Prostaglandins: A Novel Synthesis of ±-$PGF_{1\alpha}$ *via* Cyclopentane-1,3-dione Derivatives

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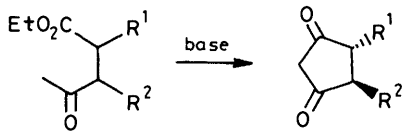
An efficient synthesis of $PGF_{1\alpha}$ *via* cyclization of an easily available acyclic precursor is described. Thus, alkylation of ethyl acetoacetate with ethyl α-iodo-oleate to give (**1**), followed by cyclization with LDA, provided an expeditious route to the cyclopentanedione (**2**). Sequential protection by means of ethylene glycol and selective deprotection of (**2**) afforded the monoacetal (**4**) in good yield. Stereospecific reduction of (**4**) by L-Selectride, followed by deacetalization and stereospecific reduction with $NaBH_4$, efficiently furnished the derivative (**8**). Oxidative cleavage of the side-chain of (**8**) after protection of the hydroxy group with dihydropyran led in good yield to compound (**10**), which was converted into $PGF_{1\alpha}$ according to literature procedures.

Substituted cyclopentane-1,3-diones may be easily obtained by base-induced cyclization of a γ-ketoester.[1] This reaction appears very promising for the synthesis of prostaglandins since it allows the one-step preparation of a PG-ring containing two oxygen functionalities in the correct position and actual or potential forms of the two side-chains in the natural *trans* configuration [equation (1)]. This simple and direct approach



(1)

has, however, received only scant attention until now owing to the lack of reliable chemoselective methods of discriminating between the two ring-carbonyls.[2] We report here a simple and efficient solution to this problem which we illustrate with a novel and stereoselective synthesis of compound (**10**), a useful intermediate in PGF_1 synthesis.

The acyclic precursor chosen for our synthesis is 3,4-bis(ethoxycarbonyl)eicos-11(*Z*)-en-2-one (**1**), easily prepared by alkylation of ethyl acetoacetate with ethyl α-iodo-oleate[3] and potassium carbonate in dimethylformamide (DMF).[4] Cyclization of (**1**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at room temperature afforded in good yield the expected cyclopentane-1,3-dione (**2**).

Concerning the stereochemistry of the two side-chains, the thermodynamically more stable *trans* configuration is expected to be formed under equilibrium conditions, since it is known that prostaglandin precursors bearing activating groups directly linked to the cyclopentane ring easily undergo base- or acid-induced equilibration to the *trans* isomer.[5] Moreover the *trans* configuration of the two protons at C-8 and C-12 (prostaglandin numbering) in (**2**) has been demonstrated by ^1H n.m.r. analysis using the double-irradiation technique. The value of 2.5 Hz for the coupling constant between 8-H and 12-H is consistent with the assigned *trans* configuration.[6]

To follow our synthetic strategy it was necessary to reduce stereospecifically the two carbonyl groups into the corresponding alcohols with the proper configuration. Since the highly enolized 1,3-diketone system could be directly reduced only under rather drastic conditions to give complex mixtures of products, it was necessary to protect regioselectively one of the two ring carbonyls. This proved to be a rather difficult task since the two carbonyls behave very similarly towards a large number of reagents. Finally, we utilized the remarkable difference in the rate of hydrolysis shown by the corresponding ethylideneacetals. This difference may be ascribed to the electron-withdrawing effect of the ester group, which reduces the reactivity of the dioxolane ring in the β-position.

Treatment of (**2**) with excess of ethylene glycol in boiling benzene in the presence of a catalytic amount of toluene-*p*-sulphonic acid with azeotropic removal of water led to the corresponding bisacetal (**3**) in good yield. The monoacetal (**4**) was then obtained as a single product by carefully controlled exposure of (**3**) to sulphuric acid in methylene dichloride in the presence of silica gel at room temperature until no more starting material was detected by t.l.c.[7] It is worth mentioning that this difference in the rate of hydrolysis seems to be general for bis(ethylideneacetals) of this kind.[8] The structure of compound (**4**) has been determined by its spectroscopic properties and by the lack of u.v. absorption under basic conditions which excluded the presence of a carbonyl group in a β-position to the ester group.

