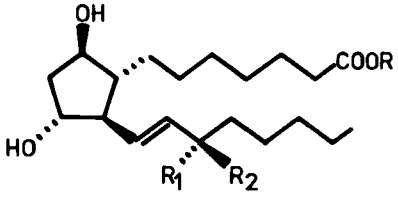
13a ; R_1 = OH, R_2 = H

14a ; R_1 = H , R_2 = OH



15a ; R_1 = OH , R_2 = H

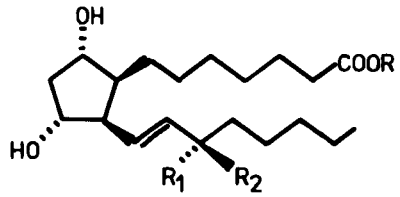
16a ; R_1 = H , R_2 = OH



$PGF_{1\beta}$; R_1 = OH, R_2 = H

15R epimer ; R_1 = H , R_2 = OH

(R = H or CH_3)

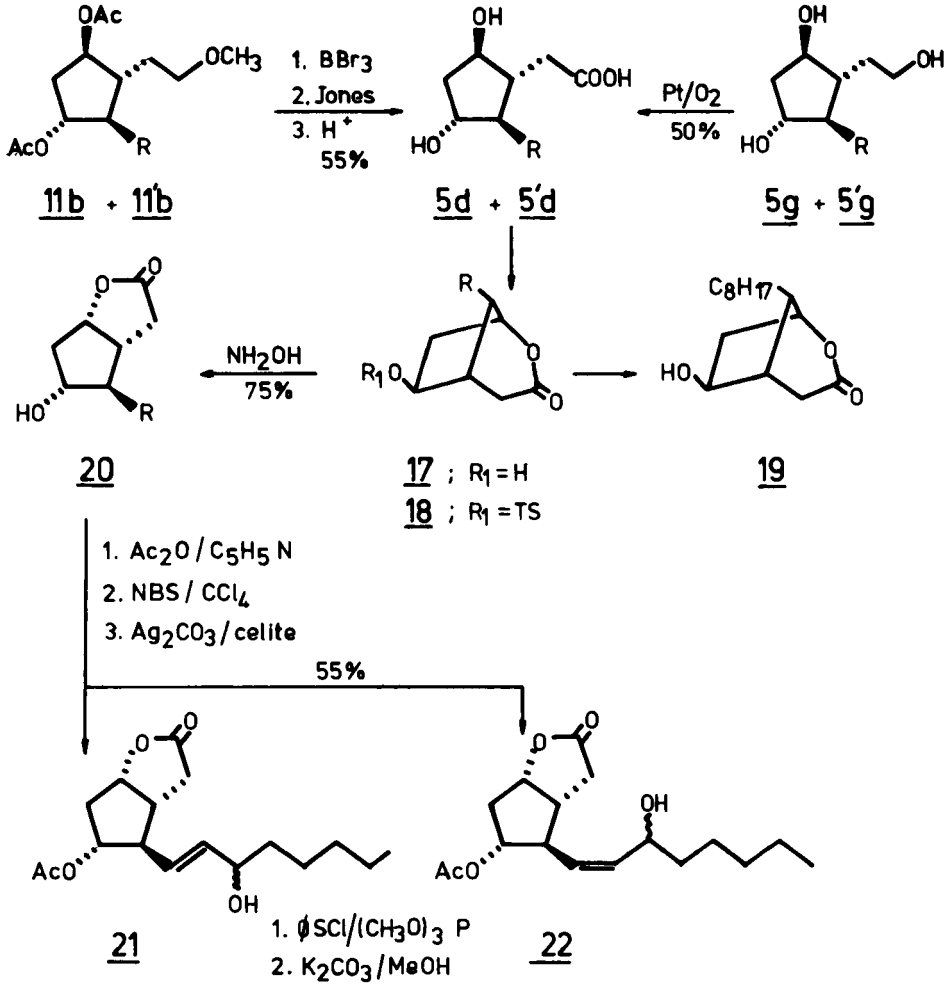


8-iso-$PGF_{1\alpha}$; R_1 = OH, R_2 = H

15R epimer ; R_1 = H , R_2 = OH

(R = H or CH_3)

SCHEME 5



R = Z and E 1'-octenyl

SCHEME 6

The results of the lithium-liquid ammonia-alcohol reductions of compounds 1a, b and c do not follow the general trend as was found for similar hydroxycyclopentenones with the side chains attached to the cyclopentane ring through a methylene unit. Thus the acetylenic function not only has an influence on the yield of the reduction, but also on the stereochemical outcome.

Once the desired cyclopentanediols obtained, the further transformation to prostaglandins were undertaken. In the case of 5a and 6a only the 15-hydroxyl group remained to be introduced for the synthesis of respectively $PGF_{1\beta}$ and 8-epi-$PGF_{1\alpha}$; the reaction sequence is identical for both compounds (Scheme 5). The corresponding methyl esters (11a or 12a) were refluxed with NBS in carbon tetrachloride; the resulting unstable allylic bromides were directly converted to the alcohols with freshly prepared silver carbonate on celite and 1 eq water in acetone[13]. After purification the overall yield (from 5a or 6a) was 60 %. Separation of the 15-epimers 13a, 14a and 15a, 16a was accomplished by column chromatography on silica gel with chloroform-ethyl acetate (7:3) as eluent. On the basis of their TLC behaviour (silica gel) the more polar isomers (13a and 15a) were given the 15S configuration[14]. The ^{1}H-NMR[11] and other spectral data are in complete accordance with those structures.

