Cyclopentanoids from Phenol. Part 4.[1] 3-Substituted 4-Hydroxycyclopent-2-enones

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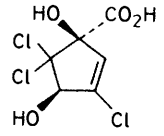
Various 3-halogeno- and 3,5,5-trihalogeno-4-hydroxycyclopent-2-enone derivatives were prepared from 3,5,5-trichloro-4-hydroxycyclopent-2-enone (2), which is available in two steps from phenol *via* (1*R**,4*R**)-3,5,5-trichloro-1,4-dihydroxycyclopent-2-ene-1-carboxylic acid (1). Conjugate addition–elimination reactions of the 3-chloro-4-(dimethy-t-butylsilyloxy)-, the 3-chloro-4-tetrahydropyranyloxy-, and the 5,5-dichloro-3-iodo-4-tetrahydropyranyloxycyclopent-2-enones (20), (21), and (7), respectively, with lithium and magnesium cuprate reagents lead to synthetically useful 3-alkyl-4-hydroxycyclopent-2-enones in high yield.

THE reaction of phenol in alkaline solution with chlorine, first described in 1887 by Hantzsch,[2] gives in 50—60% yield an acid shown by more recent studies to have the structure [3,4] and stereochemistry [5] (1), namely (1*R**,



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4*R**)-3,5,5-trichloro-1,4-dihydroxycyclopent-2-ene-1-carboxylic acid. Despite intense synthetic interest in natural products containing cyclopentanoid rings, the generation of this nucleus by phenol ring contraction has hitherto found limited application. Acid (1) has served as a precursor to (±)-caldariomycin,[4] and the 2-propyl homologue of the acid (1), a product of alkaline chlorination of 3-propylphenol,[6] has been used in a synthesis of (±)-cryptosporiopsin.[7] Since the acid (1) is readily available from phenol or 2,4,6-trichlorophenol in racemic form with the potential for resolution if required, we have studied the selective modification of this highly functionalised cyclopentenoid with a particular view towards prostaglandin synthesis. The realisation of this goal by two efficient routes has been described in preliminary publications.[1,8]

We describe here syntheses from the racemic acid (1) of the typical 3-alkyl-4-hydroxycyclopent-2-enone derivatives [(16) and (17)] in overall yields of *ca.* 50 and 60%, respectively, in which the 3-alkyl substituent is introduced by a conjugate addition–elimination reaction between the corresponding 3-halogeno-4-hydroxycyclopentenone and an organo-copper reagent. 3-Alkyl-substituted cyclopentenones of this type are valuable prostanoid precursors [8-10] by virtue of their further conversion [8,10,11] into the isomeric 2-alkyl-4-hydroxycyclopent-2-enones.

RESULTS AND DISCUSSION

The syntheses were initiated by oxidative decarboxylation of the Hantzsch acid (1) with lead tetra-acetate [12] to afford 3,5,5-trichloro-4-hydroxycyclopent-2-enone (2) in quantitative yield. The resulting carbonyl function greatly facilitates subsequent modifications of the cyclopentenoid nucleus, which, for the present purpose, include suitable protection of the 4-hydroxy-function, reductive removal of the *gem* chlorine atoms, and replacement of the vinylic chlorine atom by an alkyl group. The preferred sequence and mode of these operations have been studied extensively.

Route A; Protection–Alkylation–Reduction.—The acetate (3) was produced in good yield upon treatment of the trichloro-enone (2) with acetic anhydride and a trace of acid, and was reduced in moderate yield to the monochloro-enone (22) with zinc–hydrochloric acid in ether.[13] However, since acetate is of limited value as a protecting group in prostaglandin synthesis, we turned to the preparation of ethers. The tetrahydropyranyl ether (4) of the trichloro-enone (2) is a mixture of diastereoisomers, which can be separated by crystallisation or chromatography. Not unexpectedly, it suffered extensive degradation under the acidic conditions used to reduce the corresponding acetate. Attempts to prepare the dimethyl-t-butylsilyl ether (5) of the trichloro-enone using imidazole as base [14] resulted in substitution at C-3 by an addition–elimination process, with formation of the 3-imidazol-1-yl-4-hydroxycyclopentenone (8) together with its silyl ether (9). None of the desired silyl ether (5) could be detected.

We next examined the possible alkylation of the protected trichloro-enones (3) and (4) by conjugate addition–elimination processes with various organometallic reagents. Preliminary reactions of the acetate (3) with lithium dibutylcuprate and dibutylcadmium reagents were not promising, and only limited success was achieved in the reaction between the tetrahydropyranyl ether (4) and the sodium salt of diethyl 2-heptylmalonate.[13] The reports by Piers *et al.*[15] that cyclic β-halogeno-αβ-unsaturated ketones undergo efficient addition–elimination reactions with lithium alkyl (phenylthio)cuprates prompted us to treat the tetrahydropyranyl ether (4) with lithium butyl(phenylthio)-cuprate. Low yields (5—11%) of the desired 3-butylcyclopentenone (11) resulted, together with the monodechlorinated analogues, (12) and (13), of this product (15—34%) and of the starting material (40%), respectively. The formation of these two analogues reflects the ease of reduction [16] of the α′α′-dichloroketone systems in both the product (11) and the starting material (4), the

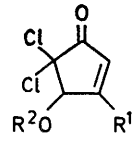
resulting intermediate enolate anions (14) and (15) being protected from conjugate addition and protonated only upon work-up. The thermodynamically more stable *trans*-arrangement of chlorine and tetrahydropyranyloxy substituents in these major reduction products (12) and (13) is indicated by the 3-Hz coupling constant between C-4-H and C-5-H in the ^{1}H n.m.r. spectra of these compounds.[17]

