Cyclopentanoids from Phenol. Part 5.[1] Terminally Functionalised 2- and 3-Alkyl-4-hydroxycyclopent-2-enones. A Versatile Approach to Prostanoids

By **Melvyn Gill** and **Rodney W. Rickards,*** Research School of Chemistry, Australian National University, Canberra, A.C.T. 2600, Australia

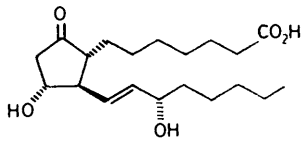
Terminally functionalised 3-alkyl-4-hydroxycyclopent-2-enones are prepared by conjugate addition–elimination reactions of magnesiocuprate reagents with ethers of 3-chloro-4-hydroxycyclopent-2-enone. The side-chain functionality can be modified either selectively, or simultaneously with modification of the nucleus. Stereospecific transposition of the ring-oxygen functions converts these compounds into terminally functionalised 2-alkyl-4-hydroxycyclopent-2-enones which are important intermediates in prostanoid synthesis. Thus the 2-substituted cyclopentenone (2) is prepared in *ca.* 60% yield from the 3-chlorocyclopentenone (7), itself available in four steps from phenol.

ETHERS of terminally functionalised 2-alkyl-4-hydroxycyclopent-2-enones are important and versatile prostaglandin precursors [2] and new processes for their synthesis continue to be reported.[3] The utility of these compounds resides in the ease with which a second functionalised side-chain can be added to the cyclopentenone ring by conjugate addition with an organometallic reagent. These reactions are stereospecific, and yield 2,3-disubstituted 4-hydroxycyclopentanones which possess the thermodynamically stable *trans–trans* relative configuration of ring substituents which is characteristic of most natural prostaglandins. The use of such precursors in unresolved form is illustrated by the synthesis of (—)-PGE_1 (1) from cyclopentenone (2) and the cuprate prepared from (3S)-(1-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene,[4] and the synthesis of some analogues of (±)-PGE_1 (1) structurally modified in the ω side chain by conjugate addition of the appropriate organocuprate to the cyclopentenone (3).[5]

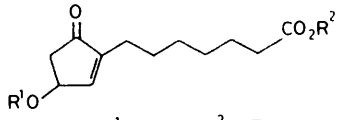
In Part 4 of this series we described the synthesis of 3-alkyl-4-hydroxycyclopent-2-enones by conjugate addition–elimination reactions with organocuprate reagents on 3-chloro-4-[dimethyl-(t-butyl)silyloxy]cyclopent-2-enone (7) and the corresponding tetrahydropyranyl ether (8), which are accessible in four steps from phenol *via* the Hantzsch acid (18). Thus the 3-butylcyclopentenone (9) was obtained in 59% overall yield from the readily available acid (18). We now describe the extension of this approach to the synthesis of terminally functionalised 3-heptyl-4-hydroxycyclopentenones (10) and (14), and the subsequent conversion of the former into the established [2,4,5] prostanoid precursors (2) and (3). The route makes a variety of 2-substituted 4-hydroxycyclopent-2-enones available from the common intermediate (7), and in conjunction with previous work [2,4,5] constitutes a new route to prostanoids in which *both* side-chains are added to the cyclopentenoid nucleus by conjugate addition reactions.

The application of this route to the synthesis of the prostanoid intermediate (3) in chiral form from the resolved Hantzsch acid (18) has been published as a preliminary communication.[6]

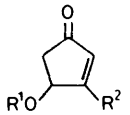
Terminally Functionalised 3-Alkyl-4-hydroxycyclopent-2-enones.—To complement our use of phenol to furnish the elements of the cyclopentenone ring,[1] commercially



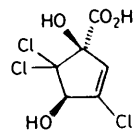
(1)



(2) R^1 = Thp, R^2 = Et
(3) R^1 = Thp, R^2 = Me
(4) R^1 = Thp, R^2 = H
(5) R^1 = H, R^2 = Et
(6) R^1 = H, R^2 = Me



(7) R^1 = Me_2Bu^tSi, R^2 = Cl
(8) R^1 = Thp, R^2 = Cl
(9) R^1 = Me_2Bu^tSi, R^2 = Bu^n
(10) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_7OSiMe_2Bu^t$
(11) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_7OH$
(12) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_6CO_2H$
(13) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_6CO_2Et$
(14) R^1 = Thp, R^2 = $[CH_2]_7OSiMe_2Bu^t$
(15) R^1 = H, R^2 = $[CH_2]_7OH$
(16) R^1 = Thp, R^2 = $[CH_2]_7OH$
(17) R^1 = H, R^2 = $[CH_2]_6CO_2Et$



(18)

$X[CH_2]_7OR$

(19) X = Br, R = Me_2Bu^tSi
(20) X = Cl, R = $CH_2OCH_2CH_2OMe$
(21) X = Cl, R = $CH_2O[CH_2]_7Cl$
(22) X = MgBr, R = Me_2Bu^tSi
(23) X = H, R = Me_2Bu^tSi

Thp = tetrahydropyranyl

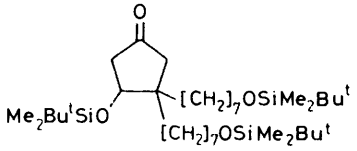
available heptane-1,7-diol provides the bifunctional C_7-unit which eventually becomes the prostaglandin α-chain. Monobromination gave 7-bromoheptan-1-ol,[7] in

which the hydroxy representing latent carboxy-functionality was cleanly protected as its silyl ether (19) using chlorodimethyl-t-butylsilane and imidazole at 0 °C over 0.5 h. Prolonged reaction led to complex mixtures of products arising from displacement of bromide by chloride and by imidazole. Although protection of the hydroxy-group in 7-bromoheptan-1-ol as the methoxyethoxymethyl (MEM) ether [8] would be compatible with subsequent synthetic steps, attempts to derivatise the bromohydrin with methoxyethoxymethyl-(triethyl)ammonium chloride gave only the *chlorohydrin* MEM ether (20) resulting from halide exchange, together with a substantial amount of the corresponding alkoxy-methoxy-ether (21) arising by acetal exchange between the chlorohydrin MEM ether (20) and 7-chloroheptan-1-ol (*cf.* ref. 9). Parallel treatment of 7-chloroheptan-1-ol itself [10] gave a similar mixture of products.

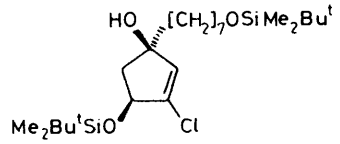
Introduction of this side-chain into the 3-chloro-cyclopentenone (7) required formation of a cuprate, but attempts to lithiate the bromohydrin silyl ether (19) and the chlorohydrin MEM ether (20) proved unsuccessful. Halogen–metal exchange with lithium metal was slow in diethyl ether, allowing the alkyl-lithium produced to suffer extensive Wurtz coupling with the alkyl bromide (19) or protonation by solvent in the case of the chloride (20). However, the Grignard reagent (22) was produced in 70—95% yield from the bromo-ether (19) with magnesium in refluxing tetrahydrofuran. 'Inverse' addition of this Grignard reagent (22) (1.9 mol equiv.) to the 3-chlorocyclopentenone (7) (1 mol equiv.) in the presence of cuprous iodide (1 mol equiv.) under conditions similar to those defined previously [1] gave the terminally functionalised 3-heptylcyclopentenone (10) in 95% yield. The heptyl silyl ether (23) formed as a by-product upon work-up was readily separated by chromatography. The use of more than 2 mol equiv. of Grignard reagent (22) resulted in the production of some dialkylated cyclopentanone (24), while reduction either of the temperature (to −20 °C) or of the amount of cuprous iodide employed (to 0.18 mol equiv.) also diminished the yield of the desired product (10) with concomitant production of the tertiary alcohol (25). The latter 1,2-adduct could not be obtained analytically pure but comparison of spectral data with those of the corresponding n-butyl analogue [1] supported the structural assignment.