Hydrolysis of the four isomers 13a, 14a, 15a and 16a with potassium carbonate in dry methanol[15] yielded the pure $PGF_{1\beta}$ methyl ester, 8-epi-$PGF_{1\alpha}$ methyl ester and the corresponding 15R epimers after purification on Sephadex[16] LH-20 with isooctane-chloroform-acetic acid-ethanol (100:100:2:30) as eluent (yield 70 %). Structures were proven by ^{1}H-NMR spectral data[11], by mass spectrometral data of the corresponding trimethylsilyl ethers[10], and by comparison of melting points and R_f values with the literature (table 3). Pure $PGF_{1\alpha}$, 8-epi-$PGF_{1\alpha}$ and the corresponding 15R epimers were obtained by hydrolysis of 13a, 15a and 14a, 16a respectively with potassium carbonate in methanol and water (1:1) and purification on Sephadex[16] LH-20 (yield 90 %). Again the structures were proven by ^{1}H-NMR spectral data[11] and by comparison of melting points and R_f values with the literature (table 3).

For the synthesis of the natural prostaglandins of the 2-series, compounds 5b (+ 5'b) and 5g (+ 5'g) are suitable intermediates. The presence of the 2-carbon side chain enables the differentiation of the two hydroxyl functions so that specific inversion at C-9 (PG numbering) is possible. The intermediates were therefore transformed to the δ-lactones 17 (scheme 6); as already mentioned these reactions were performed on a mixture (R=Z and E 1'-octenyl).

TABLE 3

	R_f value[a]	Melting point measured	Melting point literature
$PGF_{1\beta}$ methyl ester	0.20	94-96°C	101-102°C[17]
15R-$PGF_{1\beta}$ methyl ester	0.23	b	c
8-epi-$PGF_{1\alpha}$ methyl ester	0.20	78-81°C	83-84°C[17]
15R-8-epi-$PGF_{1\alpha}$ methyl ester	0.25	45-46°C	c
$PGF_{1\beta}$	0.10	117-117.5°C	116°C[18], 113-115°C[17]
15R-$PGF_{1\beta}$	0.11	b	c
8-epi-$PGF_{1\alpha}$	0.10	b	c
15R-8-epi-$PGF_{1\alpha}$	0.12	b	c

[a] Silica gel; eluent : isooctane-chloroform-acetic acid-ethanol (100:100:2:30).

[b] non crystallisable oil.

[c] no literature data available.

Definite proof of the structure of the lactone 17 was obtained by comparison of the ^{1}H-NMR spectral data of the corresponding saturated derivative 19 with compounds previously synthesised in our laboratory[3,5] (table 2). Treatment of the corresponding tosylate 18 with hydroxylamine yielded the γ-lactone 20[20].
Now that the correct configuration[5] is obtained still two reaction sequences have to be performed to obtain 23, a product already synthesised by other methods : introduction of the 15-hydroxyl function and isomerisation of the Z double bond. The formation of the 15-hydroxyl function was carried out as described above. The mixture of 21 and 22 (IR spectrum bands at 965, 740 and 695 cm^{-1}) was treated, according to the procedure of Stork[12], successively with phenyl sulphenyl chloride and trimethyl phosphite; the IR spectrum of the crude mixture showed only the band at 965 cm^{-1} typical for the E double bond. Subsequent hydrolysis of the acetate function gave 23 (75 % yield overall) identical with an authentic sample. The remaining transformations to the primary prostaglandins have already been described[19].

EXPERIMENTAL SECTION

UV-spectra were recorded on a Cary 15 spectrometer, IR-spectra on a Pye-Unicam SP-1000 or a Perkin-Elmer 337 spectrometer. Mass spectra were obtained on an AEI-MS902 or a CEC 21-104 mass spectrometer. ^{1}H-NMR-spectra were recorded on a Varian A-60, HA-100 or a Varian HR-300. R_f values are quoted for Merck silicagel 60 GF_{254} t.l.c. plates of thickness 0.25 mm.

3,5,5-triethoxy-2-(6'-carboxyhexyl)-2-cyclopenten-1-one (3a).

A solution of 2a (30 g; 0.12 mole), triethyl orthoformate (75 g; 0.51 mole) and p.toluene sulphonic acid (200 mg) in dry ethanol (400 ml) was heated for 30 hr; the ethyl formate generated was allowed to distill through an efficient reflux condenser. The reaction mixture was cooled to 20°C, treated with solid sodium carbonate, filtered and concentrated in vacuo. Ether was added, the ether solution was extracted several times with a saturated sodium carbonate solution and washed with water. The ether layer was dried (Na_2SO_4), filtrated and concentrated in vacuo. The yield on 3e was 95 %.

R_f (ethyl acetate-isooctane-acetic acid, 60:40:8) = 0.60.

UV : λ_{max} (methanol) = 265 nm (ε = 15.600).

IR : ν^1 (cm^{-1}) = 1745, 1710, 1645, 1160, 1050, 940 and 880.

MS : m/e at 370 ($M^{+\cdot}$, 1 %), 341 (9), 327 (50), 326 (100), 325 (82), 297 (62), 251 (82), 153 (66), 125 (58), 105 (61).

C-H analysis : found : C, 63.40; H, 8.90 %. $C_{20}H_{34}O_6$ requires : C, 64.84; H, 9.25 %.

