CYCLOPENTANONES. X*

A NOVEL SYNTHESIS OF (dl)-PROSTAGLANDIN $F_{1\alpha}$

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ABSTRACT

A novel total synthesis of (dl)-prostaglandin $F_{1\alpha}$ methyl ester is described. The 2,3-dialkyl-1,4-cyclopentanediol system is obtained by the reduction of an appropriate 2,3-dialkyl-4-hydroxy-2-cyclopentenone. The facile conversion of the most abundant isomeric cyclopentanediol, with the all trans relation of the four substituents to a δ-lactone enables the creation of the required prostaglandin configuration and the construction of the C-12 side chain. Extensive spectroscopic data are included.

INTRODUCTION

A key step in this total synthesis of prostaglandin $F_{1\alpha}$ (1) involves the lithium-liquid ammonia reduction, in the presence of a hydroxylic co-solvent of an appropriate 2,3-dialkyl-4-hydroxy-2-cyclopentenone[1,2] such as compound 2 and the isomer 3. During this reaction three new chiral centres are created. The reduction has a fairly high degree of stereoselectivity as only three of the possible diastereoisomers of 4 are formed. In previous papers[3,4] the configurational assignment of the diastereoisomers was performed on model compounds by means of ^{1}H-NMR analysis and chemical transformations.

The conversion of the most abundant isomer 4a to prostaglandin $F_{1\alpha}$ implies a specific inversion of the hydroxyl function at C-9 (prostaglandin numbering); it became therefore imperative to differentiate both hydroxyl functions in compound 4a. This can be done by the conversion of this diol to the δ-lactone 5[3] from which compound 6 can easily be obtained. At this stage it is obvious that there are still three reaction sequences to be performed; the inversion of the free hydroxyl function, the conversion of the protecting ether moiety ($R = CH_2OCH_3$) to the corresponding ester ($R = COOCH_3$) and the transformation of the methoxycarbonyl methyl group to the corresponding C-12 side chain of prostaglandin $F_{1\alpha}$.

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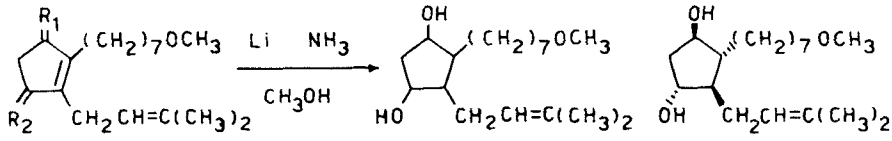
* Previous paper in this series (erroneously marked VIII) : ref. 3.

≠ Aspirant NFWO.

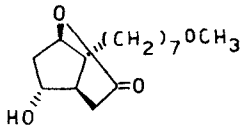


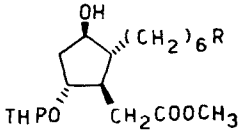
2 R_1=H, OH; R_2=O

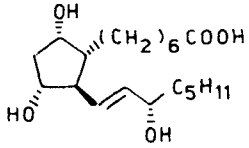
3 R_1=O; R_2=H, OH

4

4a







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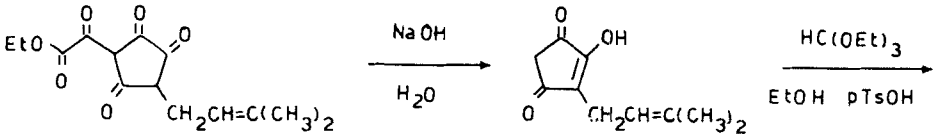
6

1

DISCUSSION

The cyclopentenolones 2 and 3 were synthesised according to a general and already described method[5,6] in which compounds of type 9 are important key intermediates. The starting trione 8 was obtained in the usual way from 6-methyl-5-hepten-2-one; however hydrolysis of 7 must be performed in alkaline medium (y. 57 %) as acid treatment yields a cyclic enol ether. The Grignard reaction and subsequent zinc-acetic acid reduction (improved method by reverse addition) gave an almost quantitative yield of the oily cyclopentenolones 2 and 3 (1:1).



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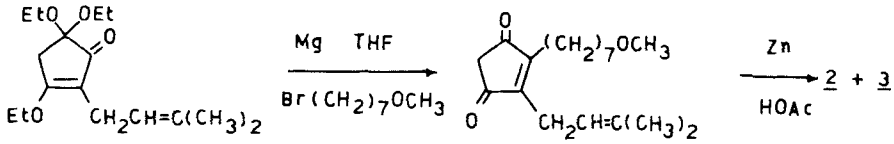

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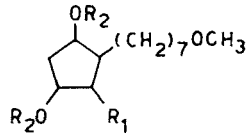
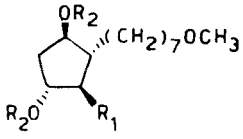
Upon reduction of the cyclopentenolones 2 and 3 with lithium in liquid ammonia, in the presence of methanol, three isomers of 3-(3'-methyl-2'-butenyl)-2-(7'-methoxyheptyl)-1,4-cyclopentanediol (4) were formed, together with three isomeric completely saturated diols (12; total amount of diols 50 %).

The isomeric diols (4 and 12) (a, b and c; relative amount 2:2:1) can be separated on silica gel with ethyl acetate as eluent. Fortunately, in case of the all trans configuration a which is of interest to us, saturation of the side chain had occurred to a lesser extent (13 %) than for the isomers b and c (66 and 23 % respectively); this makes unsaturated diol 4a available for further synthesis (total yield of 4a from 2, 3 : 17 %).

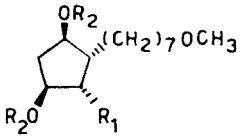
For synthetic work the separation of the reduction mixture can be avoided as is seen in the following reaction sequence[3]. The diol mixture was transformed into the diacetates 11 and 13. Oxidation of the double bound with potassium permanganate and sodium periodate led to the acids 15 from which the saturated products 13 could be separated by alkaline extraction. Acid hydrolysis of the diacetates 15 at 80°C yielded the diols 14a and 14b; in this reaction medium, the intermediate 15c was directly converted in the γ-lactone 17 which could easily be separated from the acids 14. Refluxing of the diols 14 in benzene with a catalytic amount of toluene-p-sulphonic acid led to the sole formation of the δ-lactone (5; total yield from 4a : 57 %); isomer 14b failed to form a lactone and thus could be removed at this stage of the reaction sequence.



4	R_1=-$CH_2CH{=}C(CH_3)_2$;	R_2=H	14	R_1=-CH_2COOH ;	R_2=H
11	"	R_2=Ac	15	"	R_2=Ac
12	R_1=-$CH_2CH_2CH(CH_3)_2$;	R_2=H	16	R_1=-CH_2COOCH_3;	R_2=H
13	"	R_2=Ac			



a



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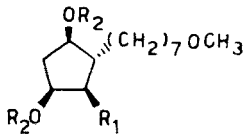
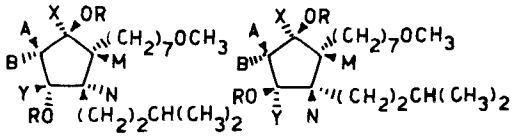


c

The configuration of the diols 4 was proven by ^{1}H-NMR analysis of the corresponding saturated diols 12 and diacetates 13, obtained by catalytic hydrogenation (table 1). Further evidence was obtained by the formation of the lactones 5 and 17, whose ^{1}H-NMR spectral parameters (table 2) are consistent with those of model compounds, whose structures were unambiguously proven[3]. Mass

spectral data of the bis-trimethylsilyl ether and n.butyl boronate derivatives of compounds 4, 12 and 16 are also consistent with their configurations[7].

