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CYCLOPENTANONES—XVI†

PROSTAGLANDIN SYNTHESIS INVOLVING CATALYTIC HYDROGENATION OF 2,3-DIALKYL-4-HYDROXY-2-CYCLOPENTENONES

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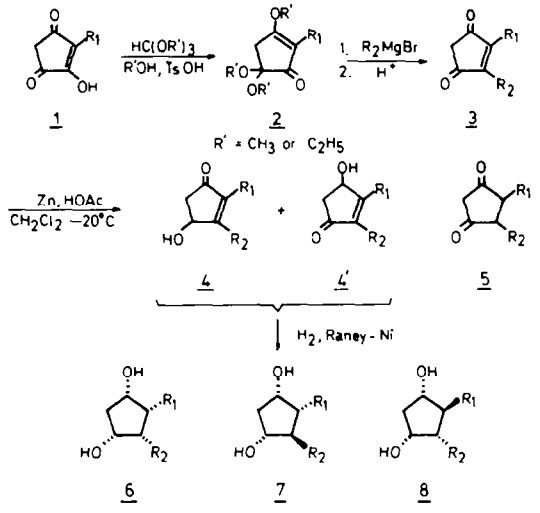
Abstract—2,3-Dialkyl-4-hydroxy-2-cyclopentenones with differently functionalised side chains yield predominantly all-cis 2,3-dialkyl-1,4-dihydroxycyclopentanes on catalytic hydrogenation. Epimerisation at C-12 (PG numbering) leads to prostaglandin synthons. Influence of the side-chain functions on these reactions is described.

2,3-Dialkyl-1,4-cyclopentenediones **3** are synthesised from compounds **1** according to a general method[1] (Scheme 1). Upon reduction with zinc and acetic acid at low temperature an isomeric mixture of cyclopentenolones **4** and **4'** is generally obtained. Due to the anticipated preferential formation of all cis 2,3 - dialkyl - 1,4 - cyclopentanediols **6** upon catalytic hydrogenation, both isomers **4** and **4'** are suitable for further work; it is also obvious that both R_1 and R_2 can be precursors for both PG side chains.



a: $R_1 = (CH_2)_2OCH_3$; $R_2 = (CH_2)_2\emptyset$
b: $R_1 = (CH_2)_2\emptyset$; $R_2 = (CH_2)_7OCH_3$
c: $R_1 = (CH_2)_2OCH_3$; $R_2 = CH_2OCH_3$
d: $R_1 = (CH_2)_2\emptyset$; $R_2 = (CH_2)_3\emptyset$

Scheme 1.

An appropriate intermediate must have side chains which can be converted to readily distinguishable two- and one-carbon units at the aldehyde oxidation level. A product of choice therefore is **3c** which has two appropriate side chains. To our disappointment however, the subsequent zinc-acetic acid reduction at −20°C in dry methylene chloride yielded exclusively the cyclopentanedione **5c**. This procedure had shown its reliability in several cases in our laboratory[2-5] and gives normally 4 - hydroxy - 2,3 - dialkyl - 2 - cyclopentenones (**4** and **4'**) in high yield (e.g. 85% for **3b**) with only a minor amount of the corresponding 1,3-cyclopentanedione **5**. At higher temperatures (above 20°C) the latter compounds are the sole reaction products; the zinc-acetic acid reduction is indeed a general procedure for the conversion of 2-ene-1,4-diones to the saturated 1,4-diones. A logical lowering of the temperature did not affect the course of the reduction of **3c**; only **5c** was formed at −55°C, using propionic acid. This dramatic change is doubtless due to the presence of ether functions in α and β position of the ring. The influence of the lone pair electrons of the ether function on the 1,2- vs 1,4-protonation of the intermediate anion radical is presently difficult to rationalise.

This unexpected result forced us to change the design of the synthesis. A β-phenylethyl side chain can also serve our purpose; it is resistant to hydrogenation under the conditions used and can be broken down to a formyl group at a later stage. We therefore undertook the synthesis of **3a**, which eventually led to Corey's lactone **32**. Obviously enedione **3d** is also a good intermediate; both side chains can be converted simultaneously to one- and two-carbon units with the desired oxidation level. For the synthesis of $PGF_{1\alpha}$ the one step introduction of the seven-carbon chain was chosen; in this case the starting dione was **3b**. Zinc-acetic acid reduction of **3b** under the usual circumstances proceeded with high yield. However, the analogous reduction at −20°C of **3a** (one ether function in β-position of the ring!) afforded a considerable amount of 1,3-cyclopentanedione **5a** (30%), next to the expected cyclopentenolones **4a** and **4'a** (70%).

The next step calls for a stereospecific reduction of the enone system in compounds **4** and **4'**. The catalytic hydrogenation of a cyclopentenolone over a Raney nickel catalyst (unspecified modification), yielding the saturated hydroxyketone (isolated as the oxime) has already been performed by Finch *et al.*[6] in a PGE_1 synthesis. In our case however, a reduction to the diol stage is preferred; β-hydroxy-ketones are unstable and in the case of **4a** and **4'a** the method leads to an intermediate for all primary

†Part XV: W. Van Brussel and M. Vandewalle, *Synthesis* 39 (1976).

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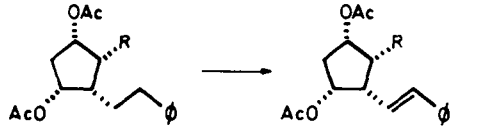
prostaglandins. The isomeric mixture of cyclopentenolones **4** and **4'** can be expected to afford mostly one isomeric cyclopentanediol, namely **6**.