Modification of the terminal functionality in the side-chain of the 3-heptylcyclopentenone (10) was readily achieved by utilising selective cleavage of the primary silyl ether. Thus hydrolysis in acetic acid–tetrahydrofuran–water at ambient temperature gave the alcohol (11) in 90% yield. Jones oxidation then yielded the acid (12) (90%), which could be ethylated as its anion to afford the ester (13) in 96% yield.

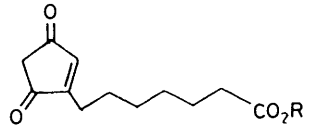
In contrast, partial hydrolysis of the silyltetrahydropyranyl ether (14), prepared similarly to the disilyl ether (10) from 3-chloro-4-(tetrahydropyran-2-yloxy)-cyclopent-2-enone [1] (8) and the Grignard reagent (22), was considerably less regioselective. The same acid medium gave a moderate amount (23%) of the diol (15) in addition to the desired primary alcohol (16) (41%) even while starting material (14) (36%) remained. Selective cleavage of the silyltetrahydropyranyl ether (14) with non-aqueous fluoride ion afforded the alcohol (16) (63%), but was complicated by the base-sensitivity of the nucleus. High yields of the diol (15) were obtained from both ethers (10) and (14) on more severe acidic hydrolysis. Jones oxidation of this diol (15) gave the



(24)



(25)



(26) R = H
(27) R = Et

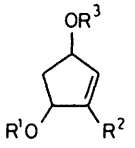
cyclopentenedione-acid (26) corresponding to the known ethyl ester (27).[4]

Terminally Functionalised 2-Alkyl-4-hydroxycyclopent-2-enones.—The conversion of the 3-alkyl-4-hydroxy-cyclopent-2-enones (10) and (13) into the 2-alkyl-4-hydroxy-compounds was achieved by transposition of the ring-oxygen functions. The feasibility of this process was first established using the simple substrate 3-butyl-4-[dimethyl-(t-butyl)silyloxy]cyclopent-2-enone (9).[1] Reduction of this enone with lithium tri-s-butylborohydride proceeded as expected exclusively in 1,2-fashion from the less hindered face to give the *cis*-diol derivative (28) in 93% yield. The relative stereochemistry was confirmed by comparison of the chemical shifts and coupling constants of the C-5 methylene protons with literature data.[11] The stereospecificity of this reduction is unimportant in the case of racemic compounds, since the initial tetrahedral centre at C-4 is ultimately destroyed. Induction of specific chirality at C-1 becomes crucial, however, when the route is applied to the synthesis of 2-alkyl-4-hydroxycyclopent-2-enones in optically pure form.[6]

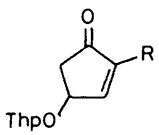
Tetrahydropyranylation of the cyclopentenol (28) gave a mixture of diastereoisomeric ethers (29) which was treated with tetrabutylammonium fluoride [12] to remove the silyl protecting group. Oxidation of the liberated hydroxy-group of the resulting cyclopentenol (30) with pyridinium chlorochromate [13] completed the

transposition of ring functionality, affording the 2-butyl-4-alkoxycyclopentenone (37) in *ca.* 50% overall yield (not optimised) from the 3-butyl-4-silyloxycyclopentenone (9). The related transformation of the 3-alkylcyclopentenone (17) into the 2-alkylcyclopentenone (5) has previously been effected *via* Meerwein–Ponndorf–Verley reduction of the intermediate enedione (27),[4] but this method exhibits only moderate regioselectivity [2 : 1 ratio of (5) to (17)] and is not applicable to chiral compounds.

The transposition sequence was then applied to the terminally functionalised 3-heptylcyclopentenone (10). Reduction gave the *cis*-diol derivative (31) (87%), the stereohomogeneity and relative configuration of which



(28) R^1 = Me_2Bu^tSi, R^2 = Bu^n, R^3 = H
(29) R^1 = Me_2Bu^tSi, R^2 = Bu^n, R^3 = Thp
(30) R^1 = H, R^2 = Bu^n, R^3 = Thp
(31) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_7OSiMe_2Bu^t$, R^3 = H
(32) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_7OSiMe_2Bu^t$, R^3 = Thp
(33) R^1 = H, R^2 = $[CH_2]_7OH$, R^3 = Thp
(34) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_6CO_2Et$, R^3 = H
(35) R^1 = Me_2Bu^tSi, R^2 = $[CH_2]_6CO_2Et$, R^3 = Thp
(36) R^1 = H, R^2 = $[CH_2]_6CO_2Et$, R^3 = Thp



(37) R = Bu^n
(38) R = $[CH_2]_6CHO$

Thp = tetrahydropyranyl

were established from its ^{13}C and ^1H n.m.r. spectra, respectively. Tetrahydropyranylation in 79% yield of the newly formed hydroxy-group, followed by cleavage of *both* silyl ethers in the product (32) with 4 mol equiv. of fluoride ion produced the diol (33) as a 1 : 1 mixture of diastereoisomers in 97% yield. Treatment of the diol (33) with Jones reagent at −20 °C to avoid cleavage of the tetrahydropyranyl ether oxidised both ring and side-chain hydroxy-functions, affording quantitatively the keto-acid (4). Finally, esterification with ethyl iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene,[14] or with diazomethane, gave the ethyl and methyl esters (2) and (3), respectively, in high yields. The identity of these esters was confirmed by comparison of spectral features with published data.[4,15,16] Further confirmation was provided by hydrolysis of the tetrahydropyranyl ethers, which removed the source of diastereoisomerism and afforded the known[4,15,16] racemic alcohols (5) and (6). The esters (2) and (3) were obtained in overall yields of 56 and 60% respectively in six steps from the key 3-chlorocyclopentenone intermediate (7).

Milder oxidation of the diol (33) with pyridinium chlorochromate[13] yielded the keto-aldehyde (38) in 81% yield.

In this synthesis of the terminally functionalised 2-alkyl-4-hydroxycyclopent-2-enones (2) and (3) described, economy of steps is achieved by simultaneous deprotection of both ring and side-chain hydroxy-functions and their subsequent simultaneous oxidation. However, transposition of ring-oxygen functionality can also be effected after elaboration of the side-chain. For example, careful reduction of the keto-ester (13) with lithium tri-s-butylborohydride, using a minimal excess of reagent at −78 °C to avoid reduction of the ester group, gave the *cis*-diol derivative (34). Tetrahydropyranylation followed by fluoride cleavage of the silyl ether in the product (35) and oxidation with pyridinium chlorochromate of the resulting cyclopentenol (36) completed the transposition, yielding the 2-alkylcyclopentenone (2). This four-step transposition from the 3-alkylcyclopentenone (13) is achieved in 78% yield. The overall yield of 57% from the 3-chlorocyclopentenone (7) is similar to that obtained in the shorter route above, but this is largely due to the quantitative tetrahydropyranylation of the allylic alcohol (34) catalysed by pyridinium toluene-*p*-sulphonate.[17]

The transformations described above, in conjunction with previous work,[1,18] constitute syntheses of the established prostanoid precursors (2) and (3) in *ca.* 20% overall yield *from phenol*. The route is versatile and is applicable to the synthesis of a wide variety of functionalised 2- and 3-alkyl-4-hydroxycyclopent-2-enones and 2-alkylcyclopentene-1,4-diols. The extension of this route to the preparation of these compounds in chiral form from the resolved Hantzsch acid (18) will be described in detail elsewhere.