Table 1

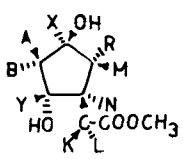
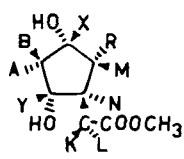
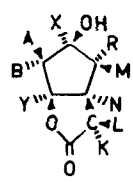
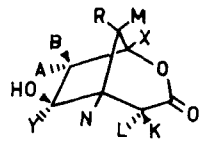


	12a	13a	12b	13b
R	-H	$-COCH_3$	-H	$-COCH_3$
MHz	300	300	300	300
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
δ_A	1.87	2.00	1.57	1.55
δ_B	1.87	2.00	2.36	2.67
δ_X	4.02	4.92	3.95	4.86
δ_Y	4.02	4.92	3.94	4.85
δ_M	1.57	1.67	1.99	2.12
δ_N	1.57	1.67	1.99	2.12
J_{AB}	-	-	-15.0	-16.3
J_{AX}	6.0	6.0	a	a
J_{AY}	6.0	6.0	a	a
J_{BX}	6.0	6.0	7.0	8.0
J_{BY}	6.0	6.0	7.0	8.0
J_{XM}	4.4	5.6	a	a
J_{YN}	4.4	5.6	a	a
J_{MN}	a	a	a	a

[a] Could not be measured.

Both hydroxyl functions being differentiated in the δ-lactone 5 it became possible to invert specifically one centre (at C-9; prostaglandin numbering). The free hydroxyl function in 5 was converted to the tetrahydropyranyl ether 18 (y. 87 %); opening of the δ-lactone in methanolic sodium hydroxide solution and esterification with diazomethane afforded pure compound 19 (y. 86 %).

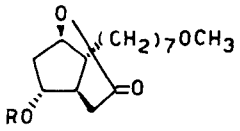
Table 2

	16a	22	17	5
R		$-(CH_2)_7OCH_3$		
MHz	300	300	300	300
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
δ_A	1.92	1.87	2.03	2.66
δ_B	1.98	2.02	2.26	2.04
δ_X	4.12	4.14	4.01	4.68
δ_Y	4.02	4.02	4.96	4.30
δ_M	1.40	1.60	1.83	2.09
δ_N	1.75	2.05	2.55	2.29
J_{AB}	-13.75	-15.0	-15.5	-16.0
J_{AX}	7.0	a	5.5	1.2
J_{AY}	6.5	a	2.25	7.5
J_{BX}	7.0	4.5	5.5	4.4
J_{BY}	4.75	6.75	6.55	3.25
J_{XM}	7.0	a	5.5	2.2
J_{YN}	4.0	a	7.0	1.2
J_{MN}	a	a	a	a
δ_K	2.64	2.57	2.81	2.75
δ_L	2.41	2.25	2.53	2.55
J_{KL}	-16.8	-16.5	-18.75	-18.8
J_{KN}	4.0	4.0	11.0	5.7
J_{LN}	10.2	10.0	2.4	1.6

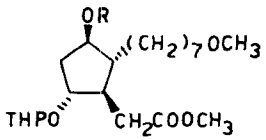
[a] Could not be measured.

Inversion of the hydroxyl function in 19 as the tosylate 20 (y. 95 %) with tetraethyl ammonium acetate[8] yielded the expected acetate 21 (y. 75 %) and the sole elimination product 23 (y. 13 %).



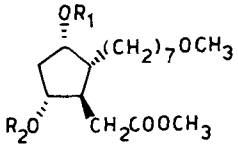
5 R=H

18 R=THP



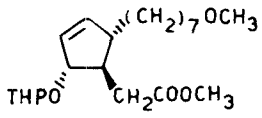
19 R=H

20 R=Ts



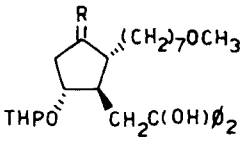
21 R_1=Ac; R_2=THP

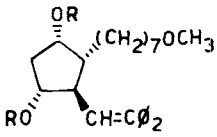
22 R_1=R_2=H

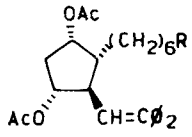


23

After conversion of 21 to the diol 22, comparison of the ^{1}H-NMR spectral data with the ^{1}H-NMR spectra of the diol 16a, obtained from 14a with diazomethane or from 19 after acidic hydrolysis in methanol proves unambiguously that inversion did indeed occur (table 2).







24 R= 

25 R= 

26 R=H

27 R=Ac

28 R=THP

29 R=CH_2OH

30 R=CH_2Br

31 R=COOH

32 R=$COOCH_3$

In the original plan, our aim was to perform a Grignard reaction with phenylmagnesium bromide on the lactone 18, thus making available in one step a C-9 hydroxyl function (25) and, after dehydratation of the tertiary alcohol, a potential aldehyde function necessary for the construction[9] of the C-12 side chain. The inversion of the hydroxyl function at C-9 could then be carried out at a later stage. Unfortunately, in our hands, during the Grignard reaction with phenylmagnesium bromide (2.2 eq) in tetrahydrofuran the starting material was recovered quantitatively. Furthermore, the same reaction (3 eq; in tetrahydrofuran-benzene) on compound 19 gave mostly the δ-lactone 18 by intramolecular alcoholysis in the alkaline medium as well as the expected diol 25 (3:1); thus demonstrating the unexpected and unusual stability of the δ-lactone

system.

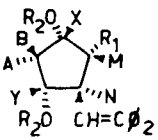
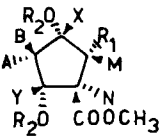
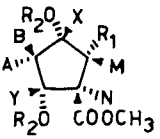
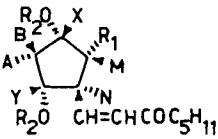
However, when the inversion was carried out first as already described, the reaction with phenylmagnesium bromide on the di-ester 21 gave the diol 24 (y. 85 %). On treatment with acid the product 26 (y. 82 %) was obtained. Transformation of 26 into the diacetate 27 (y. 72 %) is necessary to perform the ether cleavage with boron tribromide in methylene chloride at low temperature[9]; as well as the expected primary alcohol 29 (y. 70 %) some corresponding bromide 30 (y. 12 %) was also obtained. Oxidation of the alcohol 29 with Jones reagent and treatment of the acid 31 with diazomethane gave a quantitative yield of the ester 32.

Unfortunately all attempts to obtain an aldehyde function by oxidative fission of the trisubstituted double bond were unsuccessful. No oxidation of 26 occurred on treatment with osmium tetroxide and sodium periodate[10,11]. The di-ether 28 reacted with ozone[12] at low temperature in protic or aprotic solvents. Reductive work-up (zinc) of the ozonide gave no aldehyde; when the ozonide was treated with hydrogen peroxide in formic acid a poor yield of the ester 38 (after treatment with diazomethane) was obtained[13]. When the diacetate 32 was treated with an equivalent amount of osmium tetroxide in pyridine a quantitative yield of crude diol 35 (IR) was obtained after reductive cleavage of the osmate ester with sodium bisulfite[14]; oxidation of this diol with lead tetraacetate[15] afforded only a mixture of acids.

