Convenient Syntheses of 5-Substituted 2-Hydroxybenzoates and Related Reactions

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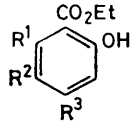
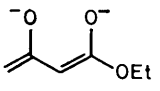
The enamine aldehydes $RC(=CHNMe_2)CHO$ (R = Et or Ph) were condensed with the bis-enolate $CH_2=C(O^-)CH=C(O^-)OEt$ to give the title aromatic compounds. Thus these products are available from the acetals $R^1CH_2CH(OR^2)_2$ ($R^1 = R^2 = Et$; $R^1 = Ph$, $R^2 = Me$) in two steps. The Vilsmeier formylation of several derivatives of butanal was examined.

RECENTLY we have described the synthesis of resorcylate (dihydroxybenzoate) derivatives *via* β-oxo-ester dianions.[1] Our manuscript unintentionally failed to mention the excellent prior publications of Weiler [2] and Hase [3] on this subject. These authors have elegantly demonstrated the application of β-oxo-esters in the rational construction of aromatic ring systems. Alternatively, Chan [4] has utilised 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene and related units as aromatic ring precursors. Herein we report syntheses of ethyl 5-ethyl- and 5-phenyl-2-hydroxybenzoates (1a and b) by a similar use [2,3] of dianions.

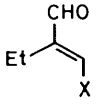


(1)

a; $R^1 = R^3 = H$, $R^2 = Et$
b; $R^1 = R^3 = H$, $R^2 = Ph$
c; $R^1 = Et$, $R^2 = Me$, $R^3 = H$
d; $R^1 = H$, $R^2 = Me$, $R^3 = Et$

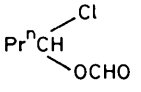


Li^+ and Na^+
(3)



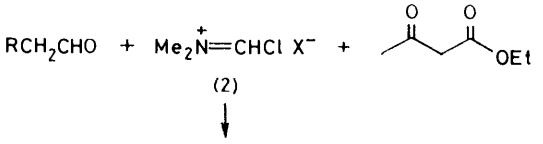
(4)

a; X = NMe_2
b; X = Cl
c; X = OEt
d; X = $CH_2-CO-CH_2-CO_2Et$
e; X = OCH_2CH_2Cl
f; X = SCH_2CH_2OH
g; X = N-$[CH_2]_4$-CH_2
h; X = SCH_2CH_2OAc



(5)

We considered that an attractive, and potentially concise route to the phenol derivatives (1) should be available *via* the condensation of an aldehyde with *N*-chloromethylene-*N*,*N*-dimethylammonium chloride (2a) and ethyl 3-oxobutanoate (Scheme). The realisation of this proposal requires the conversion of the aldehyde into a malonaldehyde derivative, followed by reaction with the bis-enolate form of ethyl 3-oxobutanoate (3). Arnold [5] has described the preparation of 2-(dimethylaminomethylene)butanal (4a) from butanal or 1,1-diethoxybutane and the Vilsmeier reagent (2b). In our



a; X = Cl
b; X = Cl_2PO_2

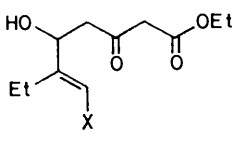
SCHEME

hands the Arnold procedures gave the enal (4a) contaminated by the known [5] enals (4b and c) and/or 1-chloro-1-formyloxybutane (5) (*see later*). Herein (see Experimental section) we describe a satisfactory procedure for the preparation of the enal (4a) in 51% yield from 1,1-diethoxybutane. The enal (4a) reacted with phosphoryl chloride to give 2-chloromethylenebutanal (4b) [5] (77%). Alternatively, 1,1,3,3-tetraethoxy-2-ethylpropane [6] and thionyl chloride gave the same enal (4b) (63%).

The dianion (3) condensed with the enal (4b) to give the 1,2-adduct (6) in 68% yield. Subsequent dehydration using thionyl chloride gave the dienone (7) (68%). On refluxing with pyrrolidine in dioxan, the dienone (7) gave ethyl 5-ethyl-2-hydroxybenzoate (1a) in 82% yield. Clearly Vilsmeier formylation and β-oxo-ester chemistry provide a route, albeit circuitous, to a substituted phenol. As a shorter alternative, the dianion (3) condensed with 2-(dimethylaminomethylene)butanal (4a) to give, on acidification, the phenol (1a) in 37% yield (of isolated product; 61% by g.l.c.).