In order to promote conjugate addition relative to the competing reduction, the 3-iodocyclopentenone (7) was prepared from the parent trichloro-enone (2) by boron trifluoride-catalysed halide exchange[12] followed by tetrahydropyranylation of the resulting alcohol (6). The reaction of lithium butyl(phenylthio)cuprate with this iodo-analogue (7) was far more regio-selective than with the chloro-compound (4), the required 3-butyl-5,5-dichloro-4-tetrahydropyranyloxycyclopent-2-enone (11) being obtained in 63% yield. Reductive removal of the *gem* chlorine substituents with chromium(II) chloride afforded 3-butyl-4-tetrahydropyranyloxycyclopent-2-enone (16) in 40% overall yield from the acid (1).

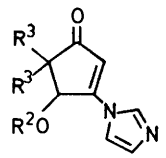
The α′α′-dichloro-substituents were clearly complicating the reactions of the β-halogeno-enone systems with organometallic reagents. Since removal of these substituents was best affected under acidic conditions which might also partially cleave ethers protecting the 4-hydroxy-group, we turned to the reduction of the unprotected trichloro-enone (2) itself.

Route B; Reduction–Protection–Alkylation.—Reduction of the trichloro-enone (2) at 0 °C with chromium(II) chloride gave the *unstable* monochloro-enone (19) in 79% yield after distillation. Treatment of this product (19) in dimethylformamide with chlorodimethyl-t-butylsilane and imidazole[14] afforded, in addition to the silyl ether (20) (61%), an unacceptably high yield (34%) of the corresponding 3-imidazolyl analogue (10). The isolation of an appreciable quantity of the desired derivative (20) in the case of this monochloro-enone (19), in contrast to that of the trichloro-enone (2), illustrates the electronic deactivation of the β-chloro-enone system which accompanies the reductive removal of the *gem* chlorine atoms. Significantly, dimethyl-t-buty-silylation of the monochloro-enone (19) in hexamethylphosphoric triamide (HMPT) *without* added base gave the desired ether (20) cleanly in 77% yield. Indeeed, it was found that silylation of the monochloro-enone (19) also occurred in dimethylformamide in the absence of imidazole (*cf.* ref. 14), but the yield was inferior to that obtained with HMPT as solvent.

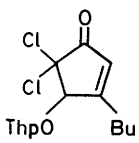
The chloro-enone (19) is sufficiently unstable at room temperature to warrant its derivatisation without prior purification. In this way the dimethyl-t-butylsilyl



(2) R^1 = Cl, R^2 = H
(3) R^1 = Cl, R^2 = Ac
(4) R^1 = Cl, R^2 = Thp
(5) R^1 = Cl, R^2 = Me_2Bu^tSi
(6) R^1 = I, R^2 = H
(7) R^1 = I, R^2 = Thp



(8) R^2 = H, R^3 = Cl
(9) R^2 = Me_2Bu^tSi, R^3 = Cl
(10) R^2 = Me_2Bu^tSi, R^3 = H



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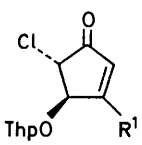
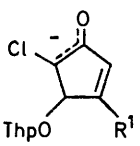
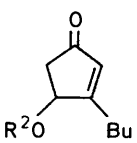


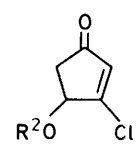
(12) R^1 = Bu
(13) R^1 = Cl



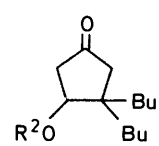
(14) R^1 = Bu
(15) R^1 = Cl



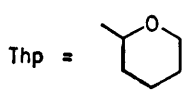
(16) R^2 = Thp
(17) R^2 = Me_2Bu^tSi
(18) R^2 = H

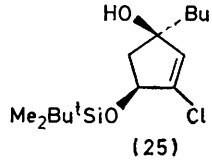


(19) R^2 = H
(20) R^2 = Me_2Bu^tSi
(21) R^2 = Thp
(22) R^2 = Ac



(23) R^2 = Me_2Bu^tSi
(24) R^2 = Thp





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ether (20) was obtained in 61% overall yield from (1), while tetrahydropyranylation of (19) gave the ether (21) in 62% overall yield.

Reaction of the ethers (20) and (21) with lithium butyl(phenylthio)cuprate at −20 °C afforded good yields (63—74%) of the required 3-butylcyclopentenones (17) and (16), respectively. A stoicheiometric 1.5-fold excess of cuprate served to optimise the yields of cyclopentenone products (*cf.* Table 1), whereas with higher

TABLE 1

Reaction of lithium butyl(phenylthio)cuprate with the chlorocyclopentenones (20) and (21)

Substrate	Cuprate (equivalents)	Temperature (°C)	Time/h	% Yield [b] (product)
(20)	1.5	−20	1.5	74 (17)
(21) [a]	2	−10	0.75	48 (16)
(21) [a]	1.5	−20	2.5	63 (16)
(21) [a]	3	−20	2.5	64 (16)
(21) [a]	5	−20	2.5	15 (16)

[a] Mixture of diastereoisomers. [b] Isolated yields.

cuprate : substrate ratios some further butylation of the initial products occurred leading to the cyclopentanones (23) and (24). A similar problem of over-alkylation was encountered when the tetrahydropyranyl ether (21) was allowed to react with lithium dibutylcuprate.