We therefore decided to build up the aldehyde function through a carboxylic acid group. An excellent oxidative cleavage of the double bond in 32 was performed with ruthenium tetroxide-sodium periodate[16] and yielded the acid 33 (y. 72 % from 29). Extensive ^{1}H-NMR spectral data of the corresponding methyl ester 34 and of the diols 38 and 26 are available (table 3). Crude acid 33 was then reduced by diborane to the primary alcohol 36 (y. $\sim$ 100 % on t.l.c.). The remaining transformations leading to $PGF_{1\alpha}$ have already been adequately described by Corey[9]. Oxidation of 36 with Collins reagent gave the aldehyde 37 which was immediately treated with the sodium salt of dimethyl-2-oxoheptylphosphonate[9] in 1,2-dimethoxyethane giving the enone 39 (y. 65 % from 36, table 3). Both 15-epimers (40 and 41; 1:1) were obtained by zinc borohydride reduction of 39 and were separated on preparative silica gel plates. Alkaline hydrolysis of the diacetate 41 afforded dl-$PGF_{1\alpha}$ methyl ester (identical with an authentic sample).

In this 25 step synthesis, starting from 3-(3'-methyl-2'-butenyl)-1,2,4-

Table 3

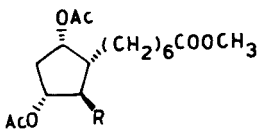





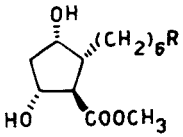
	26	38	34	39
R_1	$-(CH_2)_7OCH_3$		$-(CH_2)_6COOCH_3$	
R_2	H		Ac	
MHz	300	300	300	300
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
δ_A	1.79	1.92	1.77	1.72
δ_B	2.13	2.05	2.45	2.59
δ_X	4.17	4.27	5.13	5.18
δ_Y	4.08	4.40	5.13	4.97
δ_M	a	a	2.10	a
δ_N	2.50	2.65	2.62	2.67
J_{AB}	-14.5	-14.5	-15.5	-15.5
J_{AX}	b	b	b	1.0
J_{AY}	b	b	b	4.0
J_{BX}	4.5	4.25	5.0	5.0
J_{BY}	7.0	6.25	9.0	9.0
J_{XM}	b	b	b	5.0
J_{YN}	4.0	2.75	6.25	7.6
J_{MN}	10.0	10.0	12.0	12.0
^3J_N	11.0	-	-	9

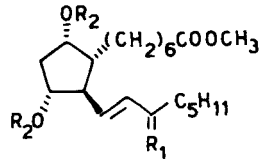
[a] Could not be located.

[b] Could not be measured.

cyclopentanetrione (8), the yields are good to excellent except for the lithium-liquid ammonia reduction. ^{1}H-NMR spectral parameters, reported in this paper are in accordance with those obtained from compounds whose configurations have already been proven[3,4]. These parameters should be of general use for configurational assignement of synthetic and modified prostaglandins. The syntheses of other primary prostaglandins via the described metal ammonia reduction and δ-lactone formation are under investigation.







33 R=COOH

34 R=$COOCH_3$

35 R=$CH(OH)C(OH)\emptyset_2$

36 R=CH_2OH

37 R=CHO

34 R=CH_2OCH_3

39 R_1=O; R_2=Ac

40 R_1=  ; R_2=Ac

41 R_1=  ; R_2=Ac

42 R_1=  ; R_2=H

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.

5-(ethoxycaronyl)carbonyl-3-(3'-methyl-2'-butenyl)-1,2,4-cyclopentanetrione (7)

To a stirred solution of sodium t.butoxide (from 100 g sodium hydride) in t.butanol (2.5 l) and dry benzene (1 l) 6-methyl-5-heptene-2-one (300 ml, 2 mole) and diethyloxalate (540 ml, 4 mole) were added at 10°C for 45 min. The mixture was stirred for 4 h at 45°C and acidified with conc. HCl (335 ml) at 0°C. After filtration of the precipitated sodium chloride the filtrate was concentrated in vacuo. The residue was treated with boiling hexane, yielding 208 g (37 %) pure compound 7.

mpt. : 82°C (from hexane).

UV : λ_{max}(methanol, 0.1 N HCl) = 260 nm ($\varepsilon \sim 9{,}400$), 275 nm ($\varepsilon \sim 9{,}800$); λ_{max} (methanol, 0.1 N NaOH) = 242, 275, 305 nm.

IR : ν^1 (cm^{-1}) = 3600-2500 (broad), 1750, 1640, 1160, 1060.

MS : m/e at 280 (M^+, 38 %), 252(4), 235(2), 225(15), 206(43), 179(14), 151(66), 69(100).

^{1}H-NMR (60 MHz, $CDCl_3$); 3-$CH_2CH=C(C\underline{H}_3)_2$: δ = 1.72(s); 3-$CH_2C\underline{H}=C(CH_3)_2$: δ = 5.19(m = 3, ^3J = 6.0 Hz); 3-$C\underline{H}_2CH=C(CH_3)_2$: δ = 3.08(m = 2, ^3J = 6.0 Hz); 5-$COCO_2CH_2C\underline{H}_3$: δ = 1.40(m = 3, ^3J = 6.0 Hz); 5-$COCO_2C\underline{H}_2CH_3$: δ = 4.40(m = 4, ^3J = 6.0 Hz).

3-(3'-methyl-2'-butenyl)-1,2,4-cyclopentanetrione (8)

7 (104 g, 0.379 mole) was treated with an aqueous solution of NaOH (44.5 g, 1.11 mole) at 80°C for 3 h. The reaction mixture was then acidified with 0.6 N HCl at -10°C whereby trione 8 precipitated. The filtrate was extracted with ether and the ether evaporated in vacuo. Both the residue and the precipitated trione 8 were dried by azeotropic distillation with benzene. After concentration in vacuo the residue was treated with boiling isooctane yielding 37 g (57 %) pure 8.

mpt. : 124.5°C (from isooctane).

UV : λ_{max} (methanol, 0.1 N HCl) = 272 nm ($\varepsilon \sim$ 9,300); λ_{max} (methanol, 0.1 N NaOH) = 245 and 320 nm.

IR : ν^1(cm^{-1}) = 3600-2500(broad), 1760, 1710, 1670, 1640.

MS : m/e at 180 (M^+, 100 %), 152(9), 137(58), 109(79), 69(40), 54(55).

^{1}H-NMR (60 MHz, $CDCl_3$); 3-$CH_2CH=C(C\underline{H}_3)_2$: δ = 1.70(s); 3-$CH_2C\underline{H}=C(CH_3)_2$: δ = 5.10(m = 3, ^3J = 8 Hz); 3-$C\underline{H}_2CH=C(CH_3)_2$: δ = 3.05(m = 2, ^3J = 8.0 Hz); 5-$\underline{H}$: δ = 2.83(s).