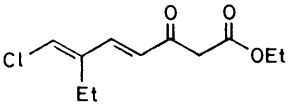
In the same way the condensation of the dianion (3)

with 3-dimethylamino-2-phenylpropenal (8) [7] gave ethyl 2-hydroxy-5-phenylbenzoate (1b) in 64—77% yield. Thus the phenols (1a and b) are now available in two steps from the acetals (9a and b).

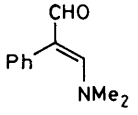


(6)

a; X = Cl
b; X = NMe_2



(7)



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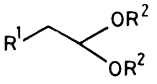
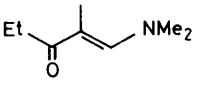


(9)

a; $R^1 = R^2$ = Et
b; R^1 = Ph, R^2 = Me



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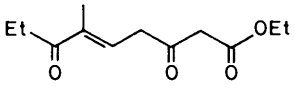

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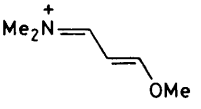

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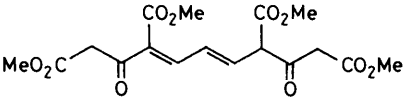

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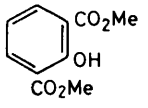
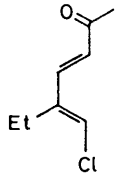


(14)

Although the dianion (3) and the enal (4b) gave only the 1,2-adduct, the condensation between (4a) and (3) may have furnished initially either the 1,2-adduct (6b) or the 1,4-adduct (4d). In order to clarify this mechanistic point the condensation of the dianion (3) with the enone (10) was examined. Since ethyl 2-ethyl-6-hydroxy-3-methylbenzoate (1c), but not the isomeric phenol (1d), was formed the initial condensation must have involved 1,4-attack *via* the adduct (11).

As an alternative to the dianion (3), dimethyl 3-oxopentanedioate was examined. The salt (12),[8] available by methylation of 3-dimethylaminoprop-2-enal,[8] was condensed with dimethyl 3-oxopentanedioate using methanolic sodium methoxide to give the dienetetracarboxylate (13).* However, when triethylamine was used as base, dimethyl 2-hydroxybenzene-1,3-dicarboxylate (14) [9] was formed, albeit in poor yield (14%). The reaction was not further explored.

As a potential route to 4-ethylphenol the condensation of the enal (4b) with acetone was considered. Thus the enal (4b) was added to diethyl 2-oxopropylphosphonate to give the expected dienone (15) (62%). Inverse addition gave the dienone (15) (20%) and the tetraenone (16) (14%). All attempts to aromatise the dienone (15) using tin(IV) chloride, boron trifluoride–ether complex, trifluoroacetic acid, hydrogen chloride in dichloromethane, or *N,N,N',N'*-tetramethylguanidine were unsuccessful.



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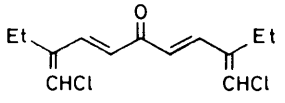

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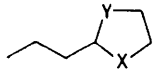
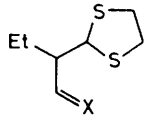


(17)

a; X = Y = O
b; X = Y = S
c; X = O, Y = S



(18)

a; X = O
b; X = $CHCO_2Et$

While investigating the synthesis of the phenols (1a—c) we had occasion to examine the Vilsmeier formylation of several butanal derivatives. On reaction with *N*-chloromethylene-*N,N*-dimethylammonium chloride (2a), butanal, 2-propyl-1,3-dioxolan (17c),[9] -1,3-dithiolan (17b),[10] and -1,3-oxathiolan (17a) [11] gave, respectively, 1-chloro-1-formyloxybutane (tentative assignment) (5) (61%), the enal (4e) (64%), the dithiolan derivative (18a) (77%), and the enal (4f) (52%). Presumably the butanal derivatives differed on account of the greater lability of any *N*-(alkylthiomethylene)-*N,N*-dimethylammonium salts or thioformate intermediates in comparison with the oxygen analogues. Reaction of the enal (4e) with piperidine cleanly gave the enamine (4g) (84%), whereas acetylation of the enal (4f) gave the derived acetate (4h).