We next examined the reactions of these chlorocyclopentenone ethers (20) and (21) with magnesium cuprate reagents. Normal additions in various proportions of the silyl ether (20) to a mixture of butylmagnesium bromide and cuprous iodide (in constant 2 : 1 mol ratio) at −20 °C produced only moderate yields of the 3-butylcyclopentenone (17) (*cf.* Table 2).

TABLE 2

Reaction of the chlorocyclopentenone (20) with butylmagnesium bromide and cuprous iodide ('*normal*' addition)

Amount Grignard reagent (equiv.)	% Yield [a] (17)	(20)	(17) + (20)
1.0	13	84	97
1.3	20	76	96
1.3 [b]	21	73	94
2.0	34	50	84
	(37 *)	(54 *)	(91 *)
4.0	30 *	62 * of (23)	92 *

[a] Yields determined by g.l.c. except those marked * which refer to isolated material. [b] Performed over 16 h.

If 2 equiv. or less of Grignard reagent were employed, a considerable amount of substrate was recovered unchanged, whereas the use of 4 equiv. produced the dibutylcyclopentanone (23) in addition to the monoalkylated species.

By employing an 'inverse' addition procedure, *i.e.* adding the butylmagnesium bromide to a mixture of the chlorocyclopentenone (20) and cuprous iodide, excellent yields of the required 3-butylcyclopentenone (17) were obtained (*cf.* Table 3). If sufficient Grignard reagent

TABLE 3

Reaction of the chlorocyclopentenone (20) with butylmagnesium bromide and cuprous iodide ('*inverse*' addition)

Amount Grignard reagent (equiv.)	% Yield [a] (17)	(20)
1.0	83	17
1.4	90	10
1.9	96	1.5
	(93 *)	(2 *)

[a] Yields determined by g.l.c. except * which refers to isolated material.

was used to produce (at least formally) *more* than 1 equiv. of a dibutylmagnesium cuprate species then some dibutylcyclopentanone (23) was also isolated. Alkylation of the tetrahydropyranyl ether (21), under similar conditions of 'inverse' addition, gave the 3-butylcyclopentenone (16) in 78% yield. Significantly, treatment of the chloro-enone (20) with butyl-lithium or butylmagnesium bromide alone yielded the tertiary allylic alcohol (25), a product not detected from the copper-mediated processes.

The 3-butyl-4-hydroxycyclopent-2-enone ethers (17) and (16) are thus accessible in 59% and 48% overall yields, respectively, from the readily available Hantzsch acid (1) by the reactions of route B. These ethers can, if required, be hydrolysed with mild acid in high yield to the free 3-butyl-4-hydroxycyclopent-2-enone (18). The reduction–protection–alkylation sequence of route B is more direct and efficient than route A, and unlike route A can also provide the silyl ethers, which offer advantages in subsequent extensions of the synthesis to prostanoids.[1,8,10]

EXPERIMENTAL

I.r. spectra were measured as KBr discs (solids) or between NaCl plates (oils) on a Perkin-Elmer 257 spectrometer. N.m.r. spectra were recorded on Varian HA-100 (^{1}H) and Jeol JNM-FX60 (^{13}C) spectrometers for solutions in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Mass spectra were run on a GEC-AEI MS 902 instrument operating at 70 eV. Melting points were determined on a Kofler hot-stage. G.l.c. analyses were performed on a Perkin-Elmer 881 chromatograph with a 72 × 0.25 in. internal diameter glass column containing 2% OV-17, and were recorded on a Hewlett Packard 3380A integrator.

Materials.—Petrol refers to light petroleum of b.p. 60—80 °C. Merck Kieselgel 60 F_{254} was used for preparative t.l.c. and column chromatography. Copper(I) iodide was continuously extracted with tetrahydrofuran in a Soxhlet extractor for 24 h and dried *in vacuo* at room temperature before use. Copper(I) thiophenoxide was prepared from red copper oxide and thiophenol according to Posner *et al.*[18] Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. Reactions were routinely performed under an argon atmosphere. Compounds (1), (2), and (6) were prepared as previously described.[12]

3,5,5-Trichloro-4-(tetrahydropyran-2-yloxy)cyclopent-2-enone (4).—Dihydropyran (277 mg, 3.3 mmol) was added dropwise over 0.5 h to the trichloro-enone (2) (604 mg, 3.0

mmol) in methylene dichloride (10 ml) containing toluene-*p*-sulphonic acid (0.01M). After stirring at ambient temperature for 16 h the solution was diluted with ether and washed successively with 5% aqueous sodium hydrogencarbonate and water before drying ($MgSO_4$). Evaporation of the solvent gave the *tetrahydropyranyl ether* (4) (860 mg, quantitative yield) as a mixture of diastereoisomers. These could be separated by fractional crystallisation from aqueous methanol to afford a *more soluble isomer*, needles, m.p. 58—62 °C (Found: C, 42.05; H, 3.75; Cl, 37.4. $C_{10}H_{11}Cl_3O_3$ requires C, 42.05; H, 3.9; Cl, 37.25%); $\nu_{max.}$ 1 725 cm^{-1}; δ 1.4—2.2 (6 H, m, CH_2 in tetrahydropyranyl ring), 3.56—4.40 (2 H, m, CH_2O), 5.07 (1 H, d, *J* 1.3 Hz, 4-H), 5.18 (1 H, br s, OCHO), and 6.37 (1 H, d, *J* 1.3 Hz, 2-H): and a *less soluble isomer*, m.p. 67—70 °C (Found: C, 41.75; H, 3.6; Cl, 37.2%); $\nu_{max.}$ 1 725 cm^{-1}; δ_H 1.5—2.0 (6 H, m, CH_2 in tetrahydropyranyl ring), 3.69 and 4.10 (total 2 H, each m, CH_2O), 5.23 (1 H, d, *J* 1.5 Hz, 4-H), 5.23 (1 H, br s, OCHO), and 6.40 (1 H, d, *J* 1.5 Hz, 2-H); δ_C 188.3, 127.9, 165.0, 83.1, and 83.1 (C-1 to C-5, respectively, of cyclopentenone ring).