3,5,5-triëthoxy-2-(3'-methyl-2'-butenyl)-2-cyclopenten-1-one (9)

8 (95 g), triethyl orthoformate (3.5 ml) and p.toluenesulphonic acid (0.75 g) were dissolved in dry ethanol (2 l) and the mixture was heated for 14 h; the ethyl formate generated was allowed to distill through an efficient reflux condenser. The reaction mixture was cooled to room temperature, treated with solid sodium carbonate, filtered and concentrated in vacuo. Ether was added to the residue, the ether was extracted several times with a saturated sodium carbonate solution and washed with water. The etherlayer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was treated with boiling pentane yielding 30 g (50 %) pure 9.

mpt. : 44°C (from pentane).

UV : λ_{max} (methanol) = 262 nm ($\varepsilon \sim$ 18,500).

IR : ν^1 (cm^{-1}) = 1710, 1640, 1250, 1050.

MS : m/e at 282 (M^+, 4 %), 268(2), 253(7), 238(76), 209(38), 207(30), 179(19),

151(17), 137(38), 109(12), 69(100).

^{1}H-NMR (60 MHz, CCl_4); 2-$CH_2CH{=}C(C\underline{H}_3)_2$: δ = 1.62(s); 2-$C\underline{H}_2CH{=}C(CH_3)_2$: δ = 2.7; 2-$CH_2C\underline{H}{=}C(CH_3)_2$: δ = 5.0(m = 3, ^{3}J = 8.0 Hz); 3-$OCH_2C\underline{H}_3$: δ = 1.36(m = 3; ^{3}J = 7.2 Hz); 3-$OC\underline{H}_2CH_3$: δ = 4.15(m = 4, ^{3}J = 7.2 Hz); 4-$\underline{H}$: δ = 2.7(s); 5-$OCH_2C\underline{H}_3$: δ = 1.12(m = 3, ^{3}J = 7.2 Hz).

2-(7'-methoxyheptyl)-3-(3'-methyl-2'-butenyl)-2-cyclopenten-1,4-dione (10)

To 7-methoxy-1-heptylmagnesium bromide (from 93 g of the corresponding bromide and 10.7 g magnesium) in dry tetrahydrofurane (600 ml) was added under nitrogen 9 (50 g) in dry tetrahydrofurane (400 ml) for 1 h. After completion of the reaction, the mixture was cooled and poured into ice-water (2 l). Ether (1 l) was added and the mixture was acidified (pH 1) with 20 % HCl. After titration with ether, the ether was washed with water and concentrated in vacuo. The residue was treated with tetrahydrofurane (600 ml) and 6 N HCl (400 ml). After 5 h water was added, the waterlayer was extracted with ether, the ether dried (Na_2SO_4) and concentrated in vacuo. The residue afforded after distillation under reduced pressure 55.5 g (100 %) pure 10.

bpy. : 100°C/0.01 nm; R_f(ether-benzene, 1:1) = 0.60.

UV : λ_{max} (methanol) = 243 nm (ε ∿ 12,100).

IR : ν^1 (cm^{-1}) = 1745, 1707, 1680, 1635, 1460, 1385, 1350, 1260, 1120.

MS : m/e at 292 (M^+, 57 %), 245(8.5), 177(34), 45(100).

^{1}H-NMR (60 MHz, CCl_4); 2-$CH_2(C\underline{H}_2)_5CH_2OCH_3$: δ = 1.34(m); 2-$C\underline{H}_2(CH_2)_5CH_2OCH_3$: δ = 2.35(m = 3, ^{3}J = 7.0 Hz); 2-$(CH_2)_6$-$C\underline{H}_2OCH_3$: δ = 3.23(m = 3, ^{3}J = 6.0 Hz); 2-$(CH_2)_7OC\underline{H}_3$: δ = 3.18(s); 3-$CH_2CH{=}C(C\underline{H}_3)_2$: δ = 1.69(s, broad); 3-$CH_2C\underline{H}{=}C(CH_3)_2$: δ = 4.95(m = 3, ^{3}J = 7.25 Hz); 3-$C\underline{H}_2CH{=}C(CH_3)_2$: δ = 3.03(m = 2, ^{3}J = 7.25 Hz); 4-$\underline{H}$: δ = 2.67(s).

The cyclopentenolones 2 and 3

To a cooled (-20°C) suspension of zinc (66 g) in glacial acetic acid (440 ml) and methylene chloride (440 ml) was added a cooled solution (-25°C) of the dione 10 (55 g) in dry methylene chloride (440 ml) during 15 min. After 3 h the reaction mixture was warmed to room temperature and concentrated in vacuo. Ether was added to the residue, the zinc was filtered off and thoroughly washed with ether. The ether layer (2 l) was extracted with 10 % aqueous sodiumcarbonate solution. After drying (Na_2SO_4) and concentration of the ether phase the cyclopentenolones 2 and 3 were obtained as colourless oils, sufficiently

pure for the next reaction (y. 54.5 g or 90 %). 2 and 3 can be separated by column chromatography on silicagel with ether-benzene (1:1) as eluent.

Compound 2 has a R_f value 0.19 (ether-benzene, 1:1).

UV : λ_{max} (methanol) = 231 nm ($\varepsilon \sim 10{,}900$).

IR : ν^1 (cm^{-1}) = 3430, 1700, 1645, 1120, 1095, 1045.

MS : m/e at 294 (M^+, 1 %), 292(2), 276(48), 261(42), 175(13),165(17), 162(37), 147(27), 111(3), 109(11), 45(100).

^{1}H-NMR (100 MHz, $CDCl_3$); 3-$CH_2(C\underline{H}_2)_5CH_2OCH_3$: δ = 1.30; 3-$(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.24(m = 3, ^3J = 6.0 Hz); 3-$CH_2)_7OC\underline{H}_3$: δ = 3.18(s); 3-$C\underline{H}_2(CH_2)_7OCH_3$: δ = 2.46(m = 3, ^3J = 6.6 Hz); 2-$C\underline{H}_2CH{=}C(CH_3)_2$: δ = 2.82(m = 2, ^3J = 6.7 Hz); 2-$CH_2C\underline{H}{=}C(CH_3)_2$: δ = 4.94(m = 3, ^3J = 6.7 Hz, ^4J = -1.30 Hz); 2-$CH_2CH{=}C(C\underline{H}_3)_2$: δ = 1.62(s); 4-$\underline{H}$: δ = 4.72(m $\sim$ 2, ^3J = 5.8 and 2.2 Hz); 5-$\underline{H}$: δ = 2.39(m = 4, ^2J = -18.0 and ^3J = 2.2 Hz) and δ = 2.67(m = 4, ^2J = -18.0 and ^3J = 5.8 Hz).

Compound 3 has a R_f value 0.23 (ether-benzene, 1:1).

UV : λ_{max} (methanol) = 231 nm ($\varepsilon \sim 10{,}900$).

IR : ν^1 (cm^{-1}) = 3420, 1700, 1640, 1120, 1065, 1050.

MS : m/e at 294 (M^+, 8 %), 292(3), 276(13), 207(7), 165(4), 147(13), 111(7), 109(17), 45(100).