Reduction of (**4**) with $NaBH_4$ in ethanol proceeded stereospecifically to give the corresponding 9β-alcohol (**5b**). The absence of the 9α-isomer (**5a**) was ascertained by ^{13}C n.m.r. spectroscopic analysis. Treatment of (**4**) with PBPH (lithium perhydro-9b-borataphenalene) in THF at −78 °C gave instead a mixture of (**5a**) and (**5b**) in the ratio 70:30. To achieve the stereoselective conversion of (**4**) into the desired 9α-isomer (**5a**), it was necessary to use L-Selectride in THF at −78 °C. The configuration of the C-9 hydroxy group of (**5a**) and (**5b**) was confirmed by ^{13}C n.m.r. spectroscopy (Table). In fact the ^{13}C n.m.r. spectra of (**5a**) and (**5b**) showed the signals of C-8 and C-9 to be more shielded in (**5a**) than in (**5b**).[9] Moreover it is well known that reduction of the C-9 carbonyl by hindered borohydrides in prostaglandin precursors bearing a side-chain at C-8 affords the α-isomer as a single, or at least the major, isomer.[10] The 9α-hydroxyacetal (**5a**) was then hydrolysed to the corresponding ketone (**6**) by protracted treatment (6 h) with the sulphuric acid–silica gel system. The structure and the stereorelationship of the substituents in compound (**6**) were in agreement with the n.m.r. spectra. Moreover the u.v. spectrum, recorded in ethanol in the presence of a small amount of sodium ethoxide, showed a maximum at 282 nm characteristic for the β-

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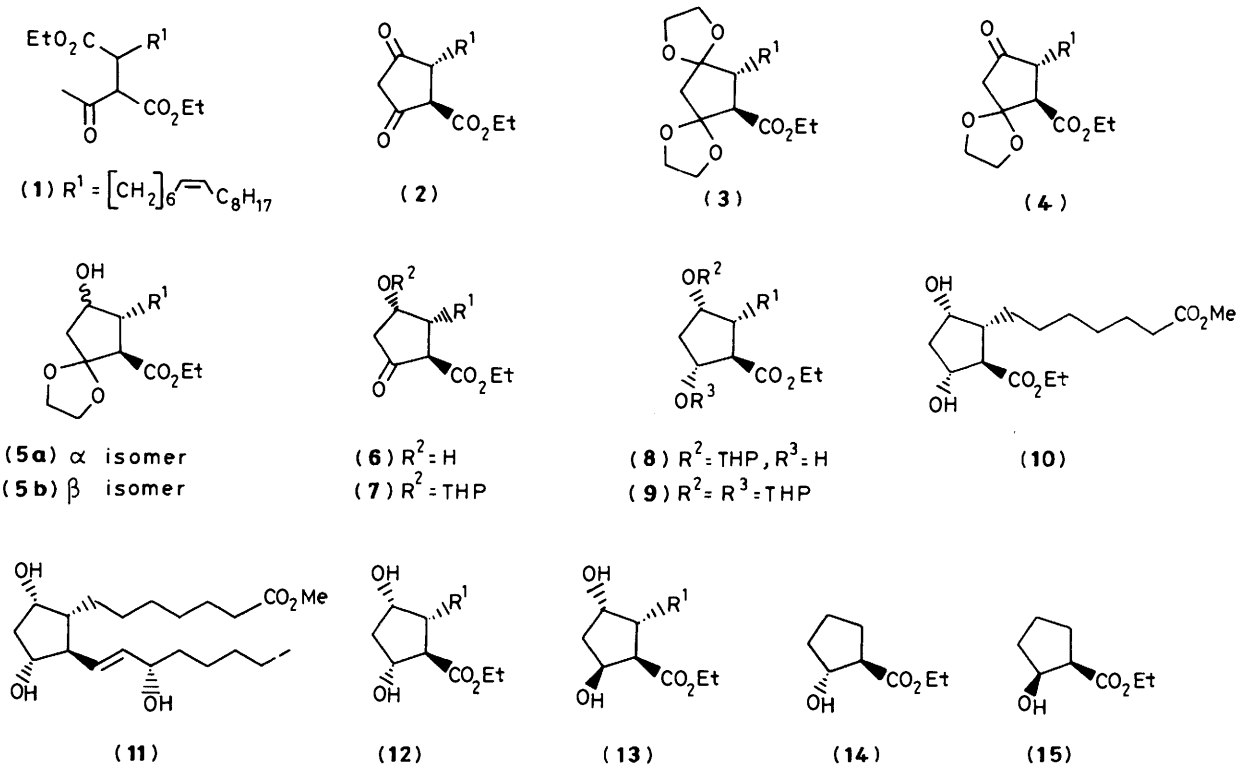