Reaction of the Trichloro-enone (2) *with Chlorodimethyl-t-butylsilane and Imidazole.*—To the trichloro-enone (2) (201 mg, 1 mmol) and chlorodimethy-t-butylsilane (181 mg, 1.2 mmol) in dimethylformamide (0.5 ml) at 0 °C was added imidazole (170 mg, 2.5 mmol) in dimethylformamide (0.5 ml). After 3 h water (5 ml) was added and the precipitated solid (155 mg) was filtered off. Extraction of the filtrate with methylene dichloride (6 × 10 ml) and removal of the washed (saturated aqueous sodium chloride) and dried ($MgSO_4$) solvent gave 5,5-*dichloro*-4-*hydroxy*-3-*imidazol*-1-*ylcyclopent*-2-*enone* (8) (59 mg) as needles from acetone, m.p. 178—180 °C (Found: C, 41.2; H, 2.7; Cl, 30.8; N, 11.55. $C_8H_6Cl_2N_2O_2$ requires C, 41.25; H, 2.6; Cl, 30.45; N, 12.0%); $\nu_{max.}$ 1 730 cm^{-1}; δ([$^2H_6$]DMSO) 5.74 (1 H, d, *J* 9 Hz, 4-H), 6.81 (1 H, s, 2-H), 7.62 (1 H, d, *J* 9 Hz, OH), and 7.28, 7.90, and 8.45 (each 1 H, br s, imidazolyl protons). Chromatographic purification of the precipitated solid (155 mg) in methylene dichloride–methanol (10 : 1) gave further enone (8) (67 mg, total 126 mg, 54% yield) and 4-(*dimethyl-t-butylsilyloxy*)-5,5-*dichloro*-3-*imidazol*-1-*ylcyclopent*-2-*enone* (9) (57 mg, 16%) as needles from methanol, m.p. 145—148 °C (Found: C, 48.35; H, 6.1; Cl, 20.65; N, 7.65. $C_{14}H_{20}Cl_2N_2O_2Si$ requires C, 48.4; H, 5.8; Cl, 20.4; N, 8.05%); $\nu_{max.}$ 1 730 cm^{-1}, δ([$^2H_6$]DMSO) 0.30 and 0.32 (each 3 H, s, $SiMe_2$), 0.86 (9 H, s, t-Bu), 6.17 (1 H, s, 4-H), 6.94 (1 H, s, 2-H), and 7.44, 7.89, and 8.60 (each 1 H, br s, imidazolyl protons).

3-*Chloro*-4-*hydroxycyclopent*-2-*enone* (19).—To the trichloro-enone (2) (201 mg, 1 mmol) in acetone (5 ml) under carbon dioxide was added an aqueous solution (8 ml) of chromium(II) chloride.[19] After 15 min the solution was extracted with ether and the extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated. Distillation of the residual oil (b.p. 45 °C at 0.1 mmHg) gave the *chloro-enone* (19) as a colourless, unstable oil (Found: C, 44.9; H, 4.15; Cl, 26.75. $C_5H_5ClO_2$ requires C, 45.3; H, 3.8; Cl, 26.75%); $\nu_{max.}$ 1 720 cm^{-1}; δ([$^2H_6$]acetone + D_2O, *cf.* ref. 12) 2.36 (1 H, dd, *J* 18.0 and 2.3 Hz, 5-H *trans* to 4-H), 2.90 (1 H, dd, *J* 18.0 and 6.2 Hz, 5-H *cis* to 4-H), 4.89 (1 H, ddd, *J* 6.2, 2.3, and 1.0 Hz, 4-H), and 6.25 (1 H, d, *J* 1.0 Hz, 2-H).

4-(*Dimethyl-t-butylsilyloxy*)-3-*chlorocyclopent*-2-*enone* (20).—Chloro-t-butyldimethylsilane (485 mg, 3.22 mmol) was added during 5 min to the crude chloro-enone (19) [247 mg, prepared from trichloro-enone (2) (1.61 mmol) by the method described above and used without purification] in hexamethylphosphoric triamide (2 ml) at 0 °C. After stirring at 4 °C for 20 h the solution was diluted with water (10 ml) and extracted with ether (3 × 10 ml). The combined ether extracts were washed with water (3 × 10 ml), dried ($MgSO_4$), and evaporated to give a pale yellow oil (456 mg) which was chromatographed on a column of silica gel (25 g) with methylene dichloride–methanol (50 : 1) as eluant. The *silyl ether* (20) [243 mg, 61% from (1)] was obtained as a colourless oil (b.p. 75 °C at 0.05 mmHg, Kugelrohr) (Found: C, 53.75; H, 7.85; Cl, 14.15. $C_{11}H_{19}ClO_2Si$ requires C, 53.55; H, 7.75; Cl, 14.35%); $\nu_{max.}$ 1 730 cm^{-1}; δ_H 0.14 and 0.16 (each 3 H, s, $SiMe_2$), 0.93 (9 H, s, t-Bu), 2.43 (1 H, dd, *J* 18.3 and 2.4 Hz, 5-H *trans* to 4-H), 2.87 (1 H, dd, *J* 18.3 and 6.0 Hz, 5-H *cis* to 4-H), 4.84 (1 H, ddd, *J* 6.0, 2.4, and 1.0 Hz, 4-H), 6.22 (1 H, d, *J* 1.0 Hz, 2-H); δ_C 200.1, 131.5, 170.2, 72.7, and 46.4 (C-1 to C-5, respectively, of cyclopentenone ring).