The hydrogenation over a Raney-nickel W_7 catalyst in ethanol proceeds smoothly to 2,3 - dialkyl - 1,4 - cyclopentanediols; no ketonic material could be detected but substantial hydrogenolysis occurred. This side reaction could be avoided by the use of catalyst modification W_2; thus, four isomeric diols were obtained in 70% yield with the following ratio (GLC analysis of the corresponding acetates): **6a**, 63%; **7a**, 11%; **8a**, 22% and 4% of an isomer with unknown configuration. Still better results were obtained by blocking the hydroxyl group as a trimethylsiloxy derivative; the yield of the diol fraction was better (85%) while the size of the trimethylsilyl ether enhanced the formation of the desired all cis isomer **6a** (**6a**, 86%; **7a**, 4%; **8a**, 10% determined by GLC analysis of the corresponding acetates). Similar results were obtained for the reduction of **4b** (and **4'b**) and **4d** (and **4'd**): a lower yield of all cis isomers **6b** and **6d** was obtained (55%). The all-cis isomers could easily be isolated by column chromatography on silica gel. Their configurations were deduced by comparing the ^{1}H NMR spectral data of the corresponding diacetates **9a**, **9b** and **10** with the data of model compounds,[7,8] whose structures were unambiguously proven (Table 1). Structures **7a** and **8a** were proven by mass spectrometry of the corresponding n-butyl boronates.[9]

In the case of the isomers **6a**, **7a** and **8a** separation on silica gel is not necessary; both **6a** and **7a** are suitable for further synthesis, while **8a** can be removed by alkaline extraction at the moment of the generation of the carboxylic acid from the methoxyl function, as its configuration does not allow lactone formation (this is also the case for the isomers **d**). Since we wanted to study the epimerisation at the future C-12 prostaglandin position, the pure all-cis isomer **6a** was taken through the complete following reaction sequence.

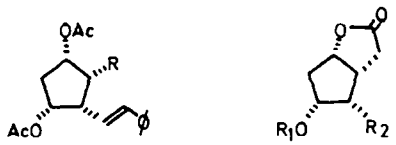


9a: R = $(CH_2)_2OCH_3$ **11a**: R = $(CH_2)_2OCH_3$
9b: R = $(CH_2)_7OCH_3$ **11b**: R = $(CH_2)_7OCH_3$
10: R = $(CH_2)_3\phi$ **11c**: R = $CH_2CH{=}CH\phi$

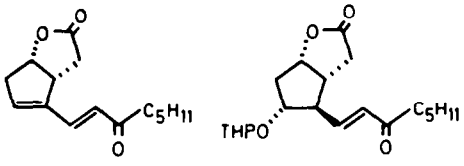
Scheme 2.

The diacetates **9a**, **9b** and **10** (Scheme 2) were treated with NBS in refluxing carbon tetrachloride. Direct elimination of the resulting benzylic bromides with lithium carbonate in DMF yielded **11a**, **11b** and **11c** (60–65% after column chromatography on silica gel). Oxidative cleavage of both double bonds in **11c** provides a short route to the lactone **30**. To our disappointment however, no suitable method could be found to effect this transformation; osmium tetroxide, potassium permanganate and ozone gave no detectable compounds. Ruthenium tetroxide afforded a small amount of the corresponding di-acid which eventually led to the lactone **30** (3%).

At this stage we decided to convert the ether function in **11a** and **11b** to the carboxylic acid (Scheme 3). Compounds **11a** and **11b** were treated with boron tribromide;[10] formation of the corresponding bromides



12: R = $(CH_2)_2OH$
13: R = CH_2COOH
14: R = CH_2COOCH_3
15: R = $(CH_2)_7OH$
16: R = $(CH_2)_6COOH$
17: R = $(CH_2)_6COOCH_3$
18: R_1 = H; R_2 = CH=CH—ϕ
19: R_1 = THP; R_2 = CHO
21: R_1 = THP; R_2 = CH=CH—CO—C_5H_{11}
23: R_1 = THP; R_2 = $COOCH_3$
30: R_1 = H; R_2 = $COOCH_3$



22 20

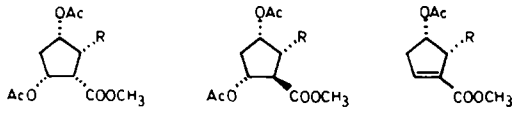
Scheme 3.

could be minimised when operating at −20°C. Oxidation of the crude alcohols **12** and **15** with Jones' reagent yielded the acids **13** and **16**, which upon treatment with diazomethane gave the esters **14** (65% overall) and **17** (60% overall). Alternatively, the crude acid **13** can be converted to the cristalline γ-lactone **18** by acid hydrolysis in an overall yield of 65% starting from **11a**.

There are several examples[11,12] of spontaneous inversion at the α-position (C-12) of the aldehyde function to the more stable trans orientation of the formyl group in compounds such as **19**. The tetrahydropyranyl ether of **18** was oxidised with osmium tetroxide-sodium periodate. The resulting unstable aldehyde **19** was, without checking the degree of epimerisation, directly treated with the sodio derivative of dimethyl - 2 - oxoheptylphosphonate, yielding the epimeric enones **20** and **21** in a ratio of 2:1 (overall yield from **18** was 55%). The configurational assignment followed from the ^{1}H NMR spectral data in accordance with the observation made by Turner *et al.*[11] who showed that in the all-cis isomer the olefinic H_{13} (δ = 7.05) is downfield compared to the same resonance for natural PG configuration (δ = 6.80). In order to increase the rate of epimerisation, some potassium bicarbonate was added at the end of the oxidation step (about 10 min before the extraction); this however led to the elimenated product yielding **22** on subsequent Horner reaction. We therefore undertook the oxidation of the double bond to the more stable carboxylic group with ruthenium tetroxide-sodium periodate; subsequent treatment with diazomethane gave the ester **23**. Several base catalysed epimerisations α to the methoxycarbonyl group of **23** were unsuccessful; only elimination to the corresponding α,β-unsaturated ester occurred.