Table. ^{13}C N.m.r. chemical shifts and assignments for cyclopentanoid derivatives[a]

	Compound									
Carbon[b]	(2)	(3)	(4)	(5b)	(5a)	(6)	(12)	(13)	(14)	(15)
C-8	47.8	48.0	52.7	49.8	47.4	47.0	49.8	46.6	28.1	26.1
C-9	201.8	114.1	211.1	74.9	70.9	68.7	74.3	72.6	22.8	22.3
C-10	105.0	48.1	48.4	45.9	46.7	48.9	43.9	45.4	34.9	34.5
C-11	197.6	113.6	112.3	115.1	117.6	209.9	77.0	72.0	76.5	74.1
C-12	56.7	59.8	56.4	59.3	58.5	58.4	58.9	53.5	53.2	50.3
CO_2Et	170.0	170.8	170.5	172.0	172.0	170.2	175.3	174.2	175.3	174.1

[a] Chemical shifts in p.p.m. downfield from Me_4Si. Spectra were taken in C_6D_6 at 20.00 MHz in the Fourier mode with a Varian FT80 spectrometer. [b] Prostaglandin numbering.

ketoester enolate. Compound (**6**) was then converted into the tetrahydropyranyl derivative (**7**) in quantitative yield by treatment with excess of 3,4-dihydro-2*H*-pyran in methylene dichloride using pyridinium toluene-*p*-sulphonate (PPTS) as acidic catalyst.[11] Compound (**7**) could be stereospecifically and quantitatively reduced to the corresponding 11α-hydroxy derivative (**8**) on exposure to $NaBH_4$ in aqueous ethanolic solution. The pyranyl group appears to be a critical factor for the stereoselective reduction of the C-11 carbonyl, since direct reduction of the unprotected α-hydroxy ketone (**6**) led to a mixture of the isomeric alcohols (**12**) and (**13**). The stereochemistry of the hydroxy group on C-11 was demonstrated by deprotection of (**8**) and comparison of the ^{13}C n.m.r. spectrum of the single alcohol thus obtained with that of the mixture of (**12**) and (**13**) arising from the reduction of (**6**) with $NaBH_4$. It was thus possible to assign all the signals to both alcohols and the fact that the signals of C-11 and C-12 are more deshielded in (**12**) than in (**13**) allowed us to assign the *trans* configuration to this junction.[9] Moreover the chemical shifts of *trans*-2-ethoxycarbonylcyclopentanol (**14**) and *cis*-2-ethoxycarbonylcyclopentanol[12] (**15**) are perfectly consistent with our assignment (Table). The remainder of the synthesis proved trivial.

Conversion of (**8**) into its bispyranyl ether (**9**) and oxidative cleavage of the double bond of the side-chain by the periodate–permanganate reagent,[13] followed by hydroxy deprotection and esterification of the carboxylic acid thus obtained with ethereal diazomethane, afforded the expected derivative (**10**) in good yield. The diol (**10**) constitutes an interesting intermediate for the synthesis of PGs and has already been converted into $PGF_{1\alpha}$ (**11**) according to the literature procedure.[14] Work is now in progress to develop further this synthetic approach to unsaturated PGs by appropriate choice of the side-chain.