Reaction of the Chloro-enone (19) *with Chlorodimethyl-t-butylsilane and Imidazole.*—To the chloro-enone (19) (132 mg, 1 mmol) and chlorodimethyl-t-butylsilane (195 mg, 1.3 mmol) in dimethylformamide (0.5 ml) at 0 °C was added imidazole (204 mg, 3 mmol) in dimethylformamide (0.5 ml). After 3 h the mixture was poured into water (10 ml), and the products were extracted with ether (3 × 15 ml). Evaporation of the washed (brine) and dried ($MgSO_4$) solvent gave an oil (325 mg) which upon silica gel chromatography [methylene dichloride–methanol (20 : 1)] furnished 3-chloro-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone (20) (150 mg, 61%) identical with that described above, and 4-(*dimethyl-t-butylsilyloxy*)-3-*imidazol*-1-*ylcyclopent*-2-*enone* (10) (94 mg, 34%) as rhombs, m.p. 90—93 °C (from petrol) (Found: C, 60.6; H, 8.0; N, 10.15. $C_{14}H_{22}N_2O_2Si$ requires C, 60.4; H, 7.95; N, 10.05%); $\nu_{max.}$ 1 700 cm^{-1}; δ 0.16 and 0.24 (each 3 H, s, $SiMe_2$), 0.87 (9 H, s, t-Bu), 2.50 (1 H, dd, *J* 18.0 and 2.5 Hz, 5-H *trans* to 4-H), 2.94 (1 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 5.37 (1 H, dd, *J* 6.0 and 2.5 Hz, 4-H), 6.08 (1 H, s, 2-H), and 7.19, 7.27, and 8.01 (each 1 H, br s, imidazolyl protons).

3-*Chloro*-4-*tetrahydropyran*-2-*yloxycyclopent*-2-*enone* (21).—Dihydropyran was added dropwise during 15 min to the crude chloro-enone (19) [prepared from trichloro-enone (2) (1.008 g, 5 mmol) by the method described above and used without purification] in methylene dichloride (10 ml) containing toluene-*p*-sulphonic acid (0.01M). When consumption of the substrate was complete (t.l.c.) the solution was diluted with ether, washed successively with 5% aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and evaporated. Distillation of the residual oil (65 °C and 0.1 mmHg) gave the *tetrahydropyranyl ether* (21) (670 mg, 62%) as a colourless, oily mixture of diastereoisomers (Found: C, 55.9; H, 6.1; Cl, 16.4. $C_{10}H_{13}ClO_3$ requires C, 55.45; H, 6.05; Cl, 16.35%); $\nu_{max.}$ 1 730 cm^{-1}; δ_H 1.4—2.0 (6 H, m, CH_2 in tetrahydropyranyl ring), 2.44 and 2.49 (each 0.5 H, dd, *J* 18.0 and 3.0 Hz, 5-H *trans* to 4-H), 2.84 and 2.96 (each 0.5 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 3.3—4.2 (2 H, m, CH_2O), 4.82 (1 H, m, 4-H), 4.99 (1 H, m, OCHO), and 6.24 and 6.31 (each 0.5 H, d, *J* 1.0 Hz, 2-H); δ_C 200.9, 133.0 and 132.3, 168.8, 77.0 and 73.8, and 44.7 and 43.1 (C-1 to C-5, respectively, of cyclopentenone ring).

5,5-*Dichloro*-3-*iodo*-4-*tetrahydropyran*-2-*yloxycyclopent*-2-*enone* (7).—Dihydropyran (420 mg, 5 mmol) was added dropwise to the dichloro-iodo-enone (6) (1.3 g, 4.5 mmol)

in methylene dichloride (20 ml) containing toluene-*p*-sulphonic acid (0.01M). After 16 h the solution was diluted with ether, washed successively with 5% aqueous sodium hydrogencarbonate and water, and dried ($MgSO_4$). Removal of the solvent gave the *tetrahydropyranyl ether* (7) in quantitative yield. Crystallisation from aqueous methanol gave the *less soluble diastereoisomer* as pale yellow tablets, m.p. 115—116 °C (Found: C, 31.9; H, 2.95; Cl, 18.65; I, 33.15. $C_{10}H_{11}Cl_2IO_3$ requires C, 31.85; H, 2.95; Cl, 18.8; I, 33.65%); $\nu_{max.}$ 1 730 cm^{-1}; δ_H 1.4—2.2 (6 H, m, CH_2 of tetrahydropyranyl ring), 3.68 and 4.20 (each 1 H, m, CH_2O), 5.26 (1 H, d, *J* 1.6 Hz, 4-H), 5.28 (1 H, m, OCHO), and 6.88 (1 H, d, *J* 1.6 Hz, 2-H); δ_C 188.9, 139.7, 135.2, 86.0, and 81.9 (C-1 to C-5, respectively, of cyclopentenone ring): and a *more soluble diastereoisomer* as leaflets, m.p. 95 °C (Found: C, 31.8; H, 2.7; Cl, 18.6; I, 33.55%), $\nu_{max.}$ 1 725 cm^{-1}; δ 1.4—2.2 (6 H, m, CH_2 of tetrahydropyranyl ring), 3.66 and 4.18 (each 1 H, m, CH_2O), 5.03 (1 H, d, *J* 1.6 Hz, 4-H), 5.20 (1 H, br s, OCHO), and 6.85 (1 H, d, *J* 1.6 Hz, 2-H).