EXPERIMENTAL

General details are given in Part 4.[1]

7-Bromo-1-[dimethyl-(t-butyl)silyloxy]heptane (19).—Imidazole (4.4 g) was added over 20 min to 7-bromoheptan-1-ol[7] (4.88 g) and chlorodimethyl-t-butylsilane (4.8 g) in dimethylformamide (30 ml) at 0 °C. After 10 min at 0 °C, ice–water (300 ml) was added and the mixture was stirred for 1 h. Extraction with ether (3 × 300 ml) and removal of the washed (aqueous NaCl, 3 × 100 ml) and dried ($MgSO_4$) solvent gave a pale yellow oil (8.37 g). Distillation (Kugelrohr, b.p. 120—130 °C at 0.02—0.04 mmHg) afforded the *ether* (19) (7.79 g, 98%) as an oil (Found: C, 50.45; H, 9.5; Br, 26.0. $C_{13}H_{29}BrOSi$ requires C, 50.45; H, 9.45; Br, 25.85%), δ 0.04 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.1—2.1 (10 H, m, CH_2), 3.38 (2 H, t, *J* 6.5 Hz, CH_2Br), and 3.59 (2 H, t, *J* 6.5 Hz, CH_2OSi).

7-Chloro-1-(methoxyethoxymethoxy)heptane (20).—7-Chloroheptan-1-ol[10] (407 mg, 2.7 mmol) and methoxyethoxymethyl(triethyl)ammonium chloride (1.24 g, 5.5 mmol) were heated in acetonitrile (5 ml) at reflux for 20 h. After cooling, triethylammonium chloride was filtered off

and the filtrate was diluted with water (20 ml) and extracted with ether (4 × 20 ml). The combined ether extracts were washed with water (3 × 10 ml), dried ($MgSO_4$), and evaporated, affording a colourless liquid (670 mg) which was applied to a column of silica gel (30 g) and eluted with methylene dichloride–methanol (50 : 1 v/v). Early fractions contained *bis-(7-chloroheptyloxy)methane* (21) (100 mg, 24%) as a liquid (Kugelrohr, b.p. 120 °C at 0.4 mmHg) (Found: C, 57.4; H, 9.5; Cl, 22.85. $C_{15}H_{30}Cl_2O_2$ requires C, 57.5; H, 9.65; Cl, 22.65%), δ 1.1—2.0 (20 H, m, CH_2), 3.51 (8 H, t, *J* 6 Hz, CH_2Cl and CH_2O), and 4.64 (2 H, s, OCH_2O). Further elution yielded *7-chloro-1-(methoxyethoxymethoxy)heptane* (20) (376 mg, 58%) as a liquid (Kugelrohr, b.p. 85 °C at 0.1 mmHg) (Found: C, 55.5; H, 9.7; Cl, 14.75. $C_{11}H_{23}ClO_3$ requires C, 55.35; H, 9.7; Cl, 14.85%), δ 1.1—1.9 (10 H, m, CH_2), 3.38 (3 H, s, OMe), 3.44—3.76 (8 H, m, CH_2Cl, CH_2OMEM, and OCH_2CH_2O), and 4.70 (2 H, s, OCH_2O).

7-[Dimethyl-(t-butyl)silyloxy]heptylmagnesium bromide (22).—7-Bromo-1-[dimethyl-(t-butyl)silyloxy]heptane (6.19 g, 20 mmol) in tetrahydrofuran (15 ml) was added dropwise over 1.5 h to magnesium (491 mg, 20.2 mmol) under tetrahydrofuran (15 ml) at reflux. The consumption of magnesium was complete after heating at reflux for a further 3 h. The concentration of reagent was measured by standard titration of an aliquot portion (1 ml) after hydrolysis.

4-[Dimethyl-(t-butyl)silyloxy]-3-{7-[dimethyl-(t-butyl)-silyloxy]heptyl}cyclopent-2-enone (10).—A suspension of cuprous iodide (78 mg, 0.4 mmol) in tetrahydrofuran (2 ml) containing the chloro-enone (7) (100 mg, 0.4 mmol) was stirred vigorously at −10 °C under argon. Dropwise addition of the Grignard reagent (22) in tetrahydrofuran (0.41M; 1.85 ml, 1.9 mol equiv.) produced a green solution which was stirred at −10 °C for 10 min. The reaction was rapidly quenched with saturated aqueous ammonium chloride (5 ml), and after the addition of ether (5 ml) the mixture was stirred at room temperature for 1 h before dilution with water (10 ml) and extraction with ether (5 × 10 ml). The combined extracts were washed with brine (2 × 5 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. on silica gel in methylene dichloride–methanol (50 : 1 v/v) gave the *cyclopentenone* (10) (167 mg, 95%) as a colourless oil (Kugelrohr, b.p. 135 °C at 0.2 mmHg) (Found: C, 65.65; H, 10.8. $C_{24}H_{48}O_3Si_2$ requires C, 65.4; H, 11.0%), $\nu_{max.}$ 1 720 cm^{-1}, δ 0.04 (6 H, s, $SiMe_2$), 0.12 and 0.14 (each 3 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 0.91 (9 H, s, Bu^t), 1.16—1.80 (10 H, m, CH_2), 2.25 (1 H, dd, *J* 18.0, 3.0 Hz, 5-H *trans* to 4-H), 2.44br (2 H, t, *J* 8 Hz, allylic CH_2), 2.72 (1 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 3.60 (2 H, t, *J* 6.0 Hz, CH_2O), 4.76 (1 H, ddm, *J* 6.0, 3.0 Hz, 4-H), and 5.90 (1 H, m, 2-H), δ_C 205.0, 129.5, 181.8, 72.1, and 46.0 (C-1 to C-5, respectively, of cyclopentenone ring).

The above reaction at −20 °C, or at −10 °C using less cuprous iodide (14 mg, 0.074 mmol), gave the cyclopentenone (10) in 80% and 72% yields, respectively. Also obtained was *3-chloro-4-[dimethyl-(t-butyl)silyloxy]-1-{7-[dimethyl-(t-butyl)silyloxy]heptyl}cyclopent-2-en-1-ol* (25) as an oil, $\nu_{max.}$ 3 420 cm^{-1}, δ 0.06 (6 H, s, $SiMe_2$), 0.12 and 0.14 (each 3 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 0.91 (9 H, s, Bu^t), 1.2—1.7 (12 H, m, CH_2), 1.83 (1 H, dd, *J* 14.0, 3.5 Hz, 5-H *trans* to 4-H), 2.0br (1 H, s, OH), 2.45 (1 H, dd, *J* 14.0, 7.0 Hz, 5-H *cis* to 4-H), 3.60 (2 H, t, *J* 6.0 Hz, CH_2OSi), 4.49 (1 H, dd, *J* 7.0, 3.5 Hz, 4-H), and 5.83br (1 H, s, 2-H), *m/e* 421/419 (M^+ − Bu), 383 (M^+ − Bu − HCl). The use of more Grignard reagent (22) (2.5 mol. equiv.) and cuprous iodide (1.25 mol equiv.) gave the cyclopentenone (10) (63%) and *4-[dimethyl-(t-butyl)silyloxy]-3,3-bis-{7-[dimethyl-(t-butyl)silyloxy]heptyl}cyclopentanone* (24) (8%) as a liquid (Found: C, 66.05; H, 11.6. $C_{37}H_{78}O_4Si_3$ requires C, 66.2; H, 11.7%), $\nu_{max.}$ 1 745 cm^{-1}, δ 0.04 (18 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 0.91 (18 H, s, Bu^t), 1.1—1.7 (24 H, m, CH_2), 1.97 and 2.25 (each 1 H, d, *J* 18.0 Hz, 2-H_2), 2.19 (1 H, dd, *J* 18.5, 3.0 Hz, 5-H *trans* to 4-H), 2.58 (1 H, dd, *J* 18.5, 6.0 Hz, 5-H *cis* to 4-H), 3.62 (4 H, t, *J* 6.5 Hz, CH_2OSi), and 4.14 (1 H, dd, *J* 6.0 3.0 Hz, 4-H).