Experimental

General.—I.r. spectra were recorded as films on a Perkin-Elmer 710 B spectrophotometer and ^{1}H and ^{13}C n.m.r. spectra were determined in $CDCl_3$ or C_6D_6 solutions on Varian EM 390 and Varian FT 80 instruments respectively; chemical shifts are expressed as δ-values in p.p.m. from internal standard $SiMe_4$.

Mass spectra were taken on a Varian MAT 111 instrument (70 eV). U.v. spectra were recorded on a 402 UVS Perkin-Elmer instrument. T.l.c. was performed on silica gel sheets (1B2F Baker) and column chromatography on a Chromatospac Prep. 10 (Jobin-Yvon instrument) using silica gel (H 60 Merck).

Materials.—Commercially available starting materials were used without prior purification, unless otherwise stated. THF was obtained anhydrous and oxygen-free by distillation over sodium benzophenone ketyl under argon. Methylene dichloride was distilled over P_2O_5. Di-isopropylamine was refluxed over molecular sieves (Type 4A, Fluka) and distilled at atmospheric pressure. n-Butyl-lithium (15% solution in hexane), PBPH (0.5M in THF), and L-Selectride (lithium tri-s-butylborohydride, 1M in THF) were purchased from Aldrich.

3,4-*Bis*(*ethoxycarbonyl*)*eicos*-11(Z)-*en*-2-*one* (**1**).—Ethyl acetoacetate (4.6 ml, 0.036 mol) was added to a suspension of powdered and dried (overnight; 100 °C) K_2CO_3 (5 g, 0.035 mol) in DMF (30 ml). The suspension was stirred at room temperature for 15 min and then ethyl α-iodo-oleate (15.6 g, 0.036 mol) was added in one portion and the mixture was stirred overnight. The reaction mixture was quenched with dil. (1:1) HCl and extracted with ether. The organic layers were washed several times with dil. HCl in order to eliminate DMF. After the extract had been dried (Na_2SO_4), the solvent was removed on a rotary evaporator and the oily residue was chromatographed at medium pressure to give *diester* (**1**) (12 g, 76%) (Found: C, 70.9; H, 10.5. $C_{26}H_{46}O_5$ requires C, 71.19; H, 10.57%); *m/z* 438 (M^+); $\nu_{max.}$(neat) 1 740br s cm^{-1}; δ_H (90 MHz; $CDCl_3$) 5.37 (2 H, t), 4.1 (4 H, 2 q), 3.75—3.70 (1 H, 2 d, *J* 10.5 Hz), 3.10 (1 H m), 2.20—2.17 (3 H, s), 2.00 (4 H, m) and 1.6—0.9 (31 H, m).

4,5-trans-4-*Ethoxycarbonyl*-5-[*hexadec*-7(Z)-*enyl*]*cyclopentane*-1,3-*dione*. (**2**).—n-Butyl-lithium (18.7 ml; 15% solution in hexane) was added at 0 °C under argon to a stirred solution of di-isopropylamine (4 ml, 28 mmol) in THF (20 ml). After 30 min the LDA solution was withdrawn and added dropwise by means of a syringe to a solution of diester (**1**) (6.13 g 14 mmol) in THF (60 ml) maintained at 0 °C. The reaction mixture was allowed to reach room temperature and was then stirred for 3 h. The mixture was quenched with aqueous HCl (30 ml of a 1:1 solution) and extracted with ether (500 ml), the extract was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude reaction product was purified by medium-pressure chromatography (ether as eluant). The title compound was isolated as a clear, pale yellow *oil* (3.44 g, 63%) (Found: C, 73.65; H, 10.3. $C_{24}H_{40}O_4$ requires C, 73.43; H, 10.27%); *m/z* 392 (M^+); $\nu_{max.}$(neat) 1 730s and 1 650s cm^{-1}; δ_H (90 MHz; $CDCl_3$) 8.8 (1 H, br s), 5.37 (2 H, t), 5.3 (1 H, s), 4.25 (2 H, q), 3.3 (1 H, d, *J* 2.5 Hz), 3 (1 H, m), 2.0 (4 H, m), and 1.7—0.9 (28 H, m).