Reaction of Lithium n-Butyl(phenylthio)cuprate with the Chloro-enone (4).—To a stirred suspension of (phenylthio)-copper [18] (260 mg, 1.5 mmol) in dry tetrahydrofuran (10 ml) at −20 °C was added dropwise n-butyl-lithium (1.0 ml, 1.5M in hexane). The pale yellow solution was stirred at −20 °C for 15 min and then cooled to −78 °C before dropwise addition of the chloro-enone (4) (285 mg, 1.0 mmol) in a little tetrahydrofuran. The mixture was allowed to warm to −20 °C, maintained there for 2.5 h, and then worked up by the sequential addition of methanol (1 ml), saturated aqueous ammonium chloride (0.5 ml), magnesium sulphate (*ca.* 4 g), and ether (10 ml), followed by application to a short column of silica gel (*ca.* 10 g) and elution with ether (100 ml).[15a] Further column chromatography [silica gel, petrol–ether (6 : 1)] gave an oil (143 mg) shown by ^1H n.m.r. to comprise 3,5-dichloro-4-tetrahydropyran-2-yloxycyclopent-2-enone (13) (40%), δ 4.26 (1 H, d, *J* 3 Hz, 5-H) and 6.32 (1 H, d, *J* 1 Hz, 2-H), 3-butyl-5-chloro-4-tetrahydropyran-2-yloxycyclopent-2-enone (12) (15%), δ 4.12 (1 H, d, *J* 3 Hz, 5-H) and 5.98 (1 H, br s, 2-H), and 3-butyl-5,5-dichloro-4-tetrahydropyran-2-yloxycyclopent-2-enone (11) (11%) (see below). Use of more cuprate (3.0 mmol) under the same conditions gave (13), (12), and (11) (40%, 34%, and 5%, respectively).

3-Butyl-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone (17).—(i) *From the chloro-enone* (20) *and lithium butyl(phenylthio)-cuprate*. The chloro-enone (20) (85 mg, 0.34 mmol) in tetrahydrofuran (1 ml) was added dropwise to lithium butyl(phenylthio)cuprate (0.51 mmol, prepared as described above) in tetrahydrofuran (5 ml)–hexane at −78 °C. The mixture was allowed to warm to −20 °C over 1 h, and after a further 1.5 h at this temperature the mixture was poured into saturated aqueous ammonium chloride (10 ml) and covered by a layer of ether (20 ml). After stirring overnight the layers were separated and the blue aqueous phase was extracted with ether (10 ml). The ether extracts were combined, washed successively with ammonium chloride solution (10 ml) and brine (2 × 10 ml), and then dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue [methylene dichloride–methanol (50 : 1)] gave the *3-butylcyclopentenone* (17) (67 mg, 74%) as a colourless liquid after distillation (Kugelrohr, b.p. 85 °C at 0.04 mmHg) (Found: C, 67.25; H, 10.3. $C_{15}H_{28}O_2Si$ requires C, 67.1; H, 10.5%); $\nu_{max.}$ 1 725 cm^{-1}; δ_H 0.12 and 0.15 (each 3 H, s, $SiMe_2$), 0.95 (3 H, t, *J* 7.0 Hz, CH_2Me), 0.92 (9 H, s, t-Bu), 1.16—1.84 (4 H, m, CH_2CH_2), 2.25 (1 H, dd, *J* 18.0 and 2.5 Hz, 5-H *trans* to 4-H), 2.47 (2 H, br t, *J* 8 Hz, allylic CH_2), 2.72 (1 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 4.78 (1 H, ddm, *J* 6.0 and 2.5 Hz, 4-H). 5.92 (1 H, dt, *J* 1.3 and 1.3 Hz, 2-H); δ_C 205.0, 129.3, 181.8, 72.1, and 45.8 (C-1 to C-5, respectively, of cyclopentenone ring).

(ii) *From the chloro-enone* (20) *and butylmagnesium bromide using inverse addition*. A suspension of copper(I) iodide (68.5 mg, 0.36 mmol) in tetrahydrofuran (2 ml) containing the chloro-enone (20) (88 mg, 0.36 mmol) was stirred vigorously at 0 °C under argon. Dropwise addition of n-butylmagnesium bromide in tetrahydrofuran (0.72M, 0.95 ml) produced a yellow-green solution which changed to deep green over 1 h at 0 °C. After this time the reaction was rapidly quenched with saturated aqueous ammonium chloride (5 ml), and after addition of ether (5 ml) the mixture was stirred at room temperature for 1 h, then diluted with water (10 ml) and extracted with ether (5 × 10 ml). The combined extracts were washed with brine (2 × 5 ml), dried ($MgSO_4$) and evaporated to yield an oil (126 mg) which on chromatography gave the 3-butylcyclopentenone (17) (90 mg, 93%) identical with that described above, together with unreacted chloro-enone (20) (*ca.* 2 mg). Yields obtained using other ratios of chloro-enone to magnesium cuprate are shown in Table 3.