4-[Dimethyl-(t-butyl)silyloxy]-3-(7-hydroxyheptyl)cyclopent-2-enone (11).—4-[Dimethyl-(t-butyl)silyloxy]-3-{7-[dimethyl-(t-butyl)silyloxy]heptyl}cyclopent-2-enone (10) (69 mg, 0.156 mmol) in acetic acid–tetrahydrofuran–water (3 : 1 : 1 v/v; 0.5 ml) was maintained at room temperature for 17 h. Removal of the solvent under reduced pressure and preparative t.l.c. of the residual oil on silica gel in methylene dichloride–methanol (20 : 1 v/v) afforded the *primary alcohol* (11) (46 mg, 90%) as a colourless oil (Kugelrohr, b.p. 150 °C at 0.05 mmHg) (Found: C, 66.6; H, 10.4. $C_{18}H_{34}O_3Si$ requires C, 66.2; H, 10.5%), $\nu_{max.}$ 3 400 and 1 715 cm^{-1}, δ 0.12 and 0.14 (each 3 H, s, $SiMe_2$), 0.91 (9 H, s, Bu^t), 1.2—1.8 (11 H, m, CH_2 and OH), 2.26 (1 H, dd, *J* 18.0, 2.8 Hz, 5-H *trans* to 4-H), 2.46br (2 H, t, *J* 8 Hz, allylic CH_2), 2.72 (1 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 3.64 (2 H, t, *J* 6.0 Hz, CH_2O), 4.78 (1 H, m, 4-H), and 5.92 (1 H, dt, *J* 1.3, 1.3 Hz, 2-H).

3-(6-Carboxyhexyl)-4-[dimethyl-(t-butyl)silyloxy]cyclopent-2-enone (12).—Jones reagent was added over 3 h to the primary alcohol (11) (175 mg, 0.536 mmol) in acetone (10 ml) at −10 °C so that an excess of oxidant was maintained. After this time, isopropyl alcohol was added to destroy the excess of oxidant. The solution was diluted with water (20 ml), extracted with ether (5 × 15 ml), and the combined extracts were washed with saturated brine (2 × 5 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the *carboxylic acid* (12) (165 mg, 90%) as rhombs from light petroleum (b.p. 60—80 °C), m.p. 49—52 °C (Found: C, 63.2; H, 9.05. $C_{18}H_{32}O_4Si$ requires C, 63.5; H, 9.45%), $\nu_{max.}$ 3 700—2 300, 1 710, and 1 680sh cm^{-1}, δ 0.12 and 0.14 (each 3 H, s, $SiMe_2$), 0.91 (9 H, s, Bu^t), 1.2—1.9 (8 H, m, CH_2), 2.25 (1 H, dd, *J* 18.0, 2.5 Hz, 5-H *trans* to 4-H), 2.35 (4 H, t, *J* 7 Hz, CH_2CO_2 and allylic CH_2), 2.72 (1 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 4.77 (1 H, m, 4-H), and 5.92 (1 H, m, 2-H).

4-[Dimethyl-(t-butyl)silyloxy]-3-(6-ethoxycarbonylhexyl)-cyclopent-2-enone (13).—1,5-Diazabicyclo[5.4.0]undec-5-ene (73.6 mg, 0.484 mmol) in benzene (0.5 ml) was added with stirring to the carboxylic acid (12) (165 mg, 0.484 mmol) and ethyl iodide (75.5 mg, 0.484 mmol) in benzene (1.5 ml) at room temperature. After 18 h the mixture was filtered and the filtrate was evaporated under reduced pressure to yield a pale yellow oil. Chromatography on silica gel in methylene dichloride–methanol (20 : 1 v/v) gave the *ethyl ester* (13) (147 mg, 96% based on acid consumed) as a colourless oil (Kugelrohr, b.p. 80 °C at 0.2 mmHg) (Found: C, 65.35; H, 9.75. $C_{20}H_{36}O_4Si$ requires C, 65.15; H, 9.85%), $\nu_{max.}$ 1 735 and 1 720 cm^{-1}, δ 0.16 and 0.18 (each 3 H, s, $SiMe_2$), 0.91 (9 H, s, Bu^t), 1.24 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.2—1.8 (8 H, m, CH_2), 2.25 (1 H, dd, *J* 18.0, 2.5 Hz, 5-H *trans* to 4-H), 2.30 (2 H, t, *J* 7.5 Hz, CH_2CO_2), 2.37 (2 H, t, *J* 8 Hz, allylic CH_2), 2.72 (1 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 4.13 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.78 (1 H, m, 4-H), and 5.91 (1 H, dt, *J* 1.2, 1.2 Hz, 2-H).

3-{7-[*Dimethyl*-(*t-butyl*)*silyloxy*]*heptyl*}-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*enone* (14).—To 3-chloro-4-(tetrahydropyran-2-yloxy)cyclopent-2-enone (8) [1] (500 mg, 2.3 mmol) and cuprous iodide (438 mg, 2.3 mmol) in tetrahydrofuran (10 ml) at −10 °C was added Grignard reagent (22) in tetrahydrofuran (0.41M; 10.7 ml). Work-up and purification as described for the preparation of (10) above gave the *cyclopentenone* (14) (786 mg, 83%) as a mixture of diastereoisomers (Kugelrohr, b.p. 140 °C at 0.2 mmHg) (Found: C, 67.2; H, 10.3. $C_{23}H_{42}O_4Si$ requires C, 67.25; H, 10.3%), $\nu_{max.}$ 1 715 cm^{-1}, δ 0.06 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.2—1.9 (16 H, m, CH_2), 2.20 and 2.23 (each 0.5 H, dd, *J* 18.0, 3.0 Hz, 5-H *trans* to 4-H), 2.40br (2 H, t, *J* 8 Hz, allylic CH_2), 2.63 and 2.75 (each 0.5 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 3.54 (2 H, t, *J* 6.0 Hz, CH_2OSi), 3.52 and 3.76 (each 1 H, m, CH_2O), 4.50—4.94 (2 H, m, 4-H and OCHO), and 5.88 (1 H, m, 2-H).

3-(7-*Hydroxyheptyl*)-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*enone* (16).—Cyclopentenone (14) (100 mg, 0.24 mmol) in acetic acid–tetrahydrofuran–water (3 : 1 : 1 v/v) (1 ml) was maintained at room temperature for 12 h. Removal of the solvent under reduced pressure and chromatography of the residue on silica gel in methylene dichloride–methanol (10 : 1 v/v) gave the *primary alcohol* (16) (30 mg, 41%) as a mixture of diastereoisomers, an oil (Found: C, 68.6; H, 9.6. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%), $\nu_{max.}$ 3 420 and 1 710 cm^{-1}, δ 1.2—2.1 (17 H, m, CH_2 and OH), 2.27 and 2.49 (each 0.5 H, dd, *J* 19.0, 3.0 Hz, 5-H *trans* to 4-H), 2.48 (2 H, t, *J* 7 Hz, allylic CH_2), 2.71 and 2.81 (each 0.5 H, dd, *J* 19.0, 6.0 Hz, 5-H *cis* to 4-H), 3.64 (2 H, t, *J* 6.0 Hz, CH_2OH), 3.62 and 3.90 (each 1 H, m, CH_2O), 4.60—5.00 (2 H, m, 4-H and OCHO), 5.95 and 5.99 (each 0.5 H, dt, *J* 1.3, 1.3 Hz, 2-H), and 4-*hydroxy*-3-(7-*hydroxyheptyl*)-*cyclopent*-2-*enone* (15) (12 mg, 23%) as an oil (Found: C, 67.6; H, 9.3. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%), $\nu_{max.}$ 3 380, 1 710sh, and 1 685 cm^{-1}, δ 1.2—1.8 (10 H, m, CH_2), 2.28 (1 H, dd, *J* 18.0, 2.5 Hz, 5-H *trans* to 4-H), 2.52 (2 H, t, *J* 7 Hz, allylic CH_2), 2.78 (1 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 3.25br (2 H, s, OH), 3.62 (2 H, t, *J* 6.5 Hz, CH_2O), 4.80 (1 H, m, 4-H), and 5.95 (1 H, m, 2-H), together with recovered substrate (14) (36 mg).