The dithiolan derivative (18a) was investigated as a phenol precursor. Although conversion into the unsaturated ester (18b) was readily carried out in 74% yield, subsequent attempted hydrolysis of the dithiolan ring gave only intractable mixtures.

The condensation of enals with the dianion (3) clearly provides a convenient synthesis of phenol derivatives.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r., n.m.r., and u.v. spectra were recorded for Nujol mulls (solids) or films (liquids), for solutions in deuteriochloroform, and for solutions in ethanol, respectively. Solvents were

* Formula (13) is not intended to represent the stereochemistry about the diene system.

purified according to standard procedures.[12] Thin-layer chromatography was carried out on Merck Kieselgel GF_{254}; developing solvents are recorded in parentheses. Silica refers to Merck Silica Gel 60 (0.040—0.063 mm). Organic extracts were dried over sodium sulphate.

2-(*Dimethylaminomethylene*)*butanal* (4a).— *N*,*N*-Dimethylformamide (73 g) in dichloromethane (100 ml) was added dropwise with stirring to phosphoryl chloride (164 g) in dichloromethane (100 ml) at 0 °C under nitrogen. The mixture was stirred overnight at room temperature, then evaporated under reduced pressure. The residue was suspended in 1,2-dichloroethane (100 ml) and cooled to 0 °C, and *N*,*N*-dimethylformamide (73 g) and 1,1-diethoxybutane (73 g) in dry 1,2-dichloroethane (100 ml) were added dropwise in sequence. The mixture was allowed to warm up to room temperature, stirred for 1 h, refluxed for 1 h, and cooled, and the resultant brown mixture was added to anhydrous potassium carbonate (100 g) and ice (300 g). Further solid and saturated aqueous potassium carbonate were added (to pH 10). Aqueous dimethylamine (0.5 mol) was added and the mixture was refluxed for 1 h. 1,2-Dichloroethane was removed by distillation and the residue heated at 95—100 °C for 1 h. On cooling the mixture was extracted with diethyl ether and ethyl acetate; the organic phase was dried (K_2CO_3), evaporated, and distilled to give 2-(dimethylaminomethylene)butanal (4a) (32.4 g, 51%), b.p. 128° at 6 mmHg (lit.,[5] 80° at 0.1 mmHg); $\nu_{max.}$ 2 960, 2 930, 1 605, 1 400, 1 300, 1 190, 1 125, and 1 060 cm^{-1}; δ 1.02 (3 H, t, *J* 7.5 Hz), 2.42 (2 H, q, *J* 7.5 Hz), 3.17 (6 H, s), 6.48 (1 H, s), and 8.87 (1 H, s); *m*/*z* 127 (M^+) and 112 (100%); g.l.c. purity 92%.

2-(*Chloromethylene*)*butanal* (4b).—(*a*) Phosphoryl chloride (36 g) in dichloromethane (100 ml) was added dropwise to 2-dimethylaminomethylene)butanal (4a) (25.4 g) in dichloromethane (200 ml) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 1 h, then evaporated. The residue was added to ice (200 g) and diethyl ether (100 ml). After stirring at room temperature the aqueous phase was separated and extracted with diethyl ether (×2). The combined organic phase was washed with water (×2), 40% aqueous sodium hydrogen carbonate and brine, dried, evaporated, and distilled to give 2-(chloromethylene)butanal (4b) (18 g, 77%), b.p. 49—50° at 20 mmHg (lit.,[5] 50—55° at 22 mmHg); $\nu_{max.}$ 2 950, 2 905, 1 685, 1 600, 1 455, 1 340, 1 295, 1 175, 1 065, and 1 050 cm^{-1}; δ 1.03 (3 H, t, *J* 7.5 Hz), 2.45 (2 H, q, *J* 7.5 Hz), 7.13 (1 H, s), and 9.47 (1 H, s); *m*/*z* 118 and 120 (M^+) and 53 (100%); g.l.c. purity 96%.

(*b*) Thionyl chloride (23.8 g) was added dropwise to 1,1,3,3-tetraethoxy-2-ethylpropane [6] (12.4 g) in dichloromethane (75 ml). Reflux was maintained until sulphur dioxide evolution ceased (6 h), and the mixture was cooled, washed with water and saturated aqueous sodium hydrogen carbonate (to pH 7), dried, evaporated, and distilled to give 2-(chloromethylene)butanal (4b) (3.7 g, 63%).