A solution of the ester 3e (13.2 g; 0.036 mole) and sodium hydroxide (1.44 g; 0.036 mole) in water-ethanol (200 ml; 1:1) was refluxed for 2 hr. The solution was then concentrated in vacuo to 100 ml. Water was added and the water layer was washed with ether. The aqueous solution was acidified with phosphoric acid to pH 6 and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4). Usual work-up gave 3a (yield : 72 %) sufficiently pure for further use.

R_f (same eluent as for 3e) = 0.49.

UV : λ_{max} (methanol) = 265 nm (ε = 14.800).

IR : ν^1 (cm^{-1}) = 3500-2500, 1735, 1710, 1630, 1160, 1050, 940 and 880.

^{1}H-NMR (100 MHz, $CDCl_3$) : 2-$(CH_2)_5\underline{CH_2}COOH$: δ = 2.32 (m = 3, ^3J = 7.37 Hz); 2-$(CH_2)_4\underline{CH_2}CH_2COOH$: δ = 1.57 (m); 2-$CH_2(\underline{CH_2})_3CH_2CH_2COOH$: δ = 1.3 (m); 2-$\underline{CH_2}(CH_2)_5COOH$: δ = 2.09 (m = 3, ^3J = 7.0 Hz); 3-$OCH_2\underline{CH_3}$: δ = 1.32 (m = 3, ^3J = 7.0 Hz); 3-$O\underline{CH_2}CH_3$: δ = 4.17 (m = 4, ^3J = 7.0 Hz); 4-$\underline{H}$: δ = 2.78 (s); 5-$OCH_2\underline{CH_3}$: δ = 1.18 (m = 3, ^3J = 7.25 Hz); 5-$O\underline{CH_2}CH_3$: δ = 3.67 (m, ^3J = 7.25 Hz).

MS : m/e at 314 (2 %), 313 (5), 299 (14), 298 (84), 297 (30), 269 (21), 268 (24), 267 (7), 250 (67), 223 (50), 126 (48), 97 (59), 55 (100).

4-hydroxy-3-(6'-carboxyhexyl)-2-(1'-octynyl)-2-cyclopenten-1-one (1a).

To a solution of 1-octynylmagnesiumbromide (0.12 mole) in dry tetrahydrofurane (80 ml) was added under nitrogen a solution of 3a (10 g; 0.024 mole) in dry tetrahydrofurane (20 ml). After stirring for 12 hr the reaction mixture was treated with a buffer solution (600 ml; pH 6; citronic acid - K_2HPO_4) and ethanol

(100 ml). After stirring for 4 hr, the mixture was extracted with ether; the ether layer was washed with water and dried (Na_2SO_4). Working up in the usual way gave crude 4a (R_f = 0.60; ethyl acetate-isooctane-acetic acid, 60:40:8). To a solution of 4a in ethanol (150 ml) and citronic acid - K_2HPO_4 buffer (pH 7.8) was added sodium borohydride (9 g; 0.25 mole) in small portions at r.t. under stirring. After 4 hr the mixture was acidified with hydrochloric acid. The ethanol was evaporated; 1a was isolated by ether extraction and purified by CCD : two-phase system, ether/citronic acid - K_2HPO_4 buffer (pH 8.16) in methanol-water (1:3). The yield is 48 %.

R_f (same eluent as for 3a) = 0.51.

UV : λ_{max} (methanol) = 263 nm (ε = 16.000).

IR : ν^1 (cm^{-1}) = 3500-2500, 2240, 1720, 1625, 1120, 740 and 620.

^{1}H-NMR (100 MHz, $CDCl_3$) : 2-C≡C-$(CH_2)_5\underline{CH_3}$: δ = 0.88 (m = 3, ^3J = 5.85 Hz); 2-C≡C-$\underline{CH_2}$-C_5H_{11} : δ = 2.41 (m = 3, ^3J = 6.0 Hz); 3-$(CH_2)_4\underline{CH_2}CH_2COOH$: δ = 1.55 (m); 3-$\underline{CH_2}$-$(CH_2)_5COOH$: δ = 2.26; 4-$\underline{H}$: δ = 4.88.

MS : m/e at 334 ($M^{+\cdot}$, 51 %), 316 (47), 247 (25), 246 (48), 245 (26), 231 (26), 219 (22), 205 (40), 163 (28), 121 (40), 95 (100), 55 (96).

C-H analysis : found : C, 71.10; H, 9.00 %. $C_{20}H_{30}O_4$ requires : C, 71.82; H, 8.98 %.

4-hydroxy-3-(2'-methoxyethyl)-2-(1'-octynyl)-2-cyclopenten-1-one (1b).

From 3b[5] as described for 1a. 1b was purified by column chromatography on silica gel with ether-benzene (1:1) as eluent; the yield is 65 %.

R_f (ether-benzene, 1:1) = 0.20.

UV : λ_{max} (methanol) = 259 nm (ε = 16.500).

IR : ν^1 (cm^{-1}) = 3430, 2230, 1720, 1625 and 1115.

^{1}H-NMR (60 MHz, CCl_4) : 2-C≡C-$(CH_2)_5\underline{CH_3}$: δ = 0.88 (m = 3); 2-C≡C-$\underline{CH_2}$-C_5H_{11} : δ = 2.39 (m = 3); 3-$CH_2CH_2O\underline{CH_3}$: δ = 3.32 (s); 3-$CH_2\underline{CH_2}OCH_3$: δ = 3.60 (m = 3, ^3J = 7.0 Hz); 3-$\underline{CH_2}CH_2OCH_3$: δ = 8.82 (m = 3, ^3J = 7.0 Hz); 4-$\underline{H}$: δ = 4.70.