Treatment of cyclopentenone (14) (290 mg, 0.7 mmol) in tetrahydrofuran (5 ml) at 0 °C with tetrabutylammonium fluoride in tetrahydrofuran (0.4M; 3.5 ml) over 3 h gave, after extractive work-up, the primary alcohol (16) (131 mg, 63%), identical with the sample described above.

4-*Hydroxy*-3-(7-*hydroxyheptyl*)*cyclopent*-2-*enone* (15).—The cyclopentenone (14) (37 mg, 0.09 mmol) in acetic acid (1 ml) containing water (0.2 ml) was maintained at room temperature for 7 h. After this time the solvent was removed and the residue chromatographed on silica gel in methylene dichloride–methanol (10 : 1 v/v) to afford the pure diol (15) (18 mg, 94%), identical with material described above.

2-(6-*Carboxyhexyl*)*cyclopent*-2-*ene*-1,4-*dione* (26).—Jones reagent was added to the diol (15) (90 mg, 0.424 mmol) in acetone (3 ml) at 0 °C so that an excess of oxidant was maintained. After a further 30 min isopropyl alcohol was added and the solution was diluted with water (15 ml), extracted with ether (5 × 10 ml), and the combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated. Crystallisation of the product from ether–light petroleum furnished the *dione* (26) (82 mg, 86%) as plates, m.p. 73—75 °C (Found: C, 64.45; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.25; H, 7.2%), $\nu_{max.}$ 3 600—2 200, 1 745, and 1 700 cm^{-1}, δ 1.2—1.9 (9 H, m, CH_2 and OH), 2.36 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.47br (2 H, t, *J* 7 Hz, allylic CH_2), 2.88 (2 H, s, 5-H_2), and 6.94 (1 H, t, *J* 1.4 Hz, 2-H).

(1R*,4S*)-3-*Butyl*-4-[*dimethyl*-(*t-butyl*)*silyloxy*]*cyclopent*-2-*en*-1-*ol* (28).—Lithium tri-s-butylborohydride in tetrahydrofuran (1M; 0.5 ml, 0.5 mmol) was added dropwise with vigorous stirring to the cyclopentenone [1] (9) (60 mg, 0.223 mmol) in tetrahydrofuran (0.5 ml) at −78 °C. After 2 h at this temperature water (1 ml) was added and the mixture allowed to warm to room temperature. Dilution with water (5 ml) and extraction with ether (5 × 8 ml) gave, after drying ($MgSO_4$) and evaporation of the extracts, a colourless oil (155 mg). Preparative t.l.c. on silica gel in methylene dichloride–methanol (50 : 1 v/v) yielded the (1R*,4S*)-*alcohol* (28) (56 mg, 93%) as an oil (Kugelrohr, b.p. 80 °C at 0.01 mmHg) (Found: C, 66.7; H, 11.3. $C_{15}H_{30}O_2Si$ requires C, 66.6; H, 11.2%), $\nu_{max.}$ 3 350 cm^{-1}, δ 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 0.90 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.1—1.7 (5 H, m, CH_2CH_2 and 5-H *trans* to 1-H and 4-H), 2.11 (2 H, m, allylic CH_2), 2.69 (1 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 4.47 (2 H, m, 1-H and 4-H), and 5.56 (1 H, m, 2-H), δ_C 76.1 or 74.1, 128.4, 150.8, 74.1 or 76.1, and 45.3 (C-1 to C-5, respectively, of cyclopentenol ring).

(1S*,4R*)-2-*Butyl*-1-[*dimethyl*-(*t-butyl*)*silyloxy*]-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*ene* (29).—Dihydropyran (16.8 mg, 0.2 mmol) was added dropwise to the (1*R**,4*S**)-alcohol (28) (40 mg, 0.15 mmol) in methylene dichloride (1 ml) containing toluene-*p*-sulphonic acid (0.01M) at 0 °C. After 3 h the solution was diluted with ether (10 ml), washed successively with 5% aqueous sodium hydrogencarbonate (5 ml), and water (2 × 5 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue (46 mg) on silica gel (10 g) in methylene dichloride–methanol (50 : 1 v/v) gave the (1S*,4R*)-*diol derivative* (29) (39 mg, 73%) as a colourless liquid mixture of diastereoisomers (Kugelrohr, b.p. 120 °C at 0.05 mmHg) (Found: C, 67.6; H, 10.85. $C_{20}H_{38}O_3Si$ requires C, 67.75; H, 10.8%), δ 0.06 (6 H, s, $SiMe_2$), 0.86 (12 H, m, Bu^t and Me), 1.1—1.9 (11 H, m, CH_2 and 5-H *trans* to 1-H and 4-H), 2.09br (2 H, t, *J* 7 Hz, allylic CH_2), 2.69 and 2.72 (each 0.5 H, dt, *J* 13.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 3.47 and 3.87 (each 1 H, m, CH_2O), 4.29—4.90 (3 H, m, 1-H, 4-H and OCHO), and 5.50br (1 H, s, 3-H).

(1S*,4R*)-2-*Butyl*-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*en*-1-*ol* (30).—To the (1*S**,4*R**)-diol derivative (29) (24 mg, 0.068 mmol) in tetrahydrofuran (0.5 ml) at 0 °C was added slowly tetrabutylammonium fluoride in tetrahydrofuran (0.5M; 0.27 ml). After 2 h at 0 °C the solution was diluted with water (5 ml) and extracted with ether (3 × 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the residual oil (40 mg) was chromatographed on silica gel (5 g) in light petroleum–ether (1 : 1 v/v) to give the (1S*,4R*)-*alcohol* (30) (14 mg, 88%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 110 °C at 0.05 mmHg) (Found: C, 69.65; H, 10.2. $C_{14}H_{24}O_3$ requires C, 69.95; H, 10.05%), $\nu_{max.}$ 3 430 cm^{-1}, δ 0.92 (3 H, t, *J* 6.0 Hz, CH_2CH_3), 1.1—2.1 (12 H, m, CH_2, OH, and 5-H *trans* to 1-H and 4-H), 2.23br (2 H, t, *J* 7 Hz, allylic CH_2), 2.65 and 2.73 (each 0.5 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 3.52 and 3.92 (each 1 H, m, CH_2O), 4.2—4.8 (3 H, m, 1-H, 4-H and OCHO), and 5.64br (1 H, s, 3-H).

2-*Butyl*-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*enone* (37).—Pyridinium chlorochromate (12.9 mg, 0.06 mmol) was

added to a suspension of anhydrous sodium acetate (1 mg, 0.012 mmol) in methylene dichloride (0.3 ml) containing the (1*S**,4*R**)-alcohol (30) (8 mg, 0.033 mmol). After stirring at room temperature for 2 h the mixture was diluted with ether (1 ml) and filtered through a pad of Celite. Evaporation of the filtrate under reduced pressure and chromatography of the residual oil (10 mg) on a layer of silica gel in methylene dichloride–methanol (50 : 1 v/v) gave the *cyclopentenone* (37) (6.6 mg, 83%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 90 °C at 0.05 mmHg) (Found: C, 70.55; H, 9.2. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%), $\nu_{max.}$ 1 720 cm^{-1}, δ 0.92 (3 H, t, *J* 6.0 Hz, CH_2-CH_3), 1.1—2.1 (10 H, m, CH_2), 2.20br (2 H, t, *J* 7 Hz, allylic CH_2), 2.31 and 2.45 (each 0.5 H, dd, *J* 18.0, 3.0 Hz, 5-H *trans* to 4-H), 2.75 and 2.81 (each 0.5 H, dd, *J* 18.0, 6.0 Hz, 5-H *cis* to 4-H), 3.58 and 3.94 (each 1 H, m, CH_2O), 4.66—4.98 (2 H, m, 4-H and OCHO), and 7.22 (1 H, m, 3-H).