Ethyl 6-(*Chloromethylene*)-5-*hydroxy*-3-*oxo*-*octanoate* (6a).—Ethyl 3-oxobutanoate (1.17 g) was added dropwise to sodium hydride (50% oil dispersion; 483 mg) in tetrahydrofuran (THF) (20 ml) under nitrogen. After 10 min at 0 °C n-butyl-lithium (1.5M; 6.6 ml) was added dropwise. After 10 min at 0 °C, 2-(chloromethylene)butanal (4b) (1.06 g) in THF (2 ml) was added and the mixture stirred at room temperature for 1 h. The mixture was quenched with conc. hydrochloric acid, diluted with water, and extracted with diethyl ether. The organic phase was washed with brine, dried, and evaporated, and the residue was separated by p.l.c. (diethyl ether–light petroleum 3 : 7) and distillation to give *ethyl* 6-(*chloromethylene*)-5-*hydroxy*-3-*oxo*-*octanoate* (6a) (1.51 g, 68%), b.p. 110° at 0.1 mmHg; $\nu_{max.}$ 3 800, 2 860, 1 740, 1 714, and 1 635 cm^{-1}; $\lambda_{max.}$ (EtOH) 245 nm (ε 1 500); δ 1.06 (3 H, t, *J* 8 Hz), 1.24 (3 H, t, *J* 7 Hz), 2.07 (2 H, q, *J* 8 Hz), 2.67 (2 H, d, *J* 6 Hz), 3.35 (2 H, s), 4.13 (2 H, q, *J* 7 Hz), 4.5 (1 H, t, *J* 6 Hz), and 6.08 (1 H, s); *m*/*z* 230 (M^+ − 18) and 83 (100%) (Found: C, 53.0; H, 7.1. $C_{11}H_{17}ClO_4$ requires C, 53.1; H, 6.9%).

Ethyl 6-(*Chloromethylene*)-3-*oxo*-*oct*-4-*enoate* (7).—Thionyl chloride (357 mg) in benzene (1 ml) was added to the hydroxy-ester (6a) (496 mg) in benzene (2 ml). After 5 h at room temperature the mixture was added to saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether. After drying, evaporation and p.l.c. (diethyl ether–light petroleum 1 : 19) gave *ethyl* 6-(*chloromethylene*)-3-*oxo*-*oct*-4-*enoate* (7) (312 mg, 68%), b.p. 95—97° at 0.1 mmHg; $\nu_{max.}$ 1 740, 1 690, 1 640, 1 600, 1 572, 1 301, and 918 cm^{-1}; $\lambda_{max.}$ (EtOH) 288 nm (ε 19 500); δ 1.08 (3 H, t, *J* 8 Hz), 1.33 (3 H, t, *J* 7 Hz), 2.43 (2 H, q, *J* 8 Hz), 3.57 (2 H, s), 4.16 (2 H, q, *J* 7 Hz), 5.83, 6.27 (1 H, 2d, *J* 16 Hz), 6.3 and 6.47 (1 H, 2s), and 6.9 and 7.07 (1 H, 2d, *J* 16 Hz); *m*/*z* 230 (M^+) and 195 (100%) (Found: C, 57.45; H, 6.65. $C_{11}H_{15}ClO_3$ requires C, 57.25; H, 6.55%).

Ethyl 5-*Ethyl*-2-*hydroxybenzoate* (1a).—(*a*) Pyrrolidine (36 mg) in dioxan (1 ml) was added to the dienone (7) (115 mg) in dioxan (1 ml). After 2 h under reflux the mixture was cooled, added to 10% hydrochloric acid and extracted with diethyl ether. The organic phase was washed with brine, dried, evaporated, and distilled to give *ethyl* 5-*ethyl*-2-*hydroxybenzoate* (1a) (79 mg, 82%), b.p. 130—132° at 0.1 mmHg; $\nu_{max.}$ 3 200, 2 920, 1 673, 1 618, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 238 (ε 5 700) and 313 nm (2 500); δ 1.2 (3 H, t, *J* 7 Hz), 1.4 (3 H, t, *J* 7 Hz), 2.58 (2 H, q, *J* 7 Hz), 4.46 (2 H, q, *J* 7 Hz), 6.93 (1 H, d, *J* 7 Hz), 7.31 (1 H, dd, *J* 7 and 2 Hz), and 7.65 (1 H, d, *J* 2 Hz); *m*/*z* 194 (M^+) and 148 (100%) (Found: C, 67.8; H, 7.4. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%).