In the meantime we had found that the epimerisation of the di-ester **25**, readily obtained from **17**, could be carried out with potassium acetate in methanol;[13] epimer **27** was obtained in 85% yield and only traces of the eliminated product **29** could be detected (Scheme 4). Identification of compound **27** was made by comparison of ^{1}H NMR

spectral data with the data of the product we already made by another route.[4]

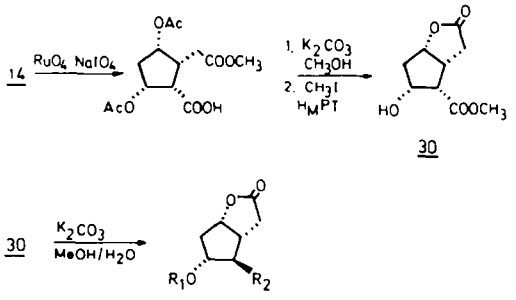


24: R = CH_2COOCH_3 **27**: R = $(CH_2)_6COOCH_3$
25: R = $(CH_2)_4COOCH_3$ **28**: R = CH_2COOCH_3
26: R = CH_2COOCH_3 **29**: R = $(CH_2)_4COOCH_3$

Scheme 4.

Its transformation to $PGF_{1\alpha}$ has already been described by Kojima and Sakai[14] and by us.[4]

As the unstability of compound **23** could be due to unfavourable 1,3-interactions in the bicyclic structure, we decided to perform the inversion on the monocyclic precursor **24**, a homologue of **25**. Unfortunately, reaction of compound **24** under identical conditions as for **25** gave no inverted product **26** but exclusively the elimination product **28**. In order to change the leaving group capacity, the acetate functions of the crude acid obtained by oxidative cleavage of the double bond of product **14**, were hydrolysed with potassium carbonate in methanol (Scheme 5). Direct esterification with methyl iodide in HMPT gave the lactone **30** in an overall yield of 50% (^{1}H NMR data in Table 1). Treatment of **30** with potassium carbonate in water-methanol finally gave the desired epimerisation with concomitant hydrolysis of the ester function, yielding the acid **31** (yield 65%). The configuration of the corresponding methyl ester **32** followed from ^{1}H NMR spectroscopy (Table 1). Treatment of the acid **31** with p-phenylbenzoyl chloride gave **33** which was identical with a product previously synthesised in our laboratory.[2] The conversion[2] of acid **33** to Corey's synthon **34** and the subsequent steps leading to the primary prostaglandins have already adequately been described.[10]



31: R_1 = H; R_2 = COOH
32: R_1 = H; R_2 = $COOCH_3$
33: R_1 = PPB; R_2 = COOH
34: R_1 = PPB; R_2 = CH_2OH

Scheme 5.

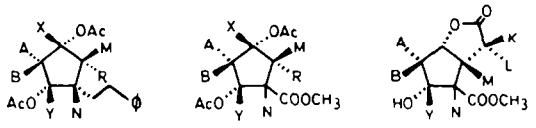
EXPERIMENTAL

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-MS 902 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 silica gel 60 GF_{254} TLC plates of thickness 0.25 mm.

3,5,5 - *Triethoxy* - 2 - (2' - *methoxyethyl*) - 2 - *cyclopenten* - 1 - *one* **2a**

Prepared by the procedure described in Ref. 2.

Table 1.[c]



	9a	**9b**	**10**	**24**	**25**	**27**	**30**	**32**
δ_A	1.60	1.69	1.68	2.00	2.16	1.77	2.33	2.13
δ_B	2.58	2.59	2.58	2.65	2.69	2.45	1.89	2.34
δ_X[d]	4.94	5.04	5.03	5.20	5.09	5.13	5.14	5.04
δ_Y[d]	5.03	5.10	5.08	5.25	5.16	5.13	4.58	4.51
δ_M or	2.17	[a]	[a]	2.98	2.27	[a]	3.37	3.20
δ_N	[a]	[a]	[a]	3.19	3.25	2.62	2.88	2.84
J_{AB}	−15.5	−15.5	−15.0	−15.0	−14.5	−15.5	−15.5	−15.0
J_{AX}	5.8	5.5	5.5	6.0	9.25	1.0	0	2.0
J_{AY}	5.2	5.5	5.5	6.0	5.0	3.0	0	4.5
J_{BX}	7.75	8.0	7.75	7.5	8.0	5.0	7.0	6.5
J_{BY}	7.75	8.0	7.75	7.5	7.5	9.0	4.0	5.75
J_{XM}	5.75	5.5	5.75	7.5	7.0	[b]	7.25	6.5
J_{YN}	5.8	5.5	5.75	6.8	7.5	6.25	3.0	5.0
J_{MN}	6.5	[b]	[b]	6.8	7.0	11.75	8.75	7.0
δ_K							2.59 or	2.87 or
δ_L							2.72	2.65
J_{KL}							−18.5	−18.75
J_{KM}							4.5 or	10.75 or
J_{LM}							12.0	2.75

[a] Could not be located.
[b] Could not be measured.
[c] All parameters obtained at 300 MHz in $CDCl_3$ (except for **27** in CCl_4).
[d] Shift values (ppm related to TMS) and coupling constants (in HZ) concerning X and Y could be interconverted, except for **30** and **32**.