MS : m/e at 264 ($M^{+\cdot}$, 28 %), 248 (2), 232 (5), 219 (5), 204 (7), 203 (5), 194 (17), 191 (16), 162 (20), 133 (15), 91 (13), 55 (18), 45 (100).

C-H analysis : found : C, 72.70; H, 9.19 %. $C_{16}H_{24}O_3$ requires : C, 72.68, H, 9.09 %.

4-hydroxy-3-(2'-benzyloxyethyl)-2-(1'-octynyl)-2-cyclopenten-1-one (1c).

From 3c (prepared as described for 3b in reference 5) as described for 1a; the yield is 65 %.

R_f (ether-benzene, 1:1) = 0.35.

UV : λ_{max} (methanol) = 259 nm.

IR : ν^1 (cm^{-1}) = 3440, 2230, 1720, 1625, 1500, 1480, 1370, 1290, 1230, 1110, 1085, 1040, 1020, 730 and 695.

^{1}H-NMR (60 MHz, CCl_4) : 2-C≡C-$(CH_2)_5\underline{CH_3}$: δ = 0.88 (m = 3); 2-C≡C-$\underline{CH_2}$-C_5H_{11} : δ = 2.33; 3-$CH_2CH_2OCH_2\underline{\emptyset}$: δ = 7.20 (s); 3-$CH_2CH_2O\underline{CH_2}\emptyset$: δ = 4.45 (s); 3-$CH_2\underline{CH_2}OCH_2\emptyset$: δ = 3.68 (m = 3, ^3J = 5.5 Hz); 3-$\underline{CH_2}CH_2OCH_2\emptyset$: δ = 2.83 (m = 3, ^3J = 5.5 Hz); 4-$\underline{H}$: δ = 4.65.

r-1-hydroxy-2-t-(6'-carboxyhexyl)-3-t-(1'-E-octenyl)-4-c-hydroxycyclopentane (6a).

1a (5 g; 0.15 mole) and sodium hydride (1.44 g; 0.03 mole) were stirred for 2 hr

in 50 ml dry tetrahydrofurane. Liquid ammonia was distilled (from sodium) in and a sodium ethoxide solution (from 0.32 mole sodium in 125 ml ethanol) was added. Lithium (8.8 g; 1.2 mole) was added in small pieces. After 1 hr the excess lithium was destroyed with ammonium chloride, the ammonia evaporated off, water added and the water layer washed with ether. The water layer was acidified with hydrochloric acid and extracted with ether. The ether was evaporated and the residue subjected to CCD : 1340 transfers in a twophase system of ether/ K_2HPO_4 (0.2 M) in water-methanol (3:1). The result is given in table 1. Compound 6a (K = 0.35) was collected; the yield is 1.86 g (39 %).
IR : ν^1 (cm^{-1}) = 3500-2500, 3380, 1720, 1420, 1050 and 970.
MS : m/e at 322 (3 %), 304 (6), 279 (14), 265 (7), 252 (2), 235 (24).

r-1-hydroxy-2-t-(6'-carboxyhexyl)-3-c-(1'-E-octenyl)-4-t-hydroxycyclopentane (5a).

To a solution of 1a (5.6 g; 0.016 mole) and phenol (12.2 g; 8 eq.) in dry tetrahydrofurane (70 ml) and liquid ammonia (700 ml; distilled from sodium), lithium (1.6 g; 16 eq.) was added in small pieces. After 15 min the excess lithium was destroyed with ammonium chloride, the ammonia evaporated off, ether added, the inorganic salts dissolved in water-hydrochloric acid. The water layer was extracted with ether. The combined ether extracts were dried (Na_2SO_4); the ether was evaporated off and the phenol was distilled off in vacuo. Column chromatography on silica gel with benzene-dioxane (5:4) as eluent gave the diol fraction. This mixture was separated on a silica gel boric acid column[18] with the upper layer of the following system as eluent : ethyl acetate (480 ml), acetic acid (40 ml), isooctane (260 ml) and water (200 ml). Pure 5a (1480 mg) was collected next to 6a (60 mg). IR and MS of 5a and 6a are almost identical.

The methyl esters of the cyclopentanediols 5a, 6a, 6'a, 7a, 8a, 9a and 10a.

From the corresponding acids 5a, 6a, 6'a, 7a, 8a, 9a and 10a with diazomethane.
R_f (ethyl acetate) : see table 1.
IR for all compounds except the methyl ester of 6'a are almost identical :
ν^1 (cm^{-1}) = 3385, 1745, 1440, 1360, 1070 and 970.
IR for the methyl ester of 6'a : ν^1 (cm^{-1}) = 3385, 1745, 1440, 1360 and 1075.
^{1}H-NMR (300 MHz, CCl_4) for the methyl esters of 5a, 6a, 6'a and 7a : see reference 11 except for data given below.
5a : 13-H : δ = 5.26 ($^3J_{13,14}$ = 15.2 Hz, $^3J_{12,13}$ = 8.5 Hz); 14-H : δ = 5.42 ($^3J_{14,15}$ = 6.50 Hz).
6a : 13-H : δ = 5.05 ($^3J_{13,14}$ = 15.2 Hz, $^3J_{12,13}$ = 9.8 Hz); 14-H : δ = 5.43 ($^3J_{14,15}$ = 6.80 Hz).
6'a : 13-H : δ = 5.0 ($^3J_{13,14}$ = 11.0 Hz, $^3J_{12,13}$ = 10.8 Hz); 14-H : δ = 5.38 ($^3J_{14,15}$ = 7.5 Hz).
7a : 13-H : δ = 5.17 ($^3J_{13,14}$ = 15.2 Hz, $^3J_{12,13}$ = 9.0 Hz); 14-H : δ = 5.42 ($^3J_{14,15}$ = 6.0 Hz).
MS for the methyl esters of 5a and 6a are almost identical : m/e at 354 ($M^{+\cdot}$, 3 %), 338 (7), 323 (2), 322 (3), 318 (2), 298 (5), 278 (6), 271 (26), 270 (22), 160 (47), 128 (41).
MS for the di-trimethylsilylether-methyl ester derivative of 7a : m/e at 498 ($M^{+\cdot}$, 1.4 %), 483 (3.5), 408 (9), 382 (93), 318 (19), 298 (27), 297 (27), 292

