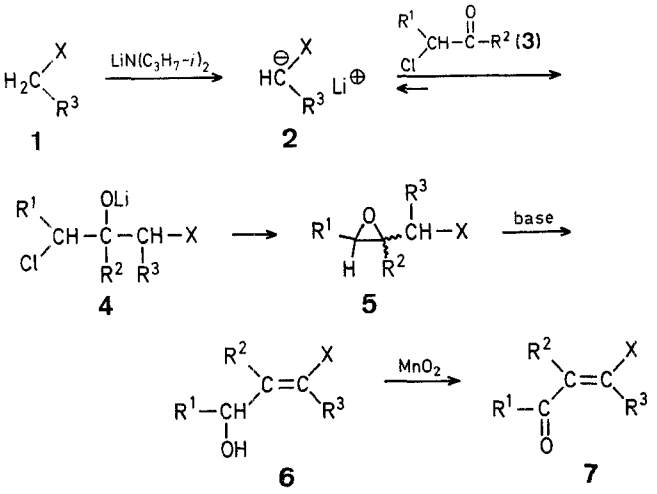
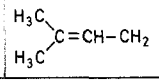


4-7	R^1	R^2	R^3	X	4-7	R^1	R^2	R^3	X
a	H	CH_3	H	−CN	f		CH_3	H	−CN
b	C_2H_5	H	H	−CN	g	H	CH_3	H	$-COOC_2H_5$
c	C_2H_5	H	C_2H_5	−CN	h	C_2H_5	H	H	$-COOC_2H_5$
d	CH_3	CH_3	H	−CN	i	CH_3	CH_3	H	$-COOC_2H_5$
e		CH_3	H	−CN	j	CH_3	CH_3	CH_3	$-COOC_2H_5$

Scheme A

A New Synthesis of γ-Hydroxy- and γ-Oxo-α,β-unsaturated Esters and Nitriles

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In connection with other synthetic work, we were interested in preparing γ-hydroxy-unsaturated esters and nitriles. These compounds are valuable intermediates in the synthesis of butenolides[1], furans[2], and some other natural products[3,4]. There is no general route to synthesise such substrates; recent methods based on the rearrangement of allylic sulphoxides are not regioselective[5] and are difficult to reproduce[6].

We report in this paper a convenient and general method for the preparation of γ-hydroxy-α,β-unsaturated esters and nitriles based on the condensation of a nitrile or ester carbanion with an α-chloro carbonyl compound followed by a rearrangement. The γ-oxo compounds **7** are obtained by oxidation of the γ-hydroxy compounds **6** (Scheme **A**).

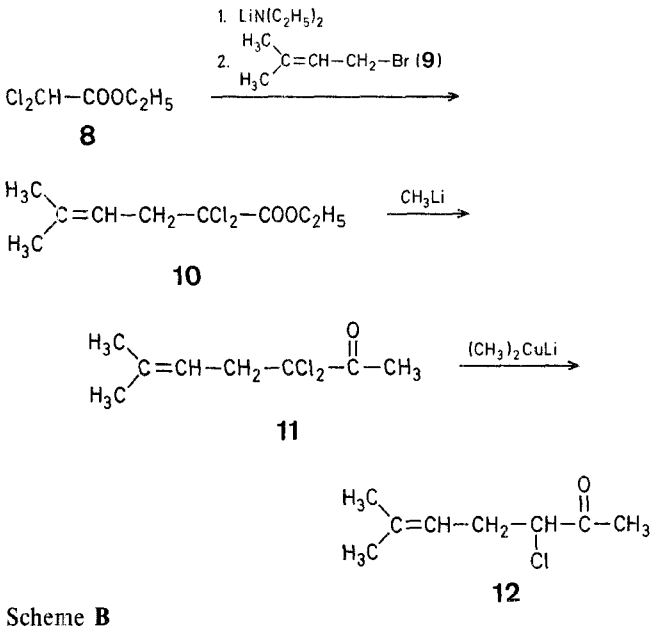
The reaction of an α-chloro aldehyde (**3**; R^2 = H) or an α-chloro ketone (**3**; R^2 = alkyl) with the carbanion **2** derived from an ester or a nitrile **1** gives a chlorohydrin **4**, or epoxide **5** after hydrolysis. In contrast to the condensation of organometallic compounds with α-chloro ketones, which is a stereoselective process[7] at low temperature, we observed the formation of several isomers. However, when the temperature is raised, cyclisation occurs and, due to thermodynamic control, only one epoxide **5** is isolated after hydrolysis (with R^3 = H). The epoxides are not always stable and are isomerised to alcohols **6**. If the reaction mixture is basic enough, this isomerisation takes place spontaneously before hydrolysis.