^{1}H-NMR (100 MHz, $CDCl_3$) : 2-$CH_2(C\underline{H}_2)_5CH_2OCH_3$: δ = 1.34(m); 2-$(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.24(m = 3, ^3J = 6.0 Hz); 2-$(CH_2)_7OC\underline{H}_3$: δ = 3.18(s); 2-$C\underline{H}_2(CH_2)_6OCH_3$: δ = 2.13; 3-$C\underline{H}_2CH{=}C(CH_3)_2$: δ = 3.12(m = 2, ^3J = 7.2 Hz); 3-$CH_2C\underline{H}{=}C(CH_3)_2$: δ = 4.08(m = 3, ^3J = 7.2 and ^4J = -1.4 Hz); 3-$CH_2CH{=}C(C\underline{H}_3)_2$: δ = 1.68(s); 4-$\underline{H}$: δ = 4.66(m $\sim$ 2, ^2J = 6.0 and 2.2 Hz); 5-$\underline{H}$: δ = 2.21(m = 4, ^2J = -18.0 and ^3J = 2.2 Hz) and δ = 2.68(m = 4, ^2J = -18.0 and ^3J = 6.0 Hz).

The cyclopentanediols 4 and 12

2 and 3 (50 g, 0.165 mole) dissolved in dry methanol (20 ml) and dry tetrahydrofuran (150 ml) were added to liquid ammonia (distilled from sodium). Lithium (9.1 g, 1.32 mole) was then added in small pieces; after 30 min. the excess lithium was destroyed by adding methanol (50 ml) and ammonium chloride (70 g). The ammonia was evaporated, ether was added and the inorganic salts filtered off. After acidifying with dil. HCl, the water layer was extracted with ether (3 x). The combined ether extracts were dried (Na_2SO_4) and evaporated. The yellow oil was purified by column chromatography (silica gel; ethyl acetate as eluent). The yield was 25 g (50 %).

Further column chromatography (silica gel, ethyl acetate as eluent) yielded

three different diol fractions with R_f values 0.39 (4c and 12c; 77/23), 0.31 (4a and 12a; 87/13) and 0.27 (4b and 12b; 34/66). The degree of saturation was determined by GC-analysis of the three different fractions[7]. Catalytic hydrogenation of each separated fraction led to the pure compounds 12a, 12b and 12c with the following spectroscopic data :

IR : ν^1 (cm^{-1}) = 3400, 2980, 1480, 1390, 1370, 1350, 1260(broad), 1205, 1175, 1125, 1050.

^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in Table 1; 2-$(CH_2)_6\underline{CH_2}OCH_3$: δ = 3.37(m = 3, ^3J = 6.75 Hz); 2-$(CH_2)_7OCH_3$: δ = 3.33(s); 2-$(CH_2)_5\underline{CH_2}CH_2OCH_3$: δ = 1.53(m = 5, ^3J = 6.5 Hz); 2-$(\underline{CH_2})_5CH_2CH_2OCH_3$: δ = 1.32(m); 3-$(CH_2)_2CH(\underline{CH_3})_2$: $\Delta\delta$ = 1.25 Hz (^3J = 6.5 Hz).

IR : ν^1 (cm^{-1}) = 3400, 2950, 1470, 1390, 1370, 1350, 1270, 1210, 1125, 1080 (broad).

^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in Table 1; 2-$(\underline{CH_2})_5CH_2CH_2OCH_3$: δ = 1.31(m); 2-$(CH_2)_5\underline{CH_2}CH_2OCH_3$: δ = 1.53(m = 5, ^3J = 6.5 Hz); 2-$(CH_2)_6\underline{CH_2}OCH_3$: δ = 3.36(m = 3, ^3J = 6.5 Hz); 2-$(CH_2)_7O\underline{CH_3}$: δ = 3.33(s); 3-$(CH_2)_2CH(\underline{CH_3})_2$: $\Delta\delta$ = 2.75 Hz(^3J = 6.5 Hz); 3-$C\underline{H}HCH_2CH(CH_3)_2$ en 2-$C\underline{H}H(CH_2)_6OCH_3$: δ = 1.14.

IR : ν^1 (cm^{-1}) = 3400, 2950, 1470, 1395, 1120, 1050(broad).

^{1}H-NMR (300 MHz, $CDCl_3$); 2-$(\underline{CH_2})_5CH_2CH_2OCH_3$: δ = 1.33; 2-$(CH_2)_6\underline{CH_2}OCH_3$: δ = 3.37(m = 3, ^3J = 6.63 Hz); 2-$(CH_2)_7O\underline{CH_3}$: δ = 3.32(s); 1-$\underline{H}$: δ = 3.94(sum of J = 10.5 Hz); 4-$\underline{H}$: δ = 4.25(sum of J = 9.0 Hz); 3-$(CH_2)_2CH(\underline{CH_3})_2$: $\Delta\delta$ = 1.5 Hz (^3J = 6.5 Hz).

The cyclopentanediacetate 13

Compound 13a has an R_f value (ethyl acetate) = 0.67.

IR : ν^1 (cm^{-1}) = 2950, 1750, 1475, 1370, 1240, 1125, 1040(broad), 980.

MS : m/e at 264 (M^+-2 x HOAc, 1 %; high resolution, 264.2447, calc. for $C_{18}H_{32}O$: 264.2453), 161(7), 143(9), 108(64), 91(80), 79(100).

^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in Table 1; 1- and 4-$OCO\underline{CH_3}$: δ = 2.02(s), 2-$(\underline{CH_2})_5CH_2CH_2OCH_3$: δ = 1.30(m); 2-$(CH_2)_5\underline{CH_2}CH_2OCH_3$: δ = 1.54(m = 5, ^3J = 6.75 Hz); 2-$(CH_2)_6\underline{CH_2}OCH_3$: δ = 3.36(m = 3, ^3J = 6.75 Hz); 2-$(CH_2)_7O\underline{CH_3}$: δ = 3.32(s); 3-$(CH_2)_2CH(\underline{CH_3})_2$: $\Delta\delta$ = 1.50 Hz(^3J = 6.5 Hz).

Compound 13b has an R_f value (ethyl acetate) : 0.66.

IR : ν^1 (cm^{-1}) : 2960, 1750, 1470, 1380, 1250, 1125, 1060, 1025, 980.

MS : identical with 13a.

^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in Table 1; 1- and 4-$OCOC\underline{H}_3$: δ = 2.05(s); 2-$(C\underline{H}_2)_5CH_2CH_2OCH_3$: δ = 1.31(m); 2-$(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.53(^3J = 6.5 Hz); 2-$(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.36(m = 3, ^3J = 6.5 Hz); 2-$(CH_2)_7OC\underline{H}_3$: δ = 3.32(s); 3-$(CH_2)_2CH(C\underline{H}_3)_2$: $\Delta\delta$ = 2.5 Hz (^3J = 6.5 Hz); 2-$C\underline{H}H$-$(CH_2)_6OCH_3$: and 3-$C\underline{H}HCH_2CH(CH_3)_2$: δ = 1.15.

The γ-lactone 17

R_f value (ethyl acetate) : 0.50.
IR : ν^1 (cm^{-1}) = 3450, 1775, 1450, 1420, 1365, 1310, 1185, 1120, 1040, 975, 920, 835.
MS : m/e at 270 (M^+, 1.5 %), 255(12), 252(6), 241(5), 237(6), 234(15), 181(6), 179(7), 169(7), 161(11), 151(15), 138(25), 124(15), 95(59), 81(71), 67(94), 55(100).
^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in Table 2; 6-$(C\underline{H}_2)_5CH_2CH_2OCH_3$: δ = 1.31(m); 6-$(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.56(m = 5, ^3J = 6.5 Hz); 6-$(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.37(m = 3, ^3J = 6.63 Hz); 6-$(CH_2)_7OC\underline{H}_3$: δ = 3.33(s).