(21), 239 (100), 217 (68), 147 (23).
C-H analysis : found : C, 70.82; H, 10.88 %. $C_{21}H_{38}O_4$ requires : C, 71.18; H, 10.73 %.

The methyl esters of the cyclopentanediols 5"a and 6"a.

A mixture of the methyl ester of 5a (55 mg; 14.10^{-5} mole), palladium on carbon (5 %; 4 mg) and dry ethanol (4 ml) was shaken under hydrogen till the theoretical amount hydrogen was taken up. Filtration and concentration in vacuo gave r-1-hydroxy-2-t-(6'-methoxycarbonylhexyl)-3-c-n.octyl-4-t-hydroxycyclopentane (yield 94 %). r-1-Hydroxy-2-t-(6'-methoxycarbonylhexyl)-3-t-n.octyl-4-c-hydroxycyclopentane was obtained in the same way from the methylester of 6a.
R_f (ethyl acetate) for the methyl ester of 5"a and 6"a = 0.33 and 0.31.
IR for both compounds are almost identical : ν^1 (cm^{-1}) = 3385, 1745, 1440, 1360, 1265, 1075 and 1025.
MS for the corresponding di-trimethylsilylether derivatives are also almost identical : m/e at 485 (3 %), 469 (2), 410 (10), 321 (5), 297 (28), 267 (31), 241 (7), 217 (100), 191 (40), 147 (18).
^{1}H-NMR (300 MHz, CCl_4) : reference 11.

The cyclopentanediacetates 11a, 12a, 11"a and 12"a.

Were obtained in the usual way (acetic anhydride-pyridine; 2 hr at 70°C) from the methyl esters of 5a, 6a, 5"a and 6"a. Purification was performed on silica gel with chloroform as eluent (yield : 70-80 %).
R_f (chloroform-ethyl acetate, 7:3) for 11"a and 12"a = 0.66 and 0.63.
R_f (chloroform) for 11a and 12a = 0.34 and 0.32.
IR for 11"a and 12"a are almost identical : ν^1 (cm^{-1}) = 1735, 1440, 1380, 1245 and 1045.
IR for 11a and 12a : ν^1 (cm^{-1}) = 1745, 1445, 1245, 1175, 1040 and 975.
MS for 11"a and 12"a : m/e at 381 (7 %), 338 (11), 320 (100), 307 (14), 289 (8), 235 (14), 222 (28) and 192 (24).
MS for 11a and 12a : m/e at 378 (10 %), 319 (81), 318 (100), 248 (31), 190 (35), 189 (46), 175 (23), 107 (23), 105 (51), 55 (78).
^{1}H-NMR for 11"a and 12"a (300 MHz, $CDCl_3$; data not mentioned in table 2) : 2O-H : δ = 0.88 (m = 3, ^3J = 7.05 Hz); 3-H : δ = 1.61 (m); 2-H : δ = 2.3 (m = 3, ^3J = 7.4 Hz); $-COOCH_3$: δ = 3.66 (s); $-OCOCH_3$: δ = 2.00 (s).
^{1}H-NMR for 11a and 12a : reference 11.
C-H analysis : found : C, 68.30; H, 9.87 %. $C_{25}H_{42}O_6$ requires : C, 68.49; H, 9.59 %.

The cyclopentanediols 5b, 5'b and 5"b.

From 1b as described for 5a. Purification was performed on silica gel with ethyl acetate as eluent (yield 20 %).
R_f (ethyl acetate) for 5b, 5'b and 5"b : 0.22, 0.24 and 0.22.
IR : ν^1 (cm^{-1}) for 5b = 3400, 1115, 965 and for 5'b = 3400, 1115, 740-720.
MS for the di-trimethylsilylether derivatives of 5b and 5'b are identical : m/e at 324 (27 %), 299 (40), 298 (42), 279 (10), 267 (10), 266 (10), 253 (37), 239 (23), 234 (32), 217 (44), 213 (44), 181 (30), 73 (100).

^{1}H-NMR (300 MHz, $CDCl_3$) for 5b, 5'b and 5"b : see reference 11 except for data given below (prostaglandin numbering).
5b : 13-H : δ = 5.23 ($^3J_{13,14}$ = 15.0 Hz, $^3J_{12,13}$ = 9.15 Hz); 14-H : δ = 5.54 ($^3J_{14,15}$ = 6.75 Hz).
5'b : 13-H : δ = 5.18 ($^3J_{13,14}$ = 10 Hz, $^3J_{12,13}$ = 10 Hz); 14-H : δ = 5.53 ($^3J_{14,15}$ = 7.6 Hz).
C-H analysis : found : C, 71.23; H, 11.21 %. $C_{16}H_{30}O_3$ requires : C, 71.11; H, 11.11 %.