3 - (2' - *Phenylethyl*) - 1,2,4 - *cyclopentanetrione* **1b**

Prepared from 1 - phenyl - 4 - pentanone as described for **1a** in Ref. 2. The trione **1b** (yield 80%) has m.p. 155°C (from ethyl acetate). TLC: R_f (ethyl acetate–isooctane–acetic acid, 60:40:8) = 0.49. UV: λ_{max} (methanol, 0.1 N HCl) = 274 nm; λ_{max} (methanol, 0.2 N NaOH) = 288 and 322 nm. IR: 3600–2500 (broad), 1750, 1690, 1665, 750, 700 cm^{-1}. MS: *m/e* at 216 ($M^{+\cdot}$, 45%), 188 (31%), 91 (100%), 65 (14%). ^1H NMR (60 MHz, pyridine): 5-H: δ = 2.78 (s); $-CH_2CH_2C_6H_5$: δ = 2.78 (m); $-C_6H_5$: δ = 7.13 (m). Found: C, 74.88; H, 5.92. $C_{13}H_{12}O_3$ requires: C, 72.22; H, 5.56%.

3,5,5 - *Trimethoxy* - 2 - (2' - *phenylethyl*) - 2 - *cyclopenten* - 1 - *one* **2b**

A solution of **1a** (25.9 g; 0.12 mole), trimethyl orthoformate (38.2 g; 0.36 mole) and a catalytic amount TsOH in absolute ethanol (900 ml) was heated for 24 h, under distillation of methyl formate through a Widmer column. The solution was cooled to 20°C, treated with solid Na_2CO_3, filtered and concentrated *in vacuo*. Ether (200 ml) was added, the ether layer was washed with a Na_2CO_3 solution (10%), water and dried (Na_2SO_4). Filtration and evaporation gave compound **2b** (yield 85%; m.p. 78°C from pentane). TLC: R_f (ether–benzene, 1:1) = 0.33. UV: λ_{max} (methanol) = 259 nm. IR: 1700, 1640, 1150, 1120, 1070, 1030, 750, 700 cm^{-1}. MS: *m/e* at 276 ($M^{+\cdot}$, 5%), 261 (4%), 246 43%), 245 (42%), 244 (47%), 229 (33%), 185 (100%), 173 (13%), 157 (51%), 141 (17%), 114 (13%), 105 (23%), 91 (52%), 65 (16%), 43 (23%). ^1H NMR (60 MHz, CCl_4): $-CH_2C_6H_5$: δ = 2.33 (m = 3, ^3J = 7.0 Hz); $-CH_2CH_2C_6H_5$: δ = 2.50 (m = 3, ^3J = 7.0 Hz); 4-H: δ = 2.63 (s); 3-OCH_3: δ = 3.73 (s); 5-OCH_3: δ = 3.31 (s); C_6H_5: δ = 7.15 (m). Found: C, 72.48; H, 6.80. $C_{16}H_{20}O_4$ requires: C, 69.59; H, 7.25%.

3 - (2' - *Methoxyethyl*) - 2 - (2' - *phenylethyl*)*cyclopentene* - 1,4 - *dione* **3a**

To 2-phenylethyl magnesium bromide (0.244 mole) in dry THF (150 ml), a solution of **2a** (33 g; 0.122 mole) in dry THF (200 ml) was added under N_2. After 30 min the mixture was poured on ice, acidified with HCl (20%) and stirred for 1 h. Ether was added, the ether layer was washed with brine and dried ($NaSO_4$). Filtration and evaporation gave **3a** (yield 95%; m.p. 102–103°C from ether). TLC: R_f (ether–benzene, 7:3) = 0.55. UV:λ_{max} (methanol) = 243 nm. IR: 1745, 1705, 1640, 1120 cm^{-1}. MS: *m/e* at 258 ($M^{+\cdot}$, 70%), 226 (13%), 115 (8%), 104 (10%), 92 (14%), 91 (100%), 77 (10%), 65 (30%), 52 (12%), 51 (13%), 45 (73%). ^1H NMR (60 MHz, CCl_4): 5-H: δ = 2.78 (s); $-OCH_3$: δ = 3.22 (s); $-CH_2OCH_3$: δ = 3.36 (m = 3); $-CH_2CH_2OCH_3$: δ = 2.51 (m = 3); $-CH_2CH_2C_6H_5$: δ = 2.78 (m). Found: C, 74.67; H, 6.94. $C_{16}H_{18}O_3$ requires: C, 74.42; H, 6.99%.

3 - (7' - *Methoxyheptyl*) - 2 - (2' - *phenylethyl*)*cyclopentene* - 1,4 - *dione* **3b**

Prepared from **2b** and 7-methoxyheptyl magnesiumbromide as described for **3a**. The dione **3b** was chromatographed on silica gel with benzene-ether (9:1) as eluent (yield 85%). TLC: R_f (ethyl acetate–isooctane, 1:1) = 0.52. UV: λ_{max} (methanol) = 243 nm. IR: 1750, 1710, 1640, 755, 705 cm^{-1}. MS: *m/e* at 328 ($M^{+\cdot}$, 31%), 104 (30%), 91 (100%), 83 (11%), 82 (19%), 65 (11%), 55 (20%), 45 (61%), 43 (12%), 41 (14%). ^1H NMR (60 MHz, CCl_4): 5-H: δ = 2.58 (s); $-OCH_3$: δ = 3.24 (s); $-CH_2OCH_3$: δ = 3.28 (m = 3, ^3J = 6.0 Hz); $-CH_2(CH_2)_6OCH_3$: δ = 2.18 (m = 3, ^3J = 6.0 Hz); $-CH_2(CH_2)_5CH_2OCH_3$: δ = 1.26 (m); $-CH_2CH_2C_6H_5$: δ = 2.53 (s); C_6H_5: δ = 7.18 (m). Found: C, 79.24; H, 8.20. $C_{21}H_{28}O_3$ requires: C, 77.13; H, 8.54%.