In the case of nitriles, tetrahydrofuran is not basic enough to induce such a reaction, but addition of one equivalent of hexamethylphosphoric triamide to the reaction mixture allows the isomerisation to be complete within a few hours at room temperature (Table 1). Similar isomerisations of epoxides into allylic alcohols were previously reported[8], however, they are never spontaneous and require the use of strong bases.

Esters are more difficult to transform especially when there is an α-substituent present. However, by increasing the concentration of hexamethylphosphoric triamide, the isomerisation sometimes becomes possible when R^3 = H. With R^3 = alkyl, the isomerisation is really slower and it is better to isolate the epoxide and to isomerise it with sodium ethoxide in ethanol in order to obtain satisfactory results (Table 1). The rearrangement affords the more stable thermodynamic isomer (*E*)-**6** (R^3 = H). With a methyl or ethyl substituent in the α-position, the (*E*)-isomers are normally formed. However, sometimes the formation of butenolides derived from (*Z*)-isomers are observed. For higher homologues, the reaction frequently affords a mixture of (*Z*)- and (*E*)-products.

The α-chloro aldehydes used are prepared according to the literature procedure[9] by chlorination of aldehydes. As the regioselective chlorination of ketones is not always satisfactory, the α-chloro ketones are prepared from *gem*-dichloro ketones[10,11] by dehalogenation with lithium dimethylcuprate[12]. The synthetic sequence is illustrated for the α-chloro ketone **12** in Scheme **B**.

This convenient synthesis of γ-hydroxy unsaturated compounds gives access to the corresponding γ-oxo unsaturated esters and nitriles. These compounds, which are very valuable synthetic intermediates[13], are difficult to obtain by other methods[14]. A simple oxidation of the allylic hydroxy function of **6** with activated manganese dioxide affords the oxo compounds **7** in nearly quantitative yields (Scheme **A**, Table 2). The reaction is very fast and clean and compounds **7** are iso-



Scheme **B**

lated by simple filtration of the manganese salt. We are currently investigating the synthetic possibilities of these substrates.

All reactions are performed under argon. Products are purified by flash chromatography[15] (Kiesel gel 60 Merck; 0.040–0.063 mm; solvent: hexane/ethyl acetate, increasing the proportion of ethyl acetate from 10% to 50%) and analysed by gas chromatography (10% SE 30, 3 m column or CP Sil 5, 40 m capillary column), thin layer chromatography (silica gel 60 F 254 on aluminium sheets), and distillation. ^{1}H-N.M.R. spectra are recorded on a Bruker WP 80 or on a Cameca TSN 250. Deuterochloroform is used as solvent with tetramethylsilane as internal standard. Mass spectra are recorded on a Nermag R10-10 (fitted with a CPV-mass coupling; column: CP Sil 5, 40 m). I.R. spectra are recorded on a Perkin-Elmer 599 spectrophotometer. Except for 3-chloro-6-methyl-5-hepten-2-one and 2-chloro-1-phenyl-3-propanone[16], all other α-chloro ketones used are commercially available.

3-Chloro-6-methyl-5-hepten-2-one (12):

Ethyl 2,2-Dichloro-5-methyl-4-hexenoate **(10):** Lithium diethylamide (0.11 mol) is prepared by stirring a suspension of lithium (0.76 g, 0.11 mol) in a solution of anhydrous diethylamine (8.8 g, 0.12 mol), anhydrous benzene (20 ml), and hexamethylphosphoric amide (20 ml) at room temperature until all metal has disappeared. The reaction mix-