4,5-trans-4-*Ethoxycarbonyl*-5-[*hexadec*-7(Z)-*enyl*]*cyclopentane*-1,3-*dione Bis*(*ethylene acetal*) (**3**).—A mixture of dione (**2**) (2.65 g, 6.8 mmol), benzene (80 ml), and toluene-*p*-sulphonic acid (30 mg) was treated with ethylene glycol (3 ml, 53 mmol) and refluxed in a Dean–Stark trap. The mixture was extracted with ether and the extract was washed successively with 10% aqueous $NaHCO_3$ and then water to give *bisacetal* (**3**) (2.71 g, 82%) with a good degree of purity (Found: C, 69.8; H, 10.10. $C_{28}H_{48}O_6$ requires: C, 69.96; H, 10.07%); *m/z* 480 (M^+); $\nu_{max.}$(film) 1 730s and 1 090s cm^{-1}; δ_H (90 MHz; C_6D_6) 5.4 (2 H, t), 4.1 (2 H, q), 3.6 (8 H, m), 3.1 (2 H, br s), 2.2 (2 H, m), 2.0 (4 H, m), and 1.7—1.0 (28 H, m).

4,5-trans-4-*Ethoxycarbonyl*-5-[*hexadec*-7(Z)-*enyl*]*cyclopentane*-1,3-*dione*-3-*ethylene Acetal* (**4**).—A solution of sulphuric acid (0.5 ml of a 50% aqueous solution) was added to a continuously magnetically stirred suspension of silica gel [7.5 g; Silica Gel 60, Merck (for column chromatography), 70—230 Mesh] in methylene dichloride (20 ml). After 2—3 min, the water phase disappeared due to absorption on the silica gel surface. The acetal (**3**) (2.47 g, 5.1 mmol) was added and the mixture was stirred at room temperature for 2 h. The solid phase was separated by suction filtration on a sintered glass funnel and then was washed several times with methylene dichloride. The combined filtrates were washed successively with aqueous sodium hydrogen carbonate, brine, and water. Evaporation of the solvent under reduced pressure gave pure *monoacetal* (**4**) as an oil (2.0 g, 90%) (Found: C, 71.7; H, 10.2. $C_{26}H_{44}O_5$ requires C, 71.52; H, 10.16%); *m/z* 436 (M^+); $\nu_{max.}$(film) 1 740br s cm^{-1}; δ_H (90 MHz; C_6D_6) 5.5 (2 H, t), 4.1 (2 H, q), 3.55 (4 H, m), 3.1 (2 H, m), 2.8—2.45 (2 H, ABq, *J* 18 Hz), 2.2 (4 H, m), and 1.6—0.9 (28 H, m).

2,3-trans-3,4-cis-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-4-*hydroxycyclopentanone Ethylene Acetal* (**5a**).—A solution of L-Selectride (1M in THF) (5 ml, 5 mmol) was slowly added to a stirred solution of ketone (**4**) (2.08 g, 4.8 mmol) in THF (30 ml) under argon at −78 °C. After 4 h the temperature was allowed to rise to 0 °C and the excess of reagent was hydrolysed by addition of water. 3M Aqueous sodium hydroxide (1.96 ml, 5.88 mmol) was then added followed by 30% H_2O_2 (2.2 ml, 19.2 mmol) and the mixture was stirred at 0 °C for 1 h. Ethereal work-up followed by flash chromatography gave the *alcohol* (**5a**) as an oil (1.40 g, 67%) (Found: C, 71.3; H, 10.6. $C_{26}H_{46}O_5$ requires C, 71.19; H, 10.57%); *m/z* 420 ($M^+ - H_2O$); $\nu_{max.}$(film) 3 500br and 1 730s cm^{-1}; δ_H (90 MHz; C_6D_6) 5.5 (2 H, t), 4.05 (2 H, q), 4.00 (1 H, m), 3.60 (4 H, m), 3.00 (3 H, m), 2.05 (1 H, d, *J* 8 Hz), 2.05 (4 H, m), 1.4 (1 H, m), and 1.3—0.9 (28 H, m).