3 - (2' - *Methoxyethyl*) - 2 - *methoxymethylcyclopentene* - 1,4 - *dione* **3c**

The reaction was carried out at 0°C in methylal with activated Mg (I_2 and $HgCl_2$). The dione **3c** was purified by distillation (yield 75%; b.p. 104–106°C at 0.01 mm Hg). TLC: R_f (ethyl acetate–isooctane, 7:3) = 0.42. UV: λ_{max} (methanol) = 250 nm. IR: 1745, 1710, 1650, 1100 cm^{-1}. MS: *m/e* at 198 ($M^{+\cdot}$, 2%), 166 (57%), 123 (8%), 95 (7%), 75 (19%), 67 (6%), 53 (6%), 52 (6%), 45 (100%). ^1H NMR (60 MHz, CCl_4): 3-$CH_2CH_2OCH_3$: δ = 3.42 (s); 3-$CH_2CH_2OCH_3$: δ = 3.54 (m = 3); 3-$CH_2CH_2OCH_3$: δ = 2.83 (m = 3); 2-CH_2OCH_3: δ = 3.28 (s); 2-CH_2OCH_3: δ = 4.33 (s); 5-H: δ = 2.82 (s).

3 - (3' - *Phenylpropyl*) - 2 - (2' - *phenylethyl*)*cyclopentene* - 1,4 - *dione* **3d**

From **2b** and 3-phenylpropyl magnesiumbromide as described for **3b**. The dione **3d** was chromatographed on silica gel with ethyl acetate–isooctane (1:4) as eluent (yield 71%). TLC:R_f (ethyl acetate–isooctane, 1:1) = 0.53. UV: λ_{max} (methanol) = 243 nm. IR: 3070, 3030, 1745, 1700, 1630, 1600, 750, 700 cm^{-1}. MS: *m/e* at 318 ($M^{+\cdot}$, 6%), 249 (1%), 226 (2%), 213 (4%), 104 (15%), 92 (12%), 91 (100%), 77 (12%), 65 (18%), 51 (10%). ^1H NMR (60 MHz, CCl_4): 3-$CH_2C_6H_5$: δ = 2.60 (m = 3, ^3J = 7.0 Hz); 3-$CH_2CH_2C_6H_5$: δ = 1.56 (m); 3-$CH_2(CH_2)_2C_6H_5$: δ = 2.16 (m); 5-H and 2-$CH_2CH_2C_6H_5$: δ = 2.68 (m); C_6H_5: δ = 7.20 (m). Found: C, 83.71; H, 6.96. $C_{22}H_{22}O$ requires: C, 83.02; H, 6.92%.

The cyclopentenolones **4a** *and* **4'a**

A cooled solution (−25°C) of **3a** (25.8 g; 0.1 mole) in CH_2Cl_2 (200 ml) was added during 30 min to a cooled suspension (−25°C) of Zn (32 g; 0.5 mole) in glacial HOAc (200 ml) and CH_2Cl_2 (200 ml). After 3 h the reaction mixture was warmed up to room temp. and concentrated *in vacuo*. Ether was added to the residue, Zn was filtered off and thoroughly washed with ether. The ether layer was washed with Na_2CO_3 solution (10%) and dried (Na_2SO_4). After filtration and evaporation the cyclopentenolones **4a** and **4'a** were purified by column chromatography on silica gel with ethyl acetate–isooctane (4:1) as eluent (yield 70%). TLC: R_f (ethyl acetate–isooctane, 4:1) = 0.44. UV: λ_{max} (methanol) = 234 nm. IR: 3420, 1710, 1650, 1120 cm^{-1}. MS: *m/e* at 260 ($M^{+\cdot}$, 12%), 242 (14%), 194 (14%), 122 (10%), 121 (10%), 92 (15%), 91 (100%), 88 (35%), 73 (14%), 65 (15%), 55 (10%). Found: C, 73.34; H, 7.44. $C_{16}H_{20}O_3$ requires: C, 73.85; H, 7.69%.

The cyclopentenolones **4b** *and* **4'b**

From **3b** as described for **4a** and **4'a**. Compounds **4b** and **4'b** were purified by column chromatography on silica gel with benzene–ether (1:1) as eluent (yield 85%). TLC: R_f (ethyl acetate) = 0.56. UV: λ_{max} (methanol) = 235 nm. IR: 3450, 1720, 1655, 1600, 1120, 1040, 755, 700 cm^{-1}. MS: *m/e* at 330 ($M^{+\cdot}$, 7%), 328 (6%), 313 (8%), 312 (27%), 198 (23%), 91 (100%), 81 (29%), 45 (86%), 43 (75%).

The cyclopentenolones **4d** *and* **4'd**

Prepared from **3d** as described for **4a** and **4'a** (yield 85%). TLC: R_f (ethyl acetate) = 0.60. UV: λ_{max} (methanol) = 235 nm. IR: 3400, 1700, 1640, 750, 700 cm^{-1}. MS: *m/e* at 320 ($M^{+\cdot}$, 5%), 302 (2%), 229 (6%), 105 (8%), 104 (12%), 92 (12%), 91 (100%).

The catalytic hydrogenation of the cyclopentenolones **4a** *and* **4'a**

The TMS ethers of **4a** and **4'a**, dissolved in dioxane, were hydrogenated with Raney nickel W_7 at 40 psi (12 h). The catalyst was filtered off and washed with dioxane. Ether was added to the filtrate; after washing with dil. HCl and water, the solution was dried ($NaSO_4$). Filtration and evaporation gave a mixture of three isomeric cyclopentanediols (yield 85%), which were separated by column chromatography on silica gel with ethyl acetate–isooctane (4:1) as eluent. The ratio of the three diols **6a**, **7a** and **8a** was 86:4:10. TLC: R_f (ethyl acetate–isooctane, 4:1) for **6a**, **7a** and **8a** = 0.39, 0.32 and 0.32. IR: 3420, 1120, 750, 700 cm^{-1}. MS of the corresponding di-trimethylsilylether of **6a**: *m/e* at 155 (7%), 143 (13%), 141 (12%), 129 (17%), 125 (9%), 117 (12%), 105 (27%), 104 (100%), 103 (13%), 97 (10%), 92 (18%), 91 (94%). ^1H NMR (300 MHz, $CDCl_3$): Ref. 15.