The δ-lactone 5

R_f value (ethyl acetate) : 0.30.
IR : ν^1 (cm^{-1}) = 3450, 2950, 2890, 1740(broad), 1470, 1390, 1370, 1325, 1240, 1200, 1175, 1125, 1085, 1055, 1035, 990, 970, 950, 925, 900, 850, 830, 805, 755, 725, 685.
MS : m/e at 270 (M^+, 2 %; high resolution, 270.1850, calc. for $C_{15}H_{26}O_4$: 270.1830), 234(14), 192(11), 138(30), 81(67), 67(88), 55(100).
^{1}H-NMR (300 MHz, $CDCl_3$) data nog mentioned in Table 2; 8-$(C\underline{H}_2)_5CH_2CH_2OCH_3$: δ = 1.33(m); 8-$(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.56(m = 5, ^3J = 6.75 Hz); 8-$(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.37(m = 3, ^3J = 6.63 Hz); 8-$(CH_2)_7OC\underline{H}_3$: δ = 3.33(s).

The δ-lactone 18

To a stirred solution of 5 (0.3 g, 1.1 mmole) dihydropyran (0.462 g, 5.5 mmole) in dry methylene chloride (4 ml) toluene-p.sulphonic acid (1 mg) was added followed (after 10 min) by solid potassium carbonate. The mixture was filtered, concentrated in vacuo and purified by column chromatography on silica gel with ethyl acetate-benzene (1:1) as eluent. The yield was 0.35 g (87 %).

R_f value (ethyl acetate) : 0.54.
IR : ν^1 (cm^{-1}) = 1750, 1460, 1390, 1370, 1330, 1250, 1205, 1200-1000, 985, 950,

925, 910, 870, 810.

MS : m/e at 271(20), 85(100).

r-1-hydroxy-2-t-(7'-methoxyheptyl)3-c-(methoxycarbonyl)methyl-4-t-(2'-tetrahydropyranyloxy)cyclopentane (19)

A solution of 18 (0.36 g, 0.97 mmole) and sodium hydroxide (0.8 g) in methanol (10 ml) was stirred at room temperature during 6 h. The mixture was then concentrated in vacuo, water was added and the solution carefully acidified at 0°C with dil. HCl (pH 5). The water layer was extracted with ether (6 x), followed by continuous extraction (24 h). After evaporation the residue was treated with diazomethane, the ether layer was dried (Na_2SO_4) and evaporated. The yield was 0.33 g (86 %).

R_f value (ethyl acetate) = 0.46.

IR : ν^1 (cm^{-1}) = 3470, 1750, 1450, 1355, 1260, 1210, 1200-1000, 920, 875, 820.

MS : m/e at 313 (0.2), 301(4), 285(14), 235(10), 229(6), 213(3), 211(3), 179 (3), 161(4), 155(3), 85(100).

The tosylate 20

A solution of 19 (0.15 g, 0.38 mmole) in dry pyridine (0.75 ml) was added at once at 0°C to a solution of recrystallised toluene-p-sulphonyl chloride (0.15 g, 0.8 mmole) in dry pyridine (0.75 ml). The reaction mixture was kept at 0°C for 16 h and poured in ice-water, stirred for 1 h and extracted (5 x) with ether. The combined ether layers were washed several times with 5 % HCl; the combined water layers were extracted with ether (3 x) and the organic layers again washed with dil. HCl. The combined organic layers were washed with saturated aqueous sodium chloride, dried (Na_2SO_4) and concentrated after filtration. The yield of crude tosylate is 0.2 g (95 %). It can be purified by column chromatography on silica gel with ethyl acetate-benzene (3:7) as eluent.

R_f value (ethyl acetate) = 0.67.

IR : ν^1 (cm^{-1}) = 1750, 1605, 1445, 4370, 1250, 1200-1000, 980, 900, 820, 670.

The inversion of the tosylate 20

A mixture of 20 (4.3 g, 8 mmole) and tetraethyl ammonium acetate (monohydrate; 6.45 g, 33 mmole) in dry acetone (45 ml) was refluxed for 16 h. The acetone was then removed in vacuo, the residue was taken up in water and extracted

with ether (5 x). After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography (silica gel) with ethyl acetate-benzene (2:3) as eluent. The yield of inverted product 21 was 2.55 g (75 %) and of elimination product 23 was 0.37 g (13 %).

Compound 21 has a R_f value (ethyl acetate) = 0.63.
IR : ν^1 (cm^{-1}) = 1745, 1445, 1375, 1245, 1200, 1200-1000, 975, 870.
MS : m/e at 368 (M^+-HOAc, 3 %), 355(3), 343(19), 327(4), 283(10), 235(20), 85 (100).

Compound 23 has a R_f value (ethyl acetate) = 0.67.
IR : ν^1 (cm^{-1}) = 1750, 1200-1000, 870, 720.
MS : m/e at 284 (M^+-DHP, 3 %), 283(7), 267(3), 235(32), 156(7), 85(100).
^{1}H-NMR (300 MHz, $CDCl_3$); the two olefinic hydrogens : δ = 5.77 and 5.86; $-COOC\underline{H}_3$: δ = 3.65 and 3.66; $-C\underline{H}_2OC\underline{H}_3$: δ = 3.35(m = 3, ^3J = 6.5 Hz) and 3.30 respectively.

The 2-(7'-methoxyheptyl)-3-(methoxycarbonyl)methyl-1,4-cyclopentanediols 16a and 22

A solution of 21 (0.1 g, 0.23 mmole) and conc. HCl (0.1 ml) in methanol (1 ml) was stirred for 2 h. The methanol was removed in vacuo, the residue was taken up in water and extracted thoroughly with ethyl acetate. The organic layers were washed with water, dried (Na_2SO_4) and evaporated. The yield of 22 was quantitative, 16a was obtained in the same way from 19.

Compound 22 has a R_f value (ethyl acetate) = 0.24.
IR : ν^1 (cm^{-1}) = 3420, 2950, 1750, 1450, 1120.
^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in table 2; $2-(C\underline{H}_2)_5CH_2CH_2OCH_3$: δ = 1.31; $2-(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.56 (^3J = 7 Hz); $2-(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.36(m = 3, ^3J = 6.63 Hz); $2-(CH_2)_7OC\underline{H}_3$: δ = 3.32(s); $3-CH_2COOC\underline{H}_3$: δ = 3.69. The sum of the vicinal coupling constants of 5-$\underline{H}_A$, 3-$\underline{H}$, 1-$\underline{H}$ and 4-$\underline{H}$ = 5, 30, 9 and 15 Hz respectively.

Compound 16a has a R_f value (ethyl acetate) = 0.20.
IR : ν^1 (cm^{-1}) = 3400, 2950, 1750(broad), 1450.
^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in table 2; $2-(C\underline{H}_2)_5CH_2CH_2OCH_3$: δ = 1.32(m); $2-(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.56; $2-(CH_2)_6C\underline{H}_2OCH_3$: δ = 3.36(m = 3, ^3J = 6.75 Hz); $2-(CH_2)_7OC\underline{H}_3$: δ = 3.33(s); $3-CH_2COOC\underline{H}_3$: δ = 3.70(s). The sum of

the coupling constants of 1-H and 4-H = 21.0 and 15.2 Hz respectively.

r-1-hydroxy-2-c-(7'-methoxyheptyl)-3-t-(2',2'-diphenyl-2'-hydroxyethyl)-4-c-(2'-tetrahydropyranyloxy)cyclopentane (24).