Table 1. Compounds **6** prepared

Product	Yield [%]	b.p. [°C]/torr	Molecular formula[a] or reference	R_f [ethyl acetate/hexane (1:1)]	I.R. (neat) ν [cm^{-1}]	M.S. *m/e* (relative intensity %)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6a	82	70°/1	[17]	0.37	3460, 2210	97 (8), 82 (32), 69 (100)	2.05 (s, 1H); 4.2 (s, 2H); 5.6 (s, 2H)
6b	67	77°/1	C_6H_9NO (111.1)	0.43	3470, 3060, 2215, 1640	110 (1), 82 (71), 55 (100)	0.95 (t, 3H, J=8 Hz); 1.6 (m, 2H); 4.2 (m, 1H); 5.7 (AB, 1H, J=16 Hz); 6.8 (AB, 1H, J=17 Hz)
6c	58	82°/0.1	$C_8H_{13}NO$ (139.2)	0.48	3420, 2210, 1635	110 (8), 96 (33), 82 (100)	0.95 (t, 3H, J=8 Hz); 1.1 (t, 3H, J=8 Hz); 1.5 (m, 2H); 2.3 (q, 2H, J=8 Hz); 4.3 (m, 1H); 6.22 (d, 1H, J=10 Hz)
6d	85	74–75°/0.1	C_6H_9NO (111.1)	0.49	3450, 2210, 1635	110 (5), 96 (38), 67 (100), 58 (15)	1.3 (d, 3H, J=8 Hz); 1.95 (s, 3H); 4.0 (m, 1H); 5.3 (s, 1H)
6e	87	112°/0.2	$C_{10}H_{15}NO$ (165.2)	0.49	3470, 2210, 1630	165 (1), 97 (45), 69 (100)	1.7 (s, 3H); 1.8 (s, 3H); 2.1 (s, 3H); 2.4 (m, 2H); 4.22 (t, 1H, J=6 Hz); 5.15 (t, 1H, J=7 Hz); 5.6 (s, 1H)
6f	51	123/0.1	$C_{11}H_{11}NO$ (173.2)	0.50	3420, 2220	173 (45), 158 (20), 130 (22), 105 (30), 77 (100)	1.84 (s, 3H); 5.05 (s, 1H); 5.75 (s, 1H); 7.35 (s, 5H)
6g	55[b]	100°/1	[18]	0.36	3460, 1700, 1640	144 (14), 126 (26), 115 (40), 98 (100)	5.1 (t, 3H, J=7 Hz); 2.06 (s, 3H); 3.37 (s, 1H); 4.12 (s, 2H); 4.2 (q, 2H, J=7 Hz); 5.97 (s, 1H)
6h	51	78°/0.1	[19]	0.48	3450, 1705, 1650	129 (100), 113 (52), 101 (127), 83 (85), 67 (48)	1.0 (t, 3H, J=7 Hz); 1.3 (t, 3H, J=7 Hz); 1.5 (m, 2H); 3.27 (s, 1H); 4.22 (q, 2H, J=7 Hz); 6.05 (d, 1H, J=16 Hz); 7.0 (AB, 1H, J=16 Hz)
6i	40[b]	72–75°/0.1	$C_8H_{14}O_3$ (158.2)	0.45	3420, 1705, 1645	158 (1), 140 (19), 125 (80), 87 (75), 64 (100)	1.25 (d, 3H, J=6 Hz); 1.27 (t, 3H, J=7 Hz); 2.12 (s, 3H); 4.1 (m, 1H); 4.17 (q, 2H, J=7 Hz); 5.97 (s, 1H)
6j	49[b,c]	79–80°/0.1	$C_9H_{16}O_3$ (172.2)	0.38	3450, 1715, 1630	172 (10), 143 (100)	1.24 (d, 3H, J=6 Hz); 1.32 (t, 3H, J=7 Hz); 1.86 (s, 3H), 1.94 (s, 3H); 3.86 (s, 1H); 4.24 (q, 2H, J=7 Hz); 4.82 (q, 1H, J=6 Hz)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.23, N ±0.2 (Exception: **6e**, C −1.29%).

[b] The intermediate epoxides are isolated.

[c] The isomerisation affords a mixture of (*E*)-isomer and butenolide in the ratio 85:15.

Table 2. Compounds 7 prepared

Product[a]	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	R_f (ethyl acetate/hexane (35:65)]	I.R. (neat) ν [cm^{-1}]	M.S. *m/e* (relative intensity, %)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
7a	87	100°/18	—[20]	0.38	2220, 1720	95 (25), 67 (100), 66 (96)	2.15 (s, 3H); 6.25 (s, 1H); 9.60 (s, 1H)
7d	83	102°/16	—[21]	0.32	2220, 1680	109 (100), 94 (74), 66 (160)	2.20 (s, 3H); 2.42 (s, 3H); 6.22 (s, 1H)
7g	79	80°/2	70–80°/10[22]	0.43	1720, 1695, 1655	142 (5), 114 (11), 96 (73), 97 (100)	1.35 (t, 3H, J=7 Hz); 2.17 (s, 3H); 4.30 (q, 2H, J=7 Hz); 6.50 (s, 1H); 9.40 (s, 1H)
7h	81[b]	64°/0.1	—[23]	0.48	1720, 1700, 1685	156 (3), 127 (90), 98 (100)	1.12 (t, 3H, J=7 Hz); 1.32 (t, 3H, J=7 Hz); 2.70 (q, 2H, J=7 Hz); 4.30 (q, 2H, J=7 Hz); 6.90 (AB, 2H, J=17 Hz)

[a] For R^1, R^2, R^3 and X, Scheme A.