(1R*,4S*)-4-[*Dimethyl-(t-butyl)silyloxy*]-3-{7-[*dimethyl-(t-butyl)silyloxy*]*heptyl*}*cyclopent-2-en-1-ol* (31).—Lithium tri-s-butylborohydride in tetrahydrofuran (1M; 1.6 ml, 1.6 mmol) was added dropwise with vigorous stirring to the cyclopentenone (10) (370 mg, 0.84 mmol) in tetrahydrofuran (5 ml) at −78 °C. After 3 h at this temperature water (5 ml) was added and the mixture allowed to warm to room temperature. Dilution with water (5 ml) and extraction with ether (4 × 10 ml) gave, after drying ($MgSO_4$) and evaporation of the extracts, a pale yellow oil (800 mg). Preparative t.l.c. on silica gel in methylene dichloride–methanol (20 : 1 v/v) yielded the (1R*,4S*)-*alcohol* (31) (325 mg, 87%) as an oil (Kugelrohr, b.p. 140 °C at 0.3 mmHg) (Found: C, 65.2; H, 11.3. $C_{24}H_{50}O_3Si_2$ requires C, 65.1; H, 11.4%), $\nu_{max.}$ 3 380 cm^{-1}, δ 0.05 (6 H, s, $SiMe_2$), 0.05 and 0.09 (each 3 H, s, $SiMe_2$), 0.88 (18 H, s, Bu^t), 1.2—1.7 (11 H, m, CH_2 and 5-H *trans* to 1-H and 4-H), 2.12 (2 H, m, allylic CH_2), 2.68 (1 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 3.59 (2 H, t, *J* 6.0 Hz, CH_2OSi), 4.52 (2 H, m, 1-H and 4-H), and 5.54br (1 H, s, 2-H), δ_C 76.0 or 74.1, 128.3, 150.9, 74.1 or 76.0, and 45.4 (C-1 to C-5, respectively, of cyclopentenol ring).

(1S*,4R*)-1-[*Dimethyl-(t-butyl)silyloxy*]-2-{7-[*dimethyl-(t-butyl)silyloxy*]*heptyl*}-4-(*tetrahydropyran-2-yloxy*)*cyclopent-2-ene* (32).—Dihydropyran (46.2 mg, 0.55 mmol) was added dropwise to the (1*R**,4*S**)-alcohol (31) (215 mg, 0.48 mmol) in methylene dichloride (2 ml) containing toluene-*p*-sulphonic acid (0.01M) at 0 °C. After 3 h the solution was diluted with ether (15 ml), washed successively with 5% aqueous sodium hydrogencarbonate (5 ml) and water (2 × 5 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on silica gel (20 g) in methylene dichloride–methanol (50 : 1 v/v) gave the (1S*,4R*)-*diol derivative* (32) (202 mg, 79%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 140 °C at 0.1 mmHg) (Found: C, 66.3; H, 11.1. $C_{29}H_{58}O_4Si_2$ requires C, 66.1; H, 11.1%), δ 0.06 and 0.08 (total 12 H, each s, $SiMe_2$), 0.89 (18 H, s, Bu^t), 1.1—1.8 (17 H, m, CH_2 and 5-H *trans* to 1-H and 4-H), 2.08 (2 H, m, allylic CH_2), 2.69 and 2.73 (each 0.5 H, dt, *J* 13.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 3.60 (2 H, t, *J* 6.0 Hz, CH_2OSi), 3.55 and 3.88 (each 1 H, m, CH_2O), 4.32—4.80 (3 H, m, 1-H, 4-H and OCHO), and 5.55br (1 H, s, 3-H).

(1S*,4R*)-2-(7-*Hydroxyheptyl*)-4-(*tetrahydropyran-2-yloxy*)*cyclopent-2-en-1-ol* (33).—To the (1*S**,4*R**)-diol derivative (32) (160 mg, 0.3 mmol) in tetrahydrofuran (2 ml) at 0 °C was added slowly tetrabutylammonium fluoride in tetrahydrofuran (0.5M; 2.4 ml). After 2.5 h at 0 °C the solution was diluted with water (5 ml) and extracted three times with ether (20 ml, 2 × 10 ml). The combined extracts were washed with saturated brine (2 × 10 ml), dried ($MgSO_4$), and evaporated. Chromatography of the residual oil on silica gel (10 g) in methylene dichloride–methanol (20 : 1 v/v) gave the (1S*,4R*)-*alcohol* (33) (88 mg, 97%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 163 °C at 0.25 mmHg) (Found: C, 68.55; H, 10.25. $C_{17}H_{30}O_4$ requires C, 68.4; H, 10.15%), $\nu_{max.}$ 3 380 cm^{-1}, δ 1.1—2.1 (19 H, m, CH_2, OH and 5-H *trans* to 1-H and 4-H), 2.22 (2 H, m, allylic CH_2), 2.63 and 2.71 (each 0.5 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 1-H and 4-H), 3.56 and 3.90 (each 1 H, m, CH_2O), 3.63 (2 H, t, *J* 6.0 Hz, CH_2OH), 4.40 and 4.50 (each 1 H, m, 1-H and 4-H), 4.74 (1 H, m, OCHO), and 5.63br (1 H, s, 3-H).

2-(6-*Carboxyhexyl*)-4-(*tetrahydropyran-2-yloxy*)*cyclopent-2-enone* (4).—Jones reagent was added over 3 h to the (1*S**,4*R**)-alcohol (33) (126 mg, 0.42 mmol) in acetone (10 ml) at −20 °C so that an excess of oxidant was maintained. After a further 30 min isopropyl alcohol was added to destroy the excess of oxidant. The solution was diluted with water (15 ml), extracted with ether (5 × 10 ml), and the combined extracts were washed with saturated brine (3 × 5 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The *carboxylic acid* (4) (135 mg, 100%) was obtained as a chromatographically homogeneous oil (Found: M^+, 310.178 0. $C_{17}H_{26}O_5$ requires M, 310.178 0), $\nu_{max.}$ ($CHCl_3$) 2 400—3 600 and 1 710 cm^{-1}, δ 1.1—2.0 (14 H, m, CH_2), 2.19 (2 H, tm, *J* 7 Hz, allylic CH_2), 2.30 and 2.44 (each 0.5 H, dd, *J* 18.5, 2.5 Hz, 5-H *trans* to 4-H), 2.33 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.74 and 2.81 (each 0.5 H, dd, *J* 18.5, 6.0 Hz, 5-H *cis* to 4-H), 3.58 and 3.92 (each 1 H, m, CH_2O), 4.7—5.0 (2 H, m, 4-H and OCHO), 6.25br (1 H, OH), and 7.21 (1 H, m, 3-H).