(iii) *From the chloro-enone* (20) *and butylmagnesium bromide using normal addition*. Copper(I) iodide (95.2 mg, 0.5 mmol) was added to a vigorously stirred, cold (0 °C) solution of n-butylmagnesium bromide in tetrahydrofuran (0.2M, 5 ml). Dropwise addition of the chloro-enone (20) (123 mg, 0.5 mmol) in tetrahydrofuran (2 ml) produced a deep green solution which was stirred at 0 °C for 1 h prior to the addition of aqueous ammonium chloride (10 ml). Ether extraction and chromatographic purification [silica gel, methylene dichloride–methanol (50 : 1)] of the crude product (145 mg) gave the 3-butylcyclopentenone (17) (50 mg, 37%) together with recovered substrate (20) (67 mg, 54%). Yields of products obtained using other ratios of chloro-enone (20) to magnesium cuprate are presented in Table 2. *3,3-Dibutyl-4-(dimethyl-t-butylsilyloxy)cyclopentanone* (23) was obtained as a very pale yellow liquid after distillation (Kugelrohr, b.p. 80 °C at 0.35 mmHg) (Found: C, 70.2; H, 11.6. $C_{19}H_{38}O_2Si$ requires C, 69.85; H, 11.75%); $\nu_{max.}$ 1 745 cm^{-1}; δ 0.05 and 0.07 (each 2 H, s, $SiMe_2$), 0.88 (15 H, m, t-Bu and CH_2Me) 1.24 (12 H, m, $CH_2CH_2CH_2$), 1.96 (1 H, d, *J* 18.0 Hz, 2-H), 2.24 (1 H, d, *J* 18.0 Hz, 2-H), 2.17 (1 H, dd, *J* 18.0 and 3.0 Hz, 5-H *trans* to 4-H), 2.56 (1 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 4.13 (1 H, m, 4-H).

3-Butyl-4-tetrahydropyran-2-yloxycyclopent-2-enone (16).—The chloro-enone (21) (*ca.* 0.5 mmol) was allowed to react in a similar manner to that described above for the dimethyl-t-butylsilyl ether (20) with the quantities of lithium butyl(phenylthio)cuprate and under the reaction conditions shown in Table 1. Work-up [15a] gave the *3-butylcyclopentenone* (16) (maximum yield 64%, *cf.* Table 1) as a colourless mixture of liquid diastereoisomers (Kugelrohr, b.p. 88 °C at 0.03 mmHg) (Found: C, 70.75; H, 9.0. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); $\nu_{max.}$ 1 720 cm^{-1}; δ 0.96 (3 H, t, *J* 7.0 Hz, Me), 1.2—2.1 (10 H, m, CH_2), 2.28 and 2.45 (each 0.5 H, dd, *J* 18.0 and 3.0 Hz, 5-H *trans* to 4-H), 2.38 and 2.51 (each 1 H, br t, *J* 7.0 Hz, allylic CH_2), 2.71 and 2.78 (each 0.5 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 2.40—4.06 (2 H, m, CH_2O), 4.73 and 4.76 (each 0.5 H, m, OCHO), 4.90 (0.5 H, ddm, *J* 6.0, 3.0 Hz,

4-H), 4.94 (0.5 H, ddd, *J* 6.0, 3.0, and 1.3 Hz, 4-H), 5.98 (0.5 H, dt, *J* 1.3 and 1.3 Hz, 2-H), and 6.02 (0.5 H, m, 2-H). The 3-butylcyclopentenone (16)(78%) was also obtained from the chloro-enone (21) and butylmagnesium bromide–copper(I) iodide in an analogous way to the dimethyl-t-butylsilyl ether (17) (see above).

3-Butyl-4-hydroxycyclopent-2-enone (18).—The tetrahydropyranyl ether (16) (130 mg, 0.55 mmol) in acetic acid–tetrahydrofuran–water (3 : 1 : 1, 5 ml) was maintained at room temperature for 24 h. Removal of the solvent under reduced pressure and chromatography [silica gel, methylene dichloride–methanol (20 : 1)] gave the *hydroxy-cyclopentenone* (18) (85 mg, 100%) as a colourless liquid (Kugelrohr, b.p. 90 °C at 0.05 mmHg) (Found: C, 70.4; H, 9.2. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}$ 3 420, 1 710(sh), and 1 690 cm^{-1}; δ 0.97 (3 H, t, *J* 7.0 Hz, Me), 1.2—1.9 (4 H, m, CH_2CH_2), 2.18 (1 H, m, OH), 2.31 (1 H, dd, *J* 18.0 and 2.5 Hz, 5-H *trans* to 4-H), 2.56 (2 H, br t, *J* 8.0 Hz, allylic CH_2), 2.82 (1 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 4.86 (1 H, dm, *J* 6.0 Hz, 4-H), and 5.96 (1 H, dt, *J* 1.2 and 1.2 Hz, 2-H).

Similar treatment of the dimethyl-t-butylsilyl ether (17) (13 mg, 0.05 mmol) gave the hydroxy-cyclopentenone (18) (6 mg, 81%).