2,3-trans-3,4-cis-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-4-*hydroxycyclopentanone* (**6**).—Protracted treatment (6 h) of the acetal (**5a**) (1.4 g, 3.2 mmol) in methylene dichloride with the sulphuric acid–silica gel system, following the above reported procedure for compound (**4**), led to *ketone* (**6**) (1.0 g, 78%) (Found: C, 73.6; H, 10.8. $C_{24}H_{42}O_4$ requires C, 73.05; H, 10.73%); *m/z* 394 (M^+), 376 ($M^+ - H_2O$), and 348; $\nu_{max.}$(film) 3 500br, 1 755s, and 1 720s cm^{-1}; δ_H (90 MHz; $CDCl_3$) 5.3 (2 H, t), 4.4 (1 H, m), 4.2 (2 H, q), 2.8—2.3 (4 H, m), 2.05 (4 H, m), and 1.8—0.8 (29 H, m).

2,3-trans-3,4-trans-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-4-*hydroxycyclopentanone Ethylene Acetal* (**5b**).—A solution of ketone (**4**) (0.750 g, 1.7 mmol) in ethanol was added dropwise at 0 °C to a stirred suspension of $NaBH_4$ (0.30 g, 8 mmol) in ethanol (20 ml, 95% solution). The resulting solution was stirred at this temperature for 2 h, then excess of reagent was destroyed with 1% hydrochloric acid. The mixture was extracted with ether (3 × 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give crude *acetal* (**5b**) as an oil (0.630 g, 82%) whose purity was estimated by t.l.c. and ^{13}C n.m.r. analysis to be 100% (Found: C, 71.3; H, 10.6. $C_{26}H_{46}O_5$ requires C, 71.19; H, 10.57%); *m/z* 438 (M^+) and 420 ($M^+ - H_2O$); $\nu_{max.}$(film) 3 500br and 1 730s cm^{-1}; δ_H (90 MHz; C_6D_6) 5.45 (2 H, t), 4.1 (2 H, q), 4.0 (1 H, m), 3.55 (4 H, m), 2.7 (3 H, m), 2.2 (1 H, d, *J* 8 Hz), 2.1 (4 H, m), 1.7 (1 H, m), and 1.5—0.8 (28 H, m).

2,3-trans-3,4-cis-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-4-(*tetrahydropyran*-2-*yloxy*)*cyclopentanone* (**7**).—A solution of hydroxyketone (**6**) (1.00 g, 2.5 mmol) and dihydropyran (0.5 ml, 5.5 mmol) in dry methylene dichloride (25 ml) containing PPTS (0.05 g, 0.2 mmol) was stirred for 4 h at room temperature. The solution was then diluted with ether and washed once with brine to remove the catalyst. Evaporation of the solvent gave an

essentially quantitative yield of the *ketoether* (**7**) (1.10 g, 92%) (Found: C, 72.8; H, 10.5. $C_{29}H_{50}O_5$ requires C, 72.86; H, 10.54%); *m/z* 478 (M^+) and 393 (M^+ − THP); $\nu_{max.}$(film) 1 755s, 1 730s, and 1 020s cm^{-1}; δ_H (90 MHz; C_6D_6) 5.5 (2 H, t), 4.7—3.8 (6 H, m), 3.4—2.3 (4 H, m), 2.1 (4 H, m), 1.8—0.8 (34 H, m).

1,2-trans-2,3-trans-3,4-cis-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-4-(*tetrahydropyran*-2-*yloxy*)*cyclopentanol* (**8**).—A solution of ketone (**7**) (1.10 g, 2.3 mmol) in ethanol (10 ml) was added dropwise at 0 °C to a suspension of ethanol (20 ml), water (5 ml), and $NaBH_4$ (0.3 g, 8 mmol). After a further 1 h at 0 °C the mixture was treated with sodium chloride until the solution was saturated and the mixture was then extracted with ether (4 × 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the crude alcohol (**8**) as an oil. This material was purified by column chromatography on silica gel with hexane–ethyl acetate (7:3) as eluant to give *compound* (**8**) as a pale yellow oil (0.6 g, 54%) (Found: C, 72.3; H, 10.9. $C_{29}H_{52}O_5$ requires C, 72.46; H, 10.90%); *m/z* 480 (M^+); $\nu_{max.}$(film) 3 500br, 1 730s, and 1 020 cm^{-1}; δ_H (90 MHz; C_6D_6) 5.7 (2 H, t), 5.1—3.8 (7 H, m), 3.6—2.6 (5 H, m), and 2.6—0.8 (38 H, m).