(*b*) Ethyl 3-oxobutanoate (3.38 g) in THF (10 ml) and, after 30 min, n-butyl-lithium (2.35M; 11 ml) were added dropwise with stirring to sodium hydride (50% in oil; 1.3 g) in THF (50 ml) at 0 °C under nitrogen. After 30 min, 2-(dimethylaminomethylene)butanal (4a) (2.54 g) in THF (10 ml) was added dropwise. The resultant red solution was stirred overnight at room temperature. Hydrochloric acid (0.5M; 10 ml), conc. hydrochloric acid (10 ml), and diethyl ether (100 ml) were added in sequence. The aqueous phase was re-extracted with diethyl ether (×3) and the combined organic phase was washed with brine, dried, and evaporated to give a crude product (5.17 g). Chromatography of a sample (2.0 g) on silica (70 g) gave (eluant hexane–ethyl acetate 1 : 1) ethyl 5-ethyl-2-hydroxybenzoate (1a) (61% by g.l.c.) (isolated pure 0.56 g, 37%), identical (g.l.c. retention time, i.r., ^1H n.m.r., and mass spectra) with the previous sample.

Ethyl 2-*Hydroxy*-5-*phenylbenzoate* (1b).—3-Dimethylamino-2-phenylpropenal [7] (8) was prepared from 1,1-dimethoxy-2-phenylethane (9b), *N*,*N*-dimethylformamide, and phosphoryl chloride (Found: C, 74.5; H, 7.35; N, 8.1. Calc. for $C_{11}H_{13}NO$: C, 75.4; H, 7.45; N, 8.0%). As in the foregoing example, sodium hydride (50% in oil; 1.2 g), ethyl 3-oxobutanoate (3.12 g), n-butyl-lithium (2.35M; 10.5 ml), and 3-dimethylamino-2-phenylpropenal (8) (3.5 g) gave a crude product (6.92 g). Bulb-to-bulb distillation of

a sample (1.5 g) gave ethyl 2-hydroxy-5-phenylbenzoate (1b) [13] (0.82 g, 77%), g.l.c. purity 93%. Alternatively chromatography of a sample (5 g) on silica (700 g) gave (eluant hexane–ethyl acetate 19 : 1—1 : 1) ethyl 2-hydroxy-5-phenylbenzoate (16) (2.2 g, 64%), g.l.c. purity 96%, which was recrystallised from hexane; m.p. 49—50°; $\nu_{max.}$ 3 180, 2 985, 1 678, 1 604, 1 480, 1 210, and 1 093 cm^{-1}; $\lambda_{max.}$ (EtOH) 234 (ε 22 400), 259 (15 600), and 324 nm (3 200); δ 1.38 (3 H, t, *J* 7 Hz), 4.37 (2 H, q, *J* 7 Hz), 6.93 (1 H, d, *J* 8 Hz), 7.1—7.6 (5 H, m) overlapping 7.57 (1 H, dd, *J* 8.2 Hz), 7.93 (1 H, d, *J* 2 Hz), and 10.85 (1 H, s); *m/z* 242 (M^+) and 196 (100%) (Found: C, 74.25; H, 5.9. Calc. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8%).