3-Butyl-5,5-dichloro-4-tetrahydropyran-2-yloxycyclopent-2-enone (11).—The 3-iodocyclopentenone (7) (188.5 mg, 0.5 mmol) in tetrahydrofuran (1 ml) was added to lithium butyl(phenylthio)cuprate [prepared as detailed above from (phenylthio)copper (108 mg) and n-butyl-lithium (1.5M, 0.42 ml)] in tetrahydrofuran (3 ml) at −78 °C. After 0.5 h at that temperature, the mixture was allowed to warm and then maintained at −10 °C for a further 0.5 h before quenching (methanol, aqueous ammonium chloride) as described earlier.[15a] Chromatographic purification of the product [silica gel (10 g), petrol–ether (6 : 1)] gave the *3-butyl-5,5-dichlorocyclopentenone* (11) in two diastereoisomeric forms; a *faster-moving isomer* (37 mg, 24%) an oil (Kugelrohr, b.p. 100 °C at 0.01 mmHg) (Found: C, 54.55; H, 6.35; Cl, 23.1. $C_{14}H_{20}Cl_2O_3$ requires C, 54.75; H, 6.55; Cl, 23.1%); $\nu_{max.}$ 1 740 cm^{-1}; δ 0.96 (3 H, t, *J* 7.0 Hz, Me), 1.2—2.1 (10 H, m, CH_2), 2.56 (2 H, td, *J* 6.0 and 1.5 Hz, allylic CH_2), 3.4—4.2 (2 H, m, CH_2O), 5.19 (2 H, m, OCHO and 4-H), and 6.07 (1 H, dt, *J* 1.5 and 1.5 Hz, 2-H): and a *slower-moving isomer* (50 mg, 33%) as needles from aqueous methanol, m.p. 131—138 °C (Found: C, 54.9; H, 6.65%); $\nu_{max.}$ 1 740 cm^{-1}; δ 0.95 (3 H, t, *J* 7.0 Hz, Me), 1.2—2.1 (10 H, m, CH_2), 2.47 (2 H, td, *J* 6.0 and 1.5 Hz, allylic CH_2), 3.4—4.4 (2 H, m, CH_2O), 4.99 (2 H, m, OCHO and 4-H), and 6.06 (1 H, dt, *J* 1.5 and 1.5 Hz, 2-H).

Similar treatment of the pure diastereoisomer, m.p. 115—116 °C, of the 3-iodocyclopentenone (7) gave the faster-moving diastereoisomer of (11) (63%).

Dechlorination of 3-Butyl-5,5-dichloro-4-tetrahydropyran-2-yloxycyclopent-2-enone (11).—To the oily diastereoisomer of the 3-butyl-5,5-dichlorocyclopentenone (11) (156 mg, 0.5 mmol) in acetone (10 ml) at 0 °C and under carbon dioxide was added an aqueous solution (15 ml) of chromium(II) chloride [19] at 0 °C. After 15 min the solution was diluted with water (10 ml) and extracted with ether (4 × 10 ml). The combined ether extracts were washed with aqueous sodium chloride, dried ($MgSO_4$), and evaporated to afford an oil (109 mg). Chromatography [silica gel (10 g), petrol–ether (1 : 1)] then yielded *3-butyl-4-tetrahydropyran-2-yloxycyclopent-2-enone* (16) (80 mg, 88%) as a single diastereoisomer, an oil (Kugelrohr, b.p. 95 °C at 0.05 mmHg) (Found: C, 70.85; H, 9.1. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%); $\nu_{max.}$ 1 720 cm^{-1}; δ 0.96 (3 H, t, *J* 7.0 Hz, Me), 1.2—2.1 (10 H, m, CH_2), 2.28 (1 H, dd, *J* 18.0 and 3.0 Hz, 5-H *trans* to 4-H), 2.51 (2 H, br t, *J* 7.0 Hz, allylic CH_2), 2.71 (1 H, dd, *J* 18.0 and 6.0 Hz, 5-H *cis* to 4-H), 3.60 and 3.94 (each 1 H, m, CH_2O), 4.73 (1 H, br s, OCHO), 4.94 (1 H, ddd, *J* 6.0, 3.0, and 1.3 Hz, 4-H), and 5.98 (1 H, dt, *J* 1.3 and 1.3 Hz, 2-H).

1-Butyl-4-(dimethyl-t-butylsilyloxy)-3-chlorocyclopent-2-en-1-ol (25).—n-Butyl-lithium in hexane (1.4M, 0.393 ml) was added dropwise to 3-chloro-4-(dimethyl-t-butylsilyloxy)-cyclopent-2-enone (20) (123 mg, 0.5 mmol) in tetrahydrofuran (2 ml) at 0 °C. After 1 h at 0 °C the bright yellow solution was poured into aqueous ammonium chloride (5 ml) and extracted with ether (3 × 10 ml). Evaporation of the washed (water) and dried ($MgSO_4$) solvent gave an oil (172 mg) which by g.l.c. and ^1H n.m.r. analysis consisted of 90% of one diastereoisomer of the *alcohol* (25); δ 0.12 (6 H, s, $SiMe_2$), 0.90 (12 H, br s, t-Bu and CH_2Me), 1.1—1.7 (6 H, m, CH_2), 1.84 (1 H, dd, *J* 14.0 and 4.0 Hz, 5-H *trans* s, $SiMe_2$), 0.90 (12 H, br s, t-Bu and CH *Me*), 1.1—1.7 (6 H, m, CH_2), 1.84 (1 H, dd, *J* 14.0 and 4.0 Hz, 5-H *trans* to 4-H), 2.48 (1 H, dd, *J* 14.0 and 7.0 Hz, 5-H *cis* to 4-H), 3.70 (1 H, br s, OH), 4.46 (1 H, dd, *J* 7.0 and 4.0 Hz, 4-H), and 5.82 (1 H, s, 2-H); *m/e* 288/286 ($M^+ - H_2O$), 249/247 (M^+ — Bu), 231/229 ($M^+ - H_2O$ — Bu).

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