1,2-trans-2,3-trans-3,4-cis-2-*Ethoxycarbonyl*-3-[*hexadec*-7(Z)-*enyl*]-1,4-*bis*(*tetrahydropyran*-2-*yloxy*)*cyclopentane* (**9**).—A solution of the alcohol (**8**) (0.6 g, 1.25 mmol) and dihydropyran (0.2 ml, 2.4 mmol) in dry methylene dichloride (15 ml) containing PPTS (0.030 g) was stirred overnight at room temperature. Usual work-up gave *ester* (**9**) as an oil (0.680 g, 96%) (Found: C, 71.7; H, 10.6. $C_{34}H_{60}O_6$ requires C, 72.34; H, 10.71%); *m/z* 479 (M^+ − THP); $\nu_{max.}$(film) 1 730 cm^{-1}; δ_H (90 MHz; C_6D_6) 5.5 (2 H, t), 5.0—3.7 (10 H, m), 3.6—3.2 (2 H, m), and 2.5—0.8 (46 H, m).

1,5-cis-3,4-trans-4,5-trans-4-*Ethoxycarbonyl*-5-(6-*methoxycarbonylhexyl*)*cyclopentane*-1,3-*diol* (**10**).—The periodate–permanganate solution used was prepared by dissolving sodium periodate (2.24 g) and potassium permanganate (0.04 g) in slightly warm distilled water (500 ml).

A mixture of the diether (**9**) (0.200 g, 0.35 mmol), pure t-butyl alcohol (90 ml), and the oxidiser solution (150 ml) was brought to pH *ca.* 8—9 by addition of powdered potassium carbonate, and the mixture was then stirred at room temperature for 7 h. The mixture was acidified with 2M HCl and treated with powdered sodium metabisulphite (disodium pyrosulphite, $Na_2S_2O_5$) to convert all the periodate into iodide (the solution at the end of the reaction was colourless). The t-butyl alcohol was stripped off by low-pressure distillation, and the remaining mixture was extracted with ethyl acetate (3 × 30 ml), washed with brine, and dried (Na_2SO_4). After evaporation of the extract, the remaining oil was treated with methanol (0.1 ml) and ether (20 ml), and ethereal diazomethane was added at 0 °C. After 15 min AcOH (1 ml) was added and the mixture was allowed to reach room temperature. The solvent was distilled off on a water-pump and the residue, purified by flash-chromatography, gave *diester* (**10**) (0.060 g, 57%) as an oil (Found: C, 60.5; H, 8.9. $C_{16}H_{28}O_6$ requires C, 60.74; H, 8.92%); *m/z* 298 (M^+ − H_2O) and 271; $\nu_{max.}$(film) 3 450 and 1 730 cm^{-1}; δ_H (90 MHz; C_6D_6) 4.5 (1 H, m), 4.0 (2 H, q), 3.95 (1 H, m), 3.4 (3 H, s), 2.8 (2 H, m), and 2.3—0.9 (19 H, m); δ_C (80 MHz; C_6D_6) 175.2 (CO_2Et), 173.7 (CO_2Me), 77.2 (C-11), 74.5 (C-9), 60.5 (OCH_2), 59.1 (C-12), and 51.0 (OCH_3), 49.7 (C-8), 43.8 (C-10), 34.0 (C-2), 29.7, 29.4, and 29.2 (C-4, -5, and -6), 28.1 (C-7), 25.1 (C-3), and 14.2 p.p.m. (OCH_2CH_3).*

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