A solution of 21 (2.54 g, 5.94 mmole) in tetrahydrofuran-benzene (30 ml, 1:1) was added under an atmosphere of nitrogen to a solution of phenylmagnesium bromide (1.73 g magnesium and 11.19 g bromobenzene, 71 mmole) at room temperature. After stirring for 30 min the reaction mixture was poured in ice-water; ether and ammonium chloride were added; the water layer was extracted thoroughly with ether. After drying ($MgSO_4$) and concentration the residue was purified by column chromatography on silica gel with ethyl acetate-benzene (2:3) as eluent. The yield was 2.57 g (85 %).

R_f value (ethyl acetate-benzene, 2:3) = 0.34.
IR : ν^1 (cm^{-1}) = 3440, 1200-1000, 910, 875, 815, 780, 755, 700.
MS : m/e at 244(10), 183(64), 105(44), 85(100).

r-1-hydroxy-2-c-(7'-methoxyheptyl)-3-t-(2',2'-diphenylethenyl)-4-c-hydroxycyclopentane (26)

A solution of 24 (0.55 g, 1.07 mmole) in dioxane-hydrochloric acid (27.5 ml; 10:1) was stirred at room temperature for 4 h. Dioxane was removed in vacuo and water was added to the residue. The water layer was thoroughly extracted with ether. The ether layer was washed with saturated sodiumchloride solution, dried ($MgSO_4$) and evaporated; the residue was purified by column chromatography on silica gel with ethyl acetate-benzene (1:1) as eluent. The yield was 0.35 g (82 %).

R_f value (ether-benzene, 1:1) = 0.21.
UV : λ_{max} (methanol) = 240(sh), 245, 251, 258(sh).
IR : ν^1 (cm^{-1}) = 3400, 3100, 3080, 3040, 2950, 1630, 1600, 1495, 1120, 760, 730, 700.
MS : m/e at 408 (M^+, 14 %; high resolution, 408.2692, calc. for $C_{27}H_{36}O_3$: 408.2664), 390(24), 372(3), 364(3), 346(9), 217(16), 205(23), 193(35), 180(100), 167(46), 115(31), 91(53).
^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in table 3; 2-($C\underline{H}_2$)$_5CH_2CH_2OCH_3$: δ = 1.28; 2-$(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.54(m; ^3J = 7.0 Hz); 2-$(CH_2)_5CH_2C\underline{H}_2OCH_3$: δ = 3.34(m = 3, ^3J = 6.63 Hz); 2-$(CH_2)_7OC\underline{H}_3$: δ = 3.31(s); 3-C$\underline{H}$= : δ = 5.85(m = 2;

^3J = 11 Hz); 3-(2'-$C_6\underline{H}_5$) : δ = 7.16-7.42. The sum of the vicinal coupling constants of 1-$\underline{H}$, 4-$\underline{H}$ and 5-$\underline{H}_A$ is respectively = 8.5, 12.5 and 5.5 Hz.

r-1-acetoxy-2-c-(7'-hydroxyheptyl)-3-t-(2',2'-diphenylethenyl)-4-c-acetoxycyclopentane (29)

To a solution of 27 (0.117 g, 0.23 mmole), obtained from 26 with acetic anhydride and pyridine, 72 %), in methylene chloride (1 ml) was added at -80°C a solution of boron tribromide (63 mg, 24 µl) in methylene chloride (1 ml). The reaction mixture was brought to -25°C and stirred at this temperature during 6 h. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture at 0°C; the water layer was extracted with ether. After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography on silica gel with ethyl acetate-benzene (1:1) as eluent. Three different fractions were collected; bromide 30 (12 %), alcohol 29 (80 mg, 70 %) and starting material 27 (12 %).

R_f value of compound 29 (ethylacetate) = 0.59.
IR : ν^1 (cm^{-1}) = 3460, 3100, 3080, 3040, 1750, 1600, 1500, 1450, 1375, 1250, 1040, 925, 765, 730, 700.

r-1-hydroxy-2-c-(7'-methoxyheptyl)-3-t-methoxycarbonyl-4-c-hydroxycyclopentane (38)

Ozone was passed through a solution of 28 (0.288 g; obtained from 26 in the usual way) in methanol at -20°C for 2 h (t.l.c.). The methanol was evaporated in vacuo and the residue treated with a solution of 30 % hydrogenperoxide (0.27 g) in formic acid (0.5 ml). After 2 h water was added and the water layer extracted with ether; the ether was concentrated in vacuo, the residue treated with diazomethane, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silicagel with ethyl acetate as eluent. The yield of 38 was 20 mg (15 %).

R_f value (ethyl acetate) = 0.39.
IR : ν^1 (cm^{-1}) = 3400, 2930, 1730, 1435, 1260, 1200, 1165, 1100(broad), 1030.
MS : m/e at 288 (M^+, 1 %), 270(4), 299(10), 220(14), 215(20), 197(29), 183(26), 55(100).
^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in table 3; 2-($C\underline{H}_2$)$_5CH_2CH_2OCH_3$: δ = 1.32; 2-$(CH_2)_5C\underline{H}_2CH_2OCH_3$: δ = 1.59(m = 5, ^3J = 6.5 Hz); 2-$(CH_2)_6C\underline{H}_2OCH_3$: δ =

3.36(m = 3, ^3J = 6.63 Hz); 2-$(CH_2)_7OCH_3$: δ = 3.32(s); 3-$COOCH_3$: δ = 3.71(s); the sum of the vicinal coupling constants of 1-H, 4-H and 5-H_A is respectively = 10, 12.5 and 4 Hz.

r-1-acetoxy-2-c-(6'-methoxycarbonyl)hexyl-3-t-methoxycarbonyl-4-c-acetoxycyclopentane (34)

To a cooled (-15°C) solution of 29 (0.15 g, 0.31 mmole) in acetone (15 ml) Jones reagent was added. After 1 h, isopropanol was added, the reaction mixture filtered and the acetone removed in vacuo. Water was added to the residue and after extraction with ether and concentration in vacuo, the residue was treated with diazomethane. The yield of 32 was quantitative (on t.l.c.).

UV : λ_{max} (methanol) = 240(sh), 245, 261 and 258(sh).
IR : ν^1 (cm^{-1}) = 2950, 1750, 1550, 1600, 1455, 1385, 1240, 1100, 1025, 765, 730, 700, 620.
MS : m/e at 386 (M^+ - 2 x HOAc, 92 %; high resolution 386.2259, calc. for $C_{27}H_{30}O_2$: 386.2245), 257(15), 244(15), 243(43), 217(12), 205(11), 191(19), 91(24), 43(100).