Catalytic hydrogenation (Pd/C 5 %) of 5b and 5'b in ethanol gave a quantitative yield of 5"b. ^{1}H-NMR data (300 MHz, of the corresponding diacetate 11"b are given in Table 2.

The cyclopentanediols 5g and 5'g.

From 1c as described for 5a, but with a mixture of phenol (15 eq.) and ethanol (100 eq.) as proton donor and co-solvent. The yield is 35 % after purification on silica gel with ethyl acetate-ethanol (95:5) as eluent.
R_f (ethyl acetate) = 0.20.
IR : ν^1 (cm^{-1}) = 3350, 1480, 1370, 1050, 965 and 725.
MS : m/e at 238 ($M^{+\cdot}-H_2O$, 5 %), 220 (18), 164 (14), 149 (10), 164 (14), 135 (10), 123 (10), 121 (10), 109 (30), 94 (20), 83 (32), 81 (57), 79 (53), 67 (64), 55 (74), 43 (54), 41 (100).

9,11-diacetoxy-$PGF_{1\beta}$ methyl ester (13a) and the 15-epimer (14a).

A solution of 11a (225 mg; 5.10^{-4} mole), NBS (88 mg; 5.10^{-4} mole) in dry carbon tetrachloride (2 ml) was warmed up to 65°C and a crystal AIBN was added. After completion of the reaction the mixture was cooled, filtered and the solvent evaporated in vacuo. The crude bromide was dissolved in acetone (+ 1 eq. water) and freshly prepared silver carbonate on celite was added in portions during 20 min. After stirring for 1 hr at 0°C the solid material was filtered off and washed with warm acetone (6 ml). Evaporation of the solvent and purification on silica gel with ethyl acetate-chloroform (1:4) as eluent yielded 13a (78 mg) and 14a (58 mg).
R_f (chloroform-ethyl acetate, 7:3) for 13a and 14a = 0.38 and 0.48.
IR for 13a and 14a are almost identical : ν^1 (cm^{-1}) = 3480, 1745, 1245, 1035 and 975.
MS for 13a and 14a : m/e at 395 (3 %), 394 (11), 335 (35), 334 (74), 324 (21), 323 (96), 316 (27), 303 (43), 263 (100), 235 (62), 220 (54).
^{1}H-NMR (300 MHz, $CDCl_3$) for 13a and 14a : reference 11.
C-H analysis : found : C, 65.84; H, 9.20 %. $C_{25}H_{42}O_7$ requires : C, 66.08; H, 9.25 %.

9,11-diacetoxy-8-epi-$PGF_{1\alpha}$ methyl ester (15a) and the 15-epimer (16a).

From 12a as described for 13a and 14a. Purification was performed on silica gel with ethyl acetate-chloroform (3:7) as eluent.
R_f (chloroform-ethyl acetate, 7:3) for 15a and 16a = 0.37 and 0.44.
IR and MS are almost identical with data found for 13a and 14a.

^{1}H-NMR (300 MHz, $CDCl_3$) for 15a and 16a : reference 11.

PGF$_{1\beta}$ methyl ester and PGF$_{1\beta}$.

13a (90 mg; 19.10^{-5} mole) and potassium carbonate (53.2 mg; 38.10^{-5} mole) were stirred for 6 hr at r.t. in dry methanol (2.4 ml). Dry dioxane (2 ml) was added and the solution kept 12 hr at 0°C. The salts were filtered off, the solvents evaporated in vacuo and the residue chromatographed on silica gel with ethyl acetate-acetone (6:4). PGF$_{1\beta}$ methyl ester was obtained in 78 % yield. Physical data are found in table 3.
IR : ν^1 (cm^{-1}) = 3380, 1745, 1205, 1180, 1045 and 970.
^{1}H-NMR (300 MHz, CD_3OD) : reference 11.

A solution of PGF$_{1\beta}$ methyl ester (18 mg; 49.10^{-6} mole) and potassium carbonate (13 mg; 2 eq.) in methanol-water (2 ml, 1:1) was stirred for 62 hr at r.t. The solvents are stripped off under nitrogen stream. The residue was taken up in potassium carbonate solution; after washing with ethyl acetate (3 x), the water layer was acidified (dilute hydrochloric acid) and extracted with ethyl acetate. The solution was concentrated (under nitrogen); PGF$_{1\beta}$ (16 mg) crystallised out (yield : 92 %). Physical data are found in table 3.
IR : ν^1 (cm^{-1}) = 3380, 2800-2500, 1720, 1260, 1100, 1045 and 970.
^{1}H-NMR (300 MHz, CD_3OD) : reference 11.

15-epi-PGF$_{1\beta}$ methyl ester and 15-epi-PGF$_{1\beta}$.

From 14a as described for PGF$_{1\beta}$.
Physical data for 15-epi-PGF$_{1\beta}$ methyl ester are given in table 3. It was purified by column chromatography on silica gel with ethyl acetate-acetone (8:2) as eluent. Almost the same spectral data (^{1}H-NMR and IR) were obtained as for PGF$_{1\beta}$ methyl ester. Physical data for 15-epi-PGF$_{1\beta}$ are given in table 3. Almost the same spectral data (IR, ^{1}H-NMR) were obtained as for PGF$_{1\beta}$.

8-epi-PGF$_{1\alpha}$ methyl ester, 8-epi-PGF$_{1\alpha}$ and the corresponding 15-epimers.