The all cis cyclopentanefiols **6b** *and* **6d**

From **4b** (and **4'b**) and **4d** (and **4'd**) as described for **6a** (yield 55%). The all cis diols were purified by column chromatography on silica gel. TLC: R_f (ethyl acetate) for **6b** and **6d** = 0.56 and 0.61. IR for **6b**: 3400, 1600, 1090, 970, 745, 695 cm^{-1}. IR for **6d**: 3400, 1600, 1090, 1070, 1030, 750, 700 cm^{-1}. MS for **6b**: *m/e* at 334 ($M^{+\cdot}$, 0.1%), 298 (6%), 201 (9%), 105 (20%), 104 (100%). MS for **6d**: *m/e* at 324 ($M^{+\cdot}$, 2%), 306 (2%), 288 (5%), 201 (12%), 117 (11%), 105 (19%), 104 (26%), 92 (17%), 91 (100%). ^1H NMR (300 MHz, $CDCl_3$): Ref. 15.

The all cis cyclopentenediacetates **9a**, **9b**, *and* **10**

Prepared from **6a**, **6b** and **6d** and acetic anhydride in dry pyridine (yield 95%). TLC: R_f (ethyl acetate–isooctane, 1:1) for **9a** = 0.59; R_f (ether–benzene, 1:1) for **9b** = 0.58; R_f (ethyl acetate–isooctane, 1:1) for **10** = 0.52. IR for **9a**: 1740, 1235, 1110, 750, 700 cm^{-1}. IR for **9b**: 3070, 3040, 1740, 1605, 1495, 1235, 1115, 1020, 750, 700 cm^{-1}. IR for **10**: 3065, 3030, 1740, 1600, 1230, 750, 700 cm^{-1}. MS for **9a**: *m/e* at 228 (2%), 141 (2%), 129 (2%), 91 (25%), 45 (26%), 43 (100%). MS for **9b**: *m/e* at 327 (1%), 299 (7%), 298 (34%), 169 (15%), 105 (25%), 104 (100%). MS for **10**: *m/e* at 348 ($M^{+\cdot}$, 0.1%), 288 (4%), 104 (42%), 91 (89%), 51 (57%), 43 (100%). ^1H NMR (300 MHz, $CDCl_3$) for **9a**: 1-OCOC$\underline{H}_3$ and 4-OCOC$\underline{H}_3$: δ = 1.97 (s) and δ = 2.00 (s); –OC$\underline{H}_3$: δ = 3.22 (s); –C$\underline{H}_2$OCH$_3$: δ = 3.20 (m); –C$\underline{H}_2$C$_6$H$_5$: δ = 2.58 (m). ^1H NMR (300 MHz, $CDCl_3$) for **9b**: 1-OCOC$\underline{H}_3$ and 4-OCOC$\underline{H}_3$: δ = 2.06 (s) and δ = 2.02 (s); –OC$\underline{H}_3$: δ = 3.33 (s); –C$\underline{H}_2$OCH$_3$: δ = 3.37 (m = 3, ^3J = 6.5 Hz); –C$\underline{H}_2$C$_6$H$_5$: δ = 2.59 (m). ^1H NMR (300 MHz, $CDCl_3$) for **10**: 1-OCOC$\underline{H}_3$ and 4-OCOC$\underline{H}_3$: δ = 2.04 (s) and δ = 1.96 (s); –(CH$_2$)$_2$C$\underline{H}_2$C$_6$H$_5$: δ = 2.58 (m = 3); –CH$_2$C$\underline{H}_2$C$_6$H$_5$: δ = 2.58 (m). The other ^1H NMR data are mentioned in Table 1. **9a**: Found: C, 68.54; H, 7.44. $C_{20}H_{28}O_5$ requires: C, 68.97; H, 8.06%. **9b**: Found: C, 73.16; H, 8.80. $C_{25}H_{38}O_5$ requires: C, 71.77; H, 9.09%. **10**: Found: C, 76.47; H, 7.84. $C_{26}H_{32}O_4$ requires: C, 77.69; H, 7.62%.

The all cis cyclopentanediacetates **11a**, **11b** *and* **11c**

To a solution of **9a** (1.95 g; 5.6×10^{-3} mole) in CCl_4 (25 ml) were added NBS (1.0 g; 5.6×10^{-3} mole) and an AIBN crystal. The mixture was radiated for 2 min with UV light (254 nm) and stirred for 15 min at 80°C. Succinimide was filtered off and washed with CCl_4; the filtrate was concentrated *in vacuo*. The resulting benzylic bromide was dissolved in DMF (50 ml), dry Li_2CO_3 (2.0 g) was added and the mixture was stirred under N_2 for 2 h at 130°C. The cooled reaction mixture was poured on ice and the water layer extracted with ether. The organic layer was washed with dil HCl and water and dried (Na_2SO_4). Filtration, evaporation and chromatography on silica gel (ethyl acetate–isooctane, 4:1) yielded **11a** (75%). The same procedure starting from **9b** and **10** gave **11b** (yield 65% after column chromatography on silica gel with benzene–ether, 9:1) and **11c** (yield 60% after column chromatography on silica gel with ethyl acetate–isooctane, 3:7). TLC: R_f (ethyl acetate–isooctane) for **11a** = 0.58; R_f (ether–benzene, 1:1) for **11b** = 0.58; R_f (ethyl acetate–isooctane, 1:1) for **11c** = 0.50. IR for **11a**: 1740, 1650, 1235, 1110, 1020, 970, 750, 700 cm^{-1}. IR for **11b**: 1745, 1650, 1230, 1110, 1020, 970, 755, 700 cm^{-1}. IR for **11c**: 3090, 3065, 3030, 1740, 1650, 1600, 1230, 1020, 960 cm^{-1}. MS for **11a**: *m/e* at 286 (3%), 226 (23%), 181 (24%), 135 (50%), 117 (20%), 105 (23%), 104 (73%), 91 (66%), 45 (80%), 43 (100%). MS for **11b**: *m/e* at 297 (14%), 296 (54%), 117 (22%), 104 (34%), 91 (52%), 45 (34%), 43 (100%), 41 (88%). MS for **11c**: *m/e* at 344 (0.5%) 284 (5%), 128 (25%), 117 (36%), 116 (20%), 115 (68%), 91 (69%), 43 (100%). ^1H NMR (300 MHz, $CDCl_3$) for **11a**, **11b** and **11c**: Ref. 15. **11a**: Found:C, 68.96; H, 6.98. $C_{20}H_{26}O_4$ requires: C, 69.36; H, 7.51%.