To a solution of ruthenium tetroxide in water (2.5 ml; from 5 mg ruthenium dioxide and 2 x 50 mg sodium periodate) a solution of the ester 32 (0.15 g) in acetone (1 ml) was added. The yellow solution turned black and precipitation occured. The black colour was maintained even after adding water (1 ml) and several portions of sodium periodate (4 x 25 mg). After filtration of the salts the acetone was removed in vacuo and water was added to the residue. After extraction with ether and concentration in vacuo the residue was treated with diazomethane. Evaporation yielded 34 (84 mg, 72 % from 29).

Compounds 29, 31, 32 and 33 have respectively R_f values (ethyl acetate) : 0.59, 0.56, 0.65 and 0.49.
Compound 34 has a R_f value (ethyl acetate) = 0.61.
IR : ν^1 (cm^{-1}) = 3450, 1750, 1440, 1275, 1240, 1170, 1030.
MS : m/e at 386 (M^+, 1 %; high resolution 386.1972, calc. for $C_{19}H_{30}O_8$: 386.1946), 343(3), 332(12), 284(16), 252(35), 234(80), 55(100).
^{1}H-NMR (300 MHz, CCl_4) data not mentioned in table 3; 2-$(CH_2)_4CH_2CH_2COOCH_3$: δ = 1.28; 2-$(CH_2)_4CH_2CH_2COOCH_3$: δ = 1.56(m = 5, ^3J = 6.63); 2-$(CH_2)_5CH_2CH_2COOCH_3$: δ = 2.21(m = 3, ^3J = 7.5 Hz); 2-$(CH_2)_6COOCH_3$: δ = 3.59 (s); 3-$COOCH_3$: δ = 3.71(s); 1-$OCOCH_3$ and 4-$OCOCH_3$: δ = 2.00 and 1.98; the

sum of the coupling constants of 1-H, 4-H, 5-H_A and 2-H is respectively = 11.5, 18.0, 4.0 and 29.0 Hz.

(dl)-9,11-diacetoxy-15-dehydro-$PGF_{1\alpha}$-methyl ester (39)

To a solution of 33 (50 mg, 0.135 mmole) in dry tetrahydrofuran (2 ml) diborane in tetrahydrofuran (2.2 ml of a 0.43 molar solution) was added at -10°C under an atmosphere of nitrogen (dry, oxygen-free). The reaction mixture was stirred for 5 min at room temperature. Dil. HCl was added, tetrahydrofuran was evaporated in vacuo and the residue taken up in water. After extraction with ether, drying (Na_2SO_4) and evaporation the residue was purified on silica gel with ethyl acetate-benzene (1:1) as eluent. The yield of 36 was 40 mg (80 %).
MS of compound 36 : m/e at 238 (M^+ - 2 x HOAc, 14 %), 81(14), 80(14), 67(13), 43(100).
To the alcohol 36 (40 mg, 0.111 mmole) dissolved in methylene chloride (0.8 ml), celite (0.45 g) and several portions of chromium trioxide dipyridine complex were added at room temperature (4 x 0.27 g, 4.2 mmole) the reaction being followed by t.l.c. Sodium hydrogen sulphate (0.5 g) was added and the mixture was stirred at room temperature for 10 min. After filtration through anhydrous magnesium sulphate (which was washed with methylene chloride) the solution was concentrated in vacuo at low temperature. The oily aldehyde (37) obtained was used as such for the next reaction.
To a suspension of sodium hydride (50 % suspension in oil (6.75 mg) in DME (1.4 ml) was added dimethyl 2-oxoheptylphosphonate (30.8 mg) in DME (0.65 ml). The mixture was stirred at room temperature for 30 min. and the aldehyde (in DME; 0.65 ml) was added. The mixture was stirred for 30 min. The excess of base was neutralised with acetic acid (1 drop) and the solvent was removed under reduced pressure without heating. The residue was purified on a silica gel column with ethyl acetate-benzene (1:4) as eluent. The yield of enone 39 was 30 mg (65 % from 36).

Compounds 36 and 37 have respectively R_f values (ethyl acetate-benzene, 1:1) = 0.34 and 0.56.
Compound 39 has an R_f value (ethyl acetate-benzene, 1:1) = 0.50.
UV : λ_{max} (methanol) = 226 nm.
IR : ν^1 (cm^{-1}) = 1750, 1680, 1630, 1235.
MS : m/e at 350(35 %), 339(10), 332(51), 276(80), 261(77), 247(21), 189(40), 133(56), 99(100).

^{1}H-NMR (300 MHz, $CDCl_3$) data not mentioned in table 3; CH_3(20) : δ = 0.9(m = 3, ^3J = 6.88 Hz); $-CH_2-$(4-7, 18, 19) : δ = 1.23-1.35(m); $-CH_2-$(3 and 17) : δ = 1.59 and 1.62 (^3J = 7.5 Hz) respectively; $-CH_2-$(2 and 16) : δ = 2.29 and 2.56 (m = 3, ^3J = 7.5 Hz) respectively; $-OCOCH_3$ (1 and 4) : δ = 2.02 and 2.08(s); -CH=(13) : δ = 6.64(m = 4, $^3J_{H13,14}$ = 16.0 Hz); -CH=(14); δ = 6.09(m = 2, ^3J = 16.0 Hz).

(dl)-prostaglandin $F_{1\alpha}$-methyl ester (42)

To sodium borohydride (1.95 g) in redistilled DME (50 ml) was added freshly fused zinc chloride (3.4 g). The mixture was stirred overnight at 0-5°C. After filtration under nitrogen, the clear solution was used immediately. To the ketone 39 (30 mg) dissolved in anhydrous DME (0.5 ml) was added 0.3 ml of the solution of zinc borohydride. The mixture was stirred at room temperature for 90 min. Saturated sodium hydrogen tartrate was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the solution was dried ($MgSO_4$), filtered and evaporated. The mixture of 15-alcohols 40 and 41 (25 mg) was separated on preparative silica gel plates (ethyl acetate-benzene, 2:3) to give 2 mg unreacted ketone and 7 mg of each isomer, in addition to a mixture of 40 and 41 (7 mg).

The R_f values (ethyl acetate-benzene, 2:3) of compounds 39, 40 and 41 = 0.56, 0.45 and 0.39.

To a solution of 41 (7 mg) in dry methanol (0.2 ml) potassium carbonate was added (5 mg). After 6 h (t.l.c.) dry dioxane was added and the solution kept at 0°C for 12 h. After filtration of the precipitate and concentration under nitrogen 42 was obtained quantitatively (t.l.c.).

The R_f values of 40, 41 and 42 (upper layer of the following system : ethyl acetate, acetic acid - isooctane - water, 50:5:25:20) = 0.66, 0.60 and 0.24.

The mass spectrum of the tri-(trimethylsilyl)ether was consistent with the mass spectrum of the derivative of an authentic $PGF_{1\alpha}$ sample, run under the same experimental GC-MS conditions. GC; Varian 1400, column : 1 % OV-1/GQ 80/100 mesh, temperature 200°C, injector temperature 250°C, Helium flow 30 ml/min. MS; Finnigan 3000-1 (mass range 0-500).

The relative intensities for 9 diagnostic peaks; m/e for the synthetic derivative at 425(1.67 %), 399(2.47), 380(2.57), 335(13.45), 309(50), 217(39.01), 191(100), 173(33), 147(38.50) and for the derivative of an authentic sample 425(4.12), 399(4.51), 380(3.59), 335(34.05), 309(50.04), 217(70.14), 191(100),

173(29.43), 147(49.82).

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