[b] Product contains 2% of (*Z*)-isomer.

ture is then cooled to −78 °C and a solution of ethyl dichloroacetate (**8**; 15.7 g, 0.1 mol) in tetrahydrofuran (50 ml) is added dropwise. After 1.5 h, 1-bromo-3-methyl-2-butene (**9**; 17.9 g, 0.12 mol) in ether (30 ml) is added and the temperature is allowed to rise to room temperature within 4 h. The reaction mixture is acidified with 3 normal hydrochloric acid (120 ml) and extracted with ether (3 × 100 ml). Removal of the solvent and distillation gives **10**; yield: 16.9 g (75%); b.p. 46–48 °C/0.01 torr.

I.R. (neat): ν = 1740, 1670 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.1 (t, 3H, J=7 Hz); 1.7 (s, 3H); 1.8 (s, 3H); 3.17 (d, 2H, J=6 Hz); 3.96 (q, 2H, J=7 Hz); 5.25 ppm (t, 1H, J=6 Hz).

3,3-Dichloro-6-methyl-5-hepten-2-one **(11):** The ester **10** (16.9 g, 0.0075 mol) dissolved in ether (60 ml) is added to an ethereal solution of methyllithium (2 equiv) at −60 °C. After stirring for 10 min, the reaction mixture is hydrolysed with 3 normal hydrochloric acid (80 ml) and extracted with ether (3 × 100 ml). Removal of the solvent and distillation affords the dichloro ketone **11**; yield: 10.8 g (81%); b.p. 81–84 °C/12 torr.

I.R. (neat): ν = 1725 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.7 (s, 3H); 1.8 (s, 3H); 2.55 (s, 3H); 3.05 (d, 2H, J=6 Hz); 5.25 ppm (t, 1H, J=6 Hz).

Conversion of **11** *to* **12:** The dichloro ketone **11** (10.8 g, 0.0061 mol) dissolved in ether (40 ml) is added to an ethereal solution of lithium dimethylcuprate (2 equiv) at −60 °C and stirred for 15 min. The reaction mixture is hydrolysed with 3 normal hydrochloric acid (80 ml) and filtered on Celite. The ether layer is separated, the solvent removed, and the residue distilled to give **12**; yield: 6.8 g (79%); b.p. 72–74 °C/12 torr.

I.R. (neat): ν = 1715 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.65 (s, 3H); 1.75 (s, 3H); 2.32 (s, 3H); 2.62 (m, 2H); 4.2 (t, 1H, J=6 Hz); 5.12 ppm (t, 1H, J=7 Hz).

γ-Hydroxy-α,β-unsaturated Esters and Nitriles 6; General Procedure: The nitrile or ester **1** (0.01 mol) in tetrahydrofuran (10 ml) is added to lithium diisopropylamide (0.011 mol) prepared from diisopropylamine (1.1 g, 0.011 mol) and butyllithium (1.5 normal hexane solution, 7.3 ml) at −80 °C. After stirring for 0.5 h the chloro ketone **3** (0.011 mol) in ether (10 ml) is added at the same temperature (−110 °C for chloro aldehydes). After 10 min, hexamethylphosphoric triamide (4.5 g, 0.025 mol) is added and the mixture is allowed to warm to room temperature. It is then stirred for 10–18 h until the epoxide has disappeared (monitored by G.L.C.). The reaction mixture is hydrolysed with 3 normal sulphuric acid (15 ml), extracted with ether (5 × 20 ml; continuous ether extraction is recommended for water soluble hydroxy compounds), purified by flash chromatography, and distilled (Table 1).

In the case of **6g, h**, the reaction mixture is stirred at room temperature for 2 h only. The mixture of chlorohydrin and epoxy ester is isolated after hydrolysis with 3 normal hydrochloric acid (20 ml) and extracted with ether (5 × 20 ml). The residue after removal of ether is treated at 0 °C with sodium ethoxide (1.4 g, 2 equiv) in ethanol (40 ml) for 0.5 h. The solution is hydrolysed with 1 normal hydrochloric acid (20 ml) and ethanol is removed under vacuum. After extraction with ether (5 × 20 ml), the hydroxy esters **6g, h** are purified by flash chromatography and distilled (Table 1).

γ-Oxo-α,β-unsaturated Esters and Nitriles 7; General Procedure: The γ-hydroxy alcohol **6** (0.01 mol) is stirred with activated manganese dioxide (8.7 g, 0.1 mol) in dichloromethane (75 ml) for 3 h at room temperature. The mixture is filtered, washed with dichloromethane (50 ml), and concentrated under reduced pressure. The crude products **7** are purified by flash chromatography (Table 2).

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