2-(6-*Formylhexyl*)-4-(*tetrahydropyran-2-yloxy*)*cyclopent-2-enone* (38).—Pyridinium chlorochromate (117 mg, 0.54 mmol) was added portionwise to a suspension of anhydrous sodium acetate (8 mg, 0.1 mmol) in methylene dichloride (2 ml) containing the diol (33) (54 mg, 0.18 mmol) at 0 °C. After stirring at room temperature for 2.5 h the mixture was diluted with ether (5 ml) and filtered through Florisil. Evaporation of the filtrate and chromatography of the residue on silica gel in methylene dichloride–methanol (10 : 1 v/v) gave the *keto-aldehyde* (38) (43 mg, 81%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 160 °C at 0.5 mmHg) (Found: C, 69.3; H, 8.85. $C_{17}H_{26}O_4$ requires C, 69.35; H, 8.9%), $\nu_{max.}$ 1 700 cm^{-1}, δ 1.2—2.0 (14 H, m, CH_2), 2.20br (2 H, t, *J* 6 Hz, allylic CH_2), 2.32 and 2.44 (each 0.5 H, dd, *J* 19.0, 3.0 Hz, 5-H *trans* to 4-H), 2.42 (2 H, td, *J* 7.0, 1.8 Hz, CH_2CHO), 2.76 and 2.81 (each 0.5 H, dd, *J* 19.0, 6.0 Hz, 5-H *cis* to 4-H), 3.58 and 3.92 (each 1 H, m, CH_2O), 4.83 (2 H, m, 4-H and OCHO), 7.20 (1 H, m, 3-H), and 9.75 (1 H, t, *J* 1.8 Hz, CHO).

2-(6-*Ethoxycarbonylhexyl*)-4-(*tetrahydropyran-2-yloxy*)*cyclopent-2-enone* (2).—1,5-Diazabicyclo[5.4.0]undec-5-ene (49 mg, 0.322 mmol) in benzene (0.5 ml) was added with stirring to the chromatographically pure carboxylic acid (4) (100 mg, 0.322 mmol) and ethyl iodide (50 mg) in benzene (1.5 ml) at room temperature. After 18 h the mixture was filtered and the filtrate evaporated. Chromatography on silica gel in methylene dichloride–methanol (20 : 1 v/v) gave the *ethyl ester* (2) (97 mg, 89%) as an oily mixture of diastereoisomers (Found: C, 67.3; H, 8.8. $C_{19}H_{30}O_5$ requires C, 67.45; H, 8.95%), $\nu_{max.}$ 1 735 and 1 715 cm^{-1}, δ 1.23 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.2—2.0 (14 H, m, CH_2), 2.20

(2 H, t, *J* 7 Hz, allylic CH_2), 2.28 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.30 and 2.44 (each 0.5 H, dd, *J* 19.0, 2.5 Hz, 5-H *trans* to 4-H), 2.74 and 2.80 (each 0.5 H, dd, *J* 19.0, 6.0 Hz, 5-H *cis* to 4-H), 3.60 and 3.90 (each 1 H, m, CH_2O), 4.12 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.82 (2 H, m, 4-H and OCHO), and 7.20 (1 H, m, 3-H), in agreement with literature data.[4]

2-(6-*Ethoxycarbonylhexyl*)-4-*hydroxycyclopent*-2-*enone* (5).—The ethyl ester (2) (70 mg, 0.21 mmol) in acetic acid–tetrahydrofuran–water (3 : 1 : 1 v/v; 2 ml) was maintained at room temperature for 24 h. Solvent was removed under reduced pressure and the residue was purified by preparative t.l.c. on silica gel in methylene dichloride–methanol (10 : 1 v/v) to yield the *hydroxy-enone* (5) (53 mg, 99%) as an oil (Found: C, 66.1; H, 8.7. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%), $\nu_{max.}$ 3 440, 1 735sh, and 1 710 cm^{-1}, δ 1.22 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.2—1.8 (8 H, m, CH_2), 2.20 (2 H, t, *J* 7 Hz, allylic CH_2), 2.28 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.28 (1 H, dd, *J* 19.0, 2.5 Hz, 5-H *trans* to 4-H), 2.81 (1 H, dd, *J* 19.0, 6.0 Hz, 5-H *cis* to 4-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.94 (1 H, m, 4-H), and 7.15 (1 H, dt, *J* 2.6, 1.3 Hz, 3-H) in agreement with reported values.[4]

2-(6-*Methoxycarbonylhexyl*)-4-(*tetrahydropyran*-2-*yloxy*)-*cyclopent*-2-*enone* (3).—The chromatographically pure carboxylic acid (4) (135 mg, 0.44 mmol) was treated with an excess of ethereal diazomethane for 1 h. The excess of reagent was destroyed by the addition of acetic acid and the solvent was removed under reduced pressure. Chromatography of the residue (158 mg) on silica gel in methylene dichloride–methanol (20 : 1 v/v) gave the *methyl ester* (3) [132 mg, 94% from the diol (33)], a mixture of diastereoisomers as a waxy solid, m.p. 31—39 °C (Found: C, 66.55; H, 8.8. $C_{18}H_{28}O_5$ requires C, 66.65; H, 8.7%), $\nu_{max.}$ 1 735 and 1 710 cm^{-1}, δ 1.1—2.0 (14 H, m, CH_2), 2.19 (2 H, tm, *J* 7 Hz, allylic CH_2), 2.30 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.30 and 2.44 (each 0.5 H, dd, *J* 18.5, 2.5 Hz, 5-H *trans* to 4-H), 2.74 and 2.81 (each 0.5 H, dd, *J* 18.5, 6.0 Hz, 5-H *cis* to 4-H), 3.60 and 3.90 (each 1 H, m, CH_2O), 3.66 (3 H, s, CO_2Me), 4.84 (2 H, m, 4-H and OCHO), and 7.20 (1 H, m, 3-H), in agreement with literature data.[15]

4-*Hydroxy*-2-(6-*methoxycarbonylhexyl*)*cyclopent*-2-*enone* (6).—Hydrolysis of the methyl ester (3) (110 mg, 0.34 mmol) with acetic acid–tetrahydrofuran–water (3 : 1 : 1 v/v), as detailed above for the ethyl ester (2), gave 4-hydroxy-2-(6-methoxycarbonylhexyl)cyclopent-2-enone (6) (66 mg, 81%) as needles, m.p. 47—49 °C (lit.,[15] 48—49.5 °C) (from chloroform–light petroleum) (Found: C, 64.75; H, 8.45. Calc. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.4%), $\nu_{max.}$ 3 390, 1 735, and 1 710 cm^{-1}, δ 1.1—1.8 (9 H, m, CH_2 and OH), 2.23 (2 H, tm, *J* 7 Hz, allylic CH_2), 2.28 (1 H, dd, *J* 18.5, 2.0 Hz, 5-H *trans* to 4-H), 2.30 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.80 (1 H, dd, *J* 18.5, 6.0 Hz, 5-H *cis* to 4-H), 3.66 (3 H, s, CO_2Me), 4.94 (1 H, m, 4-H), and 7.12 (1 H, dt, *J* 3.0, 1.5 Hz, 3-H), δ_C 206.2, 147.9, 156.0, 68.6, and 44.9 (C-1 to C-5, respectively, of cyclopentenone ring), 174.1 (CO_2Me), 51.6 ($CO_2\mathit{Me}$), in agreement with published values.[15,16]

(1R*,4S*)-4-(*Dimethyl*-*t*-*butylsilyloxy*)-3-(6-*ethoxycarbonylhexyl*)*cyclopent*-2-*en*-1-*ol* (34).—Lithium tri-s-butylborohydride in tetrahydrofuran (1M; 0.15 ml, 0.150 mmol) was added dropwise with vigorous stirring to the cyclopentenone (13) (50 mg, 0.136 mmol) in tetrahydrofuran (1 ml) at −78 °C. After 0.5 h at this temperature water (0.5 ml) was added and the mixture allowed to warm to room temperature. Dilution with water (5 ml) and extraction with ether (4 × 5 ml) gave, after drying ($MgSO_4$) and evaporation of the combined extracts, a pale yellow oil (60 mg). Preparative t.l.c. on silica gel in methylene dichloride–methanol (20 : 1 v/v) yielded the (1R*,4S*)-*alcohol* (34) (47 mg, 93%) as an oil (Kugelrohr, b.p. 80 °C at 0.01 mmHg) (Found: C, 65.1; H, 10.2. $C_{20}H_{38}O_4Si$ requires C, 64.8; H, 10.35%), $\nu_{max.}$ 3 400 and 1 740 cm^{-1}, δ 0.07 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.24 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.2—1.8 (10 H, m, CH_2, 5-H *trans* to 4-H, and OH), 2.12 (2 H, m, allylic CH_2), 2.28 (2 H, t, *J* 7.5 Hz, CH_2CO_2), 2.68 (1 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 4-H), 4.11 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.48 (2 H, m, 1-H and 4-H), and 5.54 (1 H, m, 2-H).