From 15a as described for PGF$_{1\beta}$.
Purification of 8-epi-PGF$_{1\alpha}$ methyl ester and the corresponding 15-epimer was performed on Sephadex LH-20 with as eluent a mixture of isooctane-chloroform-acetic acid-ethanol (100:100:2:30). Physical data are given in table 3.
IR spectra are almost identical with the spectra for PGF$_{1\beta}$ methyl ester and 15-epi-PGF$_{1\beta}$ methyl ester.
^{1}H-NMR (300 MHz, $CDCl_3$) for both epimers are almost identical : reference 11.
Physical data for 8-epi-PGF$_{1\alpha}$ and the 15-epimer are given in table 3.
IR spectra are almost identical with the spectra for PGF$_{1\beta}$ and 15-epi-PGF$_{1\beta}$.
^{1}H-NMR (300 MHz, CD_3OD) for both epimers are almost identical : reference 11.

The cyclopentanediols 5d and 5'd.

a. from 11b (+ 11b') :

To a solution of 11b (+ 11'b) (prepared in the usual way from 5b (+ 5'b; 200 mg; 57.10^{-5} mole) in dry methylene chloride (2 ml) was added at -80°C a solution of boron tribromide (16 mg; 65.10^{-5} mole) in methylene chloride (2 ml).

The temperature was allowed to rise to -25°C and the reaction mixture was stirred for 2 days. Saturated aqueous sodium hydrogen carbonate was added at 0°C; the water layer was extracted with ether. The crude alcohol obtained after stripping off the solvents was sufficiently pure for the next reaction (after column chromatography on silica gel with ether-benzene (6:4) as eluent the yield was 75 %).
R_f (ether-benzene, 1:1) = 0.25.
IR : ν^1 (cm^{-1}) = 3460, 1740, 1380, 1230 and 1040.
C-H analysis : found : C, 67.17; H, 10.17 %. $C_{19}H_{32}O_5$ requires : C, 67.05; H, 9.41 %.

To a cooled (-10°C) solution of the alcohol (500 mg; 15.10^{-4} mole) in acetone (25 ml) Jones reagent was dropped until persisting red coloration. Isopropanol was added, the salts filtered off, the acetone removed in vacuo and the residue dissolved in pentane. The solution is extracted with sodium carbonate solution (5 %). The combined water layers are acidified with 2 N hydrochloric acid and extracted with ether. The ether extracts are worked up in the usual way. The yield of pure acid was 400 mg (75 %).
R_f (ethyl acetate) = 0.56.
IR : ν^1 (cm^{-1}) = 3500-2300, 1740, 1380, 1230, 1140, 1035, 965, 920 and 725.

The acid was dissolved in dioxane - 4 N hydrochloric acid (10 ml; 1:1) and stirred at 80°C for 3 hr. After cooling the solution was made alkanine (5 % sodium carbonate) and washed with ether. Acidification with hydrochloric acid, extraction with ether, drying and evaporation yielded 5d (+ 5'd) (270 mg; 90 %).

b. from 5g (+ 5'g) :

Through a shaken suspension of platinum oxide (60 mg; 26.10^{-4} mole) in water (15 ml) was passed a hydrogen stream. Acetone (2 ml) was then added, oxygen passed through and the mixture heated up to 60°C. A solution of 5g (+ 5'g) (50 mg; 2.10^{-4} mole) in acetone (2 ml) was added under vigorous stirring. After 6 hr the catalyst was filtered off and washed with ether. Extraction with sodium carbonate (5 %), washing with ether, acidification of the water layer and working up as described above afforded 5d (+ 5'd) (27 mg; 50 %).
R_f (ethyl acetate) = 0.15.
IR : ν^1 (cm^{-1}) = 3500-2300, 1710, 1250, 1085, 1040 and 965.
MS for the tri-trimethylsilylether derivative : m/e at 471 (4 %), 396 (3), 381 (2), 370 (6), 306 (26), 264 (14), 239 (8), 217 (19), 167 (12), 147 (20), 117 (20), 75 (41), 73 (100).

The δ-lactone 17.

A solution of 5d (+ 5'd) in benzene (1 l) was heated for 14 hr; the water generated was removed by azeotropic distillation. The reaction mixture was cooled, treated with solid sodium carbonate, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with ethyl acetate, yielding the lactone 17 as a yellow oil (670 mg; 75 %).
R_f (ethyl acetate) = 0.55 (E-isomer) and 0.56 (Z-isomer).
For the corresponding saturated compound 19 : R_f (ethyl acetate) = 0.55.

IR : ν^1 (cm^{-1}) = 3450, 1725, 1460, 1380, 1250, 1185, 1160, 1110, 1070, 1030, 960, 885 and 800.
MS : m/e at 254 ($M^{+\cdot}$, 4 %), 236 (4), 210 (6), 195 (7), 194 (6), 186 (5), 154 (22), 139 (13), 111 (14), 109 (10), 93 (18), 97 (17), 83 (12), 69 (17), 55 (38), 41 (46), 28 (100).
^{1}H-NMR (300 MHz, $CDCl_3$) : table 2.

The γ-lactone 20.