r - 1 - *Acetoxy* - 2 - c - (2' - *phenyl* - 1' - *ethenyl*) - 3 - c - (6' - *methoxycarbonylhexyl*) - 4 - c - *acetoxycyclopentane* **17**

The crude acid **16** (from **11b** as described for **13**) was dissolved in ether and treated with CH_2N_2. The ester **17** was purified by column chromatography on silica gel with benzene–ether (1:1) as eluent (yield 60% from **11b**). TLC: R_f (ether–benzene, 1:1) = 0.61. IR: 1740, 1660, 1230, 1020, 979, 750, 700. MS: *m/e* at 310 (20%), 167 (19%), 149 (86%), 104 (28%), 97 (19%), 91 (33%), 83 (25%), 71 (30%), 56 (46%), 55 (41%), 43 (100%). ^1H NMR ($CDCl_3$, 300 MHz): Ref. 15.

r - 1 - *Acetoxy* - 2 - c - (6' - *methoxycarbonylhexyl*) - 3 - c - *methoxycarbonyl* - 4 - c - *acetoxycyclopentane* **25**

A suspension of **17** (0.150 g; 34.9×10^{-5} mole), RuO_4 (from 10 mg RuO_2 and 50 mg $NaIO_4$ in water) and $NaIO_4$ (250 mg) in water–acetone (1:1; 4 ml) was heated at 70°C for 1 h. The salts were filtered off, the acetone was removed *in vacuo* and water was added. After extraction with ether, the solution was treated with CH_2N_2 and worked up in the usual way. The resulting di-ester **25** was purified by column chromatography on silica gel with ethyl acetate–isooctane (3:7) as eluent (yield 74%). TLC: R_f (ethyl acetate–isooctane, 1:1) = 0.31. IR: 1745, 1230, 1160, 1030 cm^{-1}. MS: *m/e* at 386 ($M^{+\cdot}$, 0.1%), 343 (1%), 326 (1%), 313 (1%), 234 (8%), 105 (8%), 81 (13%), 67 (11%), 59 (33%), 55 (24%), 43 (100%). ^1H NMR (300 MHz, $CDCl_3$; data not mentioned in Table 1): 1-OCOC$\underline{H}_3$ and 4-OCOC$\underline{H}_3$: δ = 2.06 (s) and δ = 2.03 (s); 3-COOC$\underline{H}_3$ and 2-(CH$_2$)$_6$COOC$\underline{H}_3$: δ = 3.70 (s) and δ = 3.66 (s); –CH$_2$COOC$\underline{H}_3$: δ = 2.30 (m = 3 ^3J = 7.5 Hz); –C$\underline{H}_2$CH$_2$COOCH$_3$: δ = 1.60 (m); –(C$\underline{H}_2$)$_4$CH$_2$CH$_2$COOCH$_3$: δ = 1.29 (m).

r - 1 - *Acetoxy* - 2 - c - (6' - *methoxycarbonylhexyl*) - 3 - t - *methoxycarbonyl* - 4 - c - *acetoxycyclopentane* **27**

25 (16 mg; 4.14×10^{-5} mole) and dry KOAc (350 mg; 3.6×10^{-3} mole) in dry CH_3OH (9 ml) were stirred under N_2 for 14 days. The solvent was removed with N_2, water was added to the residue. Usual work up gave **27** after purification by prep TLC on silica gel with ethyl acetate–isooctane (1:1) as eluent (yield 85%). TLC: R_f (ethyl acetate–isooctane, 1:1) = 0.20. IR: 1750, 1240, 1100, 1025 cm^{-1}. MS: *m/e* at 386 ($M^{+\cdot}$, 1%; H.R. 386.1970. Calc. for $C_{19}H_{30}O_8$: 386.1946), 343 (3%), 332 (12%), 284 (16%), 252 (35%), 234 (80%), 55 (100%). ^1H NMR (300 MHz, $CDCl_3$; data not mentioned in Table 1): 1-OCOC$\underline{H}_3$ and 4-OCOC$\underline{H}_3$: δ = 2.00 (s) and δ = 1.98 (s); 2-COOC$\underline{H}_3$ and 3-COOC$\underline{H}_3$: δ = 3.59 (s) and δ = 3.71 (s); –C$\underline{H}_2$COOCH$_3$: δ = 2.21 (m = 3 ^3J = 7.5 Hz); –C$\underline{H}_2$CH$_2$COOCH$_3$: δ = 1.56 (m); –(C$\underline{H}_2$)$_4$CH$_2$COOCH$_3$: δ = 1.28 (m).