(1S*,4R*)-1-[*Dimethyl*-(*t*-*butyl*)*silyloxy*]-2-(6-*ethoxycarbonylhexyl*)-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*ene* (35).—Dihydropyran (16.8 mg, 0.2 mmol) was added dropwise to the (1*R**,4*S**)-alcohol (34) (50 mg, 0.135 mmol) in methylene dichloride containing pyridinium toluene-*p*-sulphonate (3 mg, 0.015 mmol). After 4 h at room temperature the solution was diluted with ether (10 ml), washed with saturated brine (10 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. of the residue (74 mg) on silica gel in methylene dichloride–methanol (50 : 1 v/v) gave the (1S*,4R*)-*diol derivative* (35) (61 mg, 100%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 100 °C at 0.05 mmHg) (Found: C, 66.15; H, 10.15. $C_{25}H_{46}O_5Si$ requires C, 66.05; H, 10.2%), $\nu_{max.}$ 1 740 cm^{-1}, δ 0.07 (6 H, s, $SiMe_2$), 0.88 (9 H, s, Bu^t), 1.23 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.2—1.8 (15 H, m, CH_2 and 5-H *trans* to 4-H), 2.09 (2 H, m, allylic CH_2), 2.28 (2 H, t, *J* 7.5 Hz, CH_2CO_2), 2.70 and 2.73 (each 0.5 H, dt, *J* 13.0, 7.0 Hz, 5-H *cis* to 4-H), 3.52 and 3.87 (each 1 H, m, CH_2O), 4.11 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.36—4.78 (3 H, m, 1-H, 4-H and OCHO), and 5.55 (1 H, m, 3-H).

(1S*,4R*)-2-(6-*Ethoxycarbonylhexyl*)-4-(*tetrahydropyran*-2-*yloxy*)*cyclopent*-2-*en*-1-*ol* (36).—To the (1*S**,4*R**)-diol derivative (35) (55 mg, 0.12 mmol) in tetrahydrofuran (1 ml) at 0 °C was added dropwise tetrabutylammonium fluoride in tetrahydrofuran (0.4M, 0.6 ml). After 5.5 h at 0 °C the solution was diluted with water (5 ml) and extracted with ether (3 × 10 ml). The combined extracts were washed with saturated brine (2 × 5 ml), dried ($MgSO_4$), and evaporated. Chromatography of the residue (55 mg) on silica gel in methylene dichloride–methanol (20 : 1 v/v) gave the (1S*,4R*)-*alcohol* (36) (37 mg, 90%) as an oily mixture of diastereoisomers (Kugelrohr, b.p. 100 °C at 0.1 mmHg) (Found: C, 67.35; H, 9.35. $C_{19}H_{32}O_5$ requires C, 67.05; H, 9.5%), $\nu_{max.}$ 3 420 and 1 735 cm^{-1}, δ 1.22 (3 H, t, *J* 8.0 Hz, CH_2CH_3), 1.2—1.9 (15 H, m, CH_2 and 5-H *trans* to 4-H), 2.14br (1 H, s, OH), 2.28 (2 H, t, *J* 7.0 Hz, CH_2CO_2), 2.63 and 2.72 (each 0.5 H, dt, *J* 14.0, 7.0 Hz, 5-H *cis* to 4-H), 3.56 and 3.88 (each 1 H, m, OCH_2), 4.11 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.38, 4.58, and 4.73 (each 1 H, m, 1-H, 4-H and OCHO), and 4.62br (1 H, s, 3-H).

2-(6-*Ethoxycarbonylhexyl*)-4-(*tetrahydropyran*-2-*yloxy*)-*cyclopent*-2-*enone* (2) *from* (36).—Pyridinium chlorochromate (24 mg, 0.11 mmol) was added to a suspension of anhydrous sodium acetate (2 mg, 0.025 mmol) in methylene dichloride (1 ml) containing the (1*S**,4*R**)-alcohol (36) (23 mg, 0.067 mmol). After stirring at room temperature for 2 h the mixture was diluted with ether (3 ml) and filtered through Florisil. Evaporation of the filtrate under reduced pressure and chromatographic purification of the residual oil on silica gel in methylene dichloride–methanol (20 : 1 v/v) gave the cyclopentenone (2) (21 mg, 93%), identical with the material prepared above from the acid (4).

We thank Mr. A. J. Herlt for expert technical assistance and the A.N.U. Analytical Services Unit for microanalyses.

[0/1025 *Received*, 1st *July*, 1980]

REFERENCES

[1] Part 4, R. M. Christie, M. Gill, and R. W. Rickards, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.

[2] A. Mitra, 'The Synthesis of Prostaglandins,' Wiley and Sons, New York, 1977; J. S. Bindra and R. Bindra, 'Prostaglandin Synthesis,' Academic Press, New York, 1977.

[3] See for example: T. Shono, Y. Matsumura, H. Hamaguchi, and K. Nakamura, *Chem. Lett.*, 1976, 1249; M. Kobayashi, S. Kurozumi, T. Toru, and S. Ishimoto, *ibid.*, p. 1341; T. Shono, H. Hamaguchi, and K. Aoki, *ibid.*, 1977, 1053; E. Wada, T. Nakai, and M. Okawara, *ibid.*, p. 1121; M. B. Floyd, *J. Org. Chem.*, 1978, **43**, 1641; T. Lee, *Tetrahedron Lett.*, 1979, 2297.

[4] C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *J. Am. Chem. Soc.*, 1975, **97**, 857.

[5] See for example: P. W. Collins, E. Z. Dajani, D. R. Driskill, M. S. Bruhn, C. J. Jung, and R. Pappo, *J. Med. Chem.*, 1977, **20**, 1152; W. Bornatsch and K. G. Untch, *Prostaglandins*, 1977, **14**, 617; C. Luthy, P. Konstantin, and K. G. Untch, *J. Am. Chem. Soc.*, 1978, **100**, 6211.

[6] M. Gill and R. W. Rickards, *J. Chem. Soc., Chem. Commun.*, 1979, 121.

[7] K. Mori, *Tetrahedron*, 1974, **30**, 3807.

[8] E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 1976, 809.

[9] P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, 1972, **37**, 1947.

[10] T. D. Perrine, *J. Org. Chem.*, 1953, **18**, 1356.

[11] F. G. Cocu, G. Wolczunowicz, L. Bors, and T. Posternak, *Helv. Chim. Acta*, 1970, **53**, 739; D. A. Evans, T. C. Crawford, T. T. Fujimoto, and R. C. Thomas, *J. Org. Chem.*, 1974, **39**, 3176.

[12] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.

[13] E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.

[14] N. Ono, T. Yamada, T. Saito, K. Tanaka, and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2401.

[15] F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.*, 1972, **94**, 7823.

[16] G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, 1977, **99**, 1275.

[17] N. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, 1977, **42**, 3772.

[18] R. Effenberger and R. W. Rickards, *Aust. J. Chem.*, 1975, **28**, 2731.