A solution of the tosylate 18 (100 mg; 24.10^{-5} mole; from 17 in the usual way : 80 % yield) and hydroxylamine chlorohydrate (68 mg; 1.10^{-3} mole) in collidine (2 ml) was heated at 70°C for 15 hr. After cooling, water was added and the solution was acidified (pH 1) with hydrochloric acid. Extraction with ethyl acetate, washing with water, drying ($MgSO_4$) and evaporation of the solvent afforded 20 (44 mg; 80 %) after purification on silica gel with ethyl acetate as eluent.
R_f (ether) = 0.41.
IR : ν^1 (cm^{-1}) = 3450, 1760, 1480, 1420, 1380, 1360, 1175, 1085, 1035, 995, 965 and 810.
GC-MS coupling of the corresponding trimethylsilylether derivatives (ratio E:Z = 65:35); CIMS m/e at 365 $(M + C_3H_5)^{+\cdot}$, 1 %; 353 $(M + C_2H_5)^{+\cdot}$, 5 %; 325 $(M + 1)^{+\cdot}$, 3 %, 309 (6 %); 235 $(325 - TMSOH)^{+\cdot}$; 100 %.

The γ-lactone 23.

To a solution of the acetate of lactone 20 (70 mg; 24.10^{-5} mole; prepared in the usual way : 85 %) in carbon tetrachloride was added NBS (42 mg; 24.10^{-5} mole). The reaction mixture is warmed to 80°C and a crystal AIBN is added. The reaction mixture was cooled, filtered and the solvent evaporated in vacuo under nitrogen. The crude residue was dissolved in acetone (2 ml) and the solution cooled at 0°C. Freshly prepared silver carbonate on celite (32 mg; 12.10^{-5} mole) was added in small portions. The suspension was stirred at 0°C for 6 hr. After filtration of the solid material, washing with acetone the solution was concentrated under nitrogen. The residue (21 and 22) was purified by column chromatography on silica gel with ether-benzene (1:1) as eluent (50 %). To a solution of 21 and 22 (10 mg; 3.10^{-5} mole) in dry ether (1 ml) were added triethylamine (10 mg; 10^{-4} mole) and dry sulphenyl chloride (7 mg; 5.10^{-5} mole). After stirring for 1 hr methanol (1 ml) and trimethyl phosphite (0.5 ml) were added. The residue, obtained on evaporation of the solvent (under nitrogen), was taken up in ether; the salts were filtered off and the ether was evaporated. The residue was dissolved in dry methanol (0.5 ml), potassium carbonate (14 mg) was added and the mixture stirred for 1 hr. Filtration, evaporation (under nitrogen) and column chromatography (silica gel, ethyl acetate) yielded 23, identical with an authentic sample[5].
I.R. : ν^1 (cm^{-1}) = 3400, 1760, 1480, 1460, 1380, 1360, 1190, 1170, 1125, 1105, 1065, 1035, 965, 895, 860 and 800.
C.I. MS (CH_4) m/e at 413 $(M + 1)^{+\cdot}$, 2 %; 441 $(M + 29)^{+\cdot}$, 36 %; 453 $(M + 41)^{+\cdot}$, 8 %; 397 (39 %); 341 (11 %); 323 $(M - TMSOH)^{+\cdot}$, 100 %; 233 (45 %).

ACKNOWLEDGEMENT

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

REFERENCES

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

2. M. Samson, P. De Clercq and M. Vandewalle, Tetrahedron 31, 1233 (1975).

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

4. J. Van Hooland, P. De Clercq and M. Vandewalle, Tetrah. Lett. 49-50, 4343 (1974).

5. W. Van Brussel, J. Van Hooland, P. De Clercq and M. Vandewalle, Bull. Soc. Chim. Belges 84, 813 (1975).

6. F. Van Hulle, V. Sipido and M. Vandewalle, Tetr. Lett. 24, 2213 (1973).

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

8. E.J. Kelly, H.V. Secor, C.W. Keenan and J.F. Eastham, J. Am. Chem. Soc. 84, 3611 (1962).

9. D. Van Haver, D. Tavernier, M. Anteunis and M. Vandewalle, Tetrahedron 30, 105 (1974).

10. M. Maenhaut-Claeys and M. Vandewalle, unpublished results; see also : M. Maenhaut-Claeys and M. Vandewalle, Bull. Soc. Chim. Belges 83, 343 (1974).

11. More details will be published in a subsequent paper.

12. J.G. Miller, W. Kurz, K.G. Untch and G. Stork, J. Am. Chem. Soc. 96, 6775 (1974).

13. Primary and secundary alcohols are oxidised to the corresponding aldehydes and ketones using silver carbonate on celite; M. Fetizon, M. Golfier; C.R. Acad. Sc. Paris, C, 900 (68).

14. W.P. Schneider, U. Axen, F.H. Lincoln, J.E. Pike, J.L. Thompson, J. Am. Chem. Soc. 91, 5372 (1969).

15. E.S. Ferdinandi and G. Just, Can. J. Chem. 49, 1070 (1971).

16. E. Änggård, H. Bergkvit, J. Chromatogr. 48, 542 (1970).

17. G. Just, Ch. Simonovitch, F.H. Lincoln, W.P. Schneider, U. Axen, G.B. Spero, J.E. Pike, J. Am. Chem. Soc. 91, 5364 (1969).

18. M. Miyano, C.R. Dorn, R.A. Mueller, J. Org. Chem. 37, 4810 (1972).

19. E.J. Corey, N.H. Weinshenker, T.K. Schaaf, W. Hubre, J. Am. CHem. Soc. 91, 5675 (1969) and E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarly, T.K. Schaaf, J. Am. Chem. Soc. 93, 1490 (1971).

20. R. Peel and J.F. Sutherland, Chem. Comm. 151 (1974).