The γ*-lactone* **18**

To a solution of **11a** (350 mg; 10^{-3} mole) in CH_2Cl_2 (10 ml), a solution of BBr_3 (333 mg) in CH_2Cl_2 (10 ml) was added at – 80°C. The mixture was brought at – 25°C and kept for 4 days. Saturated Na_2CO_3 solution was added at 0°C and the water layer was extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Filtration and evaporation gave **12**. To a cooled (– 5°C) solution of **12** (350 mg; 10^{-3} mole) in acetone (15 ml), Jones' reagent was added; the mixture was stirred for 1 h. After addition of i-PrOH and filtration, the acetone was removed *in vacuo*. Water was added to the residue, the water layer was extracted with ethyl acetate. The organic layers were extracted with $NaHCO_3$ solution (5%). Acidification with dil HCl, extraction, drying (Na_2SO_4), filtration and evaporation gave the crude acid **13** sufficiently pure for the next reaction. The acid **13** (350 mg; 10^{-3} mole) was dissolved in water–dioxane (1:1, 15 ml) and HCl (2N, 1.5 ml); the solution was stirred at 70°C for 5 h. After evaporation *in vacuo* and continuous extraction with ether, drying (Na_2SO_4), filtration and evaporation the γ-lactone **18** was obtained (yield 60% from **11a**; m.p. 108°C from ethyl acetate). TLC: R_f (ethyl acetate–isooctane, 4:1) = 0.50. IR: 3460 (broad), 1770, 1190, 1025, 750, 700 cm^{-1}. MS: *m/e* at 246 ($M^{+\cdot}$, 25%), 228 (6%), 168 (11%), 143 (11%), 105 (19%), 104 (100%). ^1H NMR (300 MHz, $CDCl_3$): Ref. 15. Found: C, 73.70; H, 6.65. $C_{14}H_{16}O_3$ requires: C, 73.77; H, 6.56%.

The γ*-lactones* **20** *and* **21**

To a solution of the THP ether of **18** (60 mg; 1.9×10^{-4} mole) in dioxane (3 ml), $NaIO_4$ (90 mg), a catalytic amount OsO_4 and water (1 ml) were added; the reaction mixture was stirred under N_2 for 2 h at room temp. Ether was added and the mixture was dried (Na_2SO_4). After filtration and evaporation *in vacuo*, the unstable aldehyde **19** was dissolved in dry DME (3 ml) and was added to the sodium salt of dimethyl 2-oxo-heptylphosphonate (90 mg; 4×10^{-4} mole) in DME (1 ml). After stirring under N_2 for 2 h HOAc was added, the solvent was removed *in vacuo*. Compounds **20** and **21** (2:1) were purified by column chromatography on silica gel with ethyl acetate–chloroform (2:3) as eluent. UV: λ_{max} (methanol) = 226 nm. IR: 1770, 1680, 1640, 1180, 1120, 970 cm^{-1}. MS: *m/e* at 306 (2%), 277 (20%), 249 (25%), 180 (22%), 167 (22%), 166 (50%), 151 (49%), 137 (80%), 43 (100%).

The γ*-lactone* **43**

The ester **14** (from **13** by treatment with diazomethane) was oxidised with ruthenium tetroxide–sodium periodate as described for **25**. The crude acid (300 mg; 10^{-3} mole) and K_2CO_3 (700 mg) were stirred at room temp. in dry methanol (20 ml). After

evaporation, methyl iodide (200 mg) and HMPT (5 ml) were added and the resulting solution refluxed for 3 h. Water was added to the cooled solution; after acidification with dil HCl (10%), extraction and working up the lactone **30** was obtained (yield 50%) after purification by column chromatography on silica gel with ethyl acetate as eluent (R_f = 0.30). IR: 3480, 1755, 1735, 1430, 1190, 1090 cm^{-1}. MS: *m/e* at 200 ($M^{+\cdot}$, 11%; H.R. 200.0665. Calc. for $C_9H_{12}O_5$ 200.0684), 172 (32%), 169 (27%), 156 (15%), 154 (62%), 141 (25%), 140 (35%), 127 (100%), 100 (46%), 99 (46%), 95 (43%), 71 (32%), 69 (52%), 43 (56%),. ^1H NMR (300 MHz, $CDCl_3$; data not mentioned in Table 1): $-COOCH_3$: δ = 3.78 (s).

The γ-lactone **32**

A solution of **30** (100 mg; 5×10^{-4} mole) in methanol (50 ml) was treated with a K_2CO_3 solution (10%; 10 ml); the resulting solution was stirred at 20°C for 24 h. After concentration *in vacuo*, the reaction mixture was acidified with HCl (10%), saturated with NH_4Cl and extracted with EtOAC. After treatment with CH_2N_2, drying (Na_2SO_4) and evaporation, the lactone **32** was purified by column chromatography on silica gel with ethyl acetate as eluent (yield 65%; R_f = 0.38). MS: *m/e* at 200 ($M^{+\cdot}$, 6%), 156 (10%), 154 (57%), 127 (72%), 100 (60%), 68 (54%), 43 (96%), 41 (100%). ^1H NMR (300 MHz, $CDCl_3$): see Table 1.

The γ-lactone **33**

A solution of **32** (20 mg; 10^{-4} mole) and p-phenyl benzoyl chloride (100 mg; 5×10^{-4} mole) in pyridine (0.5 ml) was stirred at 20°C. Na_2CO_3 solution (5%) was added. After extraction with EtOAc, drying (Na_2SO_4) and evaporation the residue was dissolved in pyridine; the resulting solution was added to a boiling mixture of LiI and pyridine under N_2. After 30 min the mixture was poured on ice and acidified with HCl (6N). The acid **33** was extracted with EtOAc and worked up in the usual way. **33** (yield 50%) has m.p. 94–96°C (ether). TLC: R_f (ethyl acetate) = 0.16. IR: 3500–3000, 1770, 1710, 1265, 745, 695 cm^{-1}. MS: *m/e* at 366 ($M^{+\cdot}$, 2%), 199 (17%), 198 (100%), 181 (54%), 168 (10%), 153 (25%), 152 (36%), 83 (22%), 55 (27%), 43 (37%).

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