Ethyl 2-Ethyl-6-hydroxy-3-methylbenzoate (1c).—2-(Dimethylaminomethylene)pentan-3-one [14] (10) (27%) was prepared in the usual way from 3,3-diethoxypentane, *N,N*-dimethylformamide and phosphoryl chloride. This enone (10) (7.82 g) was condensed with ethyl 3-oxobutanoate (3.12 g), sodium hydride (50% in oil; 1.20 g) and n-butyllithium (2.35M; 10.5 ml) in THF (60 ml). After 20 h the mixture was quenched with 2.5M-hydrochloric acid to pH 3 and extracted (×3) with diethyl ether. Evaporation of the organic phase gave a brown oil (4.5 g). Potassium carbonate was added (to pH 10) to the aqueous phase, which was re-extracted with diethyl ether. Evaporation of the ether layer gave a brown oil (3.0 g). Separate chromatography of samples (2.0 g) of each extract on silica (70 g) gave (eluant ethyl acetate–light petroleum 1 : 19—1 : 0) fractions containing compound (1c) (41% by g.l.c.) including one fraction (0.90 g) 95% pure by g.l.c. P.l.c. of the last fraction on silica gave pure *ethyl 2-ethyl-6-hydroxy-3-methylbenzoate* (1c) as an oil, $\nu_{max.}$ 3 500—2 900br, 2 935, 1 664, 1 601, 1 469, 1 374, 1 309, and 1 218 cm^{-1}; $\lambda_{max.}$ (EtOH) 245 (ε 1 700) and 289 nm (1 400); δ 1.2 (3 H, t, *J* 7 Hz), 1.45 (3 H, t, *J* 7 Hz), 2.27 (3 H, s), 2.93 (2 H, q, *J* 7 Hz), 4.45 (2 H, q, *J* 7 Hz), 6.77 (1 H, d, *J* 8 Hz), and 7.20 (1 H, d, *J* 8 Hz); *m/z* 208 (M^+) and 162 (100%) (Found: C, 68.95; H, 7.7. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%).

Dimethyl 4,8-Bismethoxycarbonylundeca-5,7-dienedioate (13).—3-Dimethylaminopropenal [8] (990 mg) was stirred overnight with dimethyl sulphate (1.26 g) to give the salt (12) [8] (2.2 g, 94%) as a dark oil, $\lambda_{max.}$ (EtOH) 289 nm (ε 15 500); δ 3.48 (3 H, s), 3.7 (3 H, s), 4.11 (3 H, s), 6.18 (1 H, dd, *J* 12 and 11 Hz), 8.26 (1 H, d, *J* 11 Hz), and 8.73 (1 H, d, *J* 12 Hz); *tetraphenylborate salt*, m.p. 150—151° (from ethyl acetate and light petroleum) (Found: C, 83.05; H, 7.45; N, 3.0. $C_{30}H_{32}BNO$ requires C, 83.1; H, 7.45; N, 3.25%). Sodium methoxide [from sodium (24 mg)] in methanol (1 ml) and, after 20 min, dimethyl 3-oxopentanedioate (182 mg) in methanol (1 ml) were slowly added to the sulphonate (12) (237 mg). After 24 h at room temperature and 3 days at reflux the mixture was cooled and evaporated and the residue partitioned between water and ethyl acetate. The organic phase was washed with 10% hydrochloric acid and brine, dried, and evaporated; the residue was separated by p.l.c. (benzene–diethyl ether 1 : 1) and crystallised from benzene and light petroleum to give *dimethyl 4,8-bismethoxycarbonyl-3,9-dioxoundeca-5,7-dienedioate* (13) (104 mg, 56%), m.p. 171—173°; $\nu_{max.}$ 1 745, 1 660, 1 612, 1 438, and 1 355 cm^{-1}; δ 2.13 (4 H, s, $COCH_2CO$), 3.21 (1 H, d, *J* 6 Hz, $HCCO_2Me$), 3.96 (12 H, s, OMe), 5.01 (1 H, m, CH=), 6.87 (1 H, d, *J* 7 Hz, CH=), and 8.29 (1 H, t, *J* 7 Hz, CH=); *m/z* 384 (M^+) and 320 (100%) (Found: C, 53.35; H, 4.75. $C_{17}H_{20}O_{10}$ requires C, 53.15; H, 4.7%).

Dimethyl 2-Hydroxybenzene-1,3-dicarboxylate (14).—Triethylamine (50 mg) in THF (1 ml) and dimethyl 3-oxopentanedioate (87 mg) in THF (1 ml) were added slowly in sequence to the sulphonate (12) (112 mg) in THF (1 ml) under nitrogen. After 3 days under reflux the mixture was cooled, diluted with water, and extracted with diethyl ether. The organic phase was washed with 10% hydrochloric acid and brine, dried, and evaporated, and the residue separated by p.l.c. (diethyl ether–light petroleum 3 : 7) and crystallised from benzene and light petroleum to give dimethyl 2-hydroxybenzene-1,3-dicarboxylate (14) (15 mg, 14%), m.p. 70—71° (lit.,[6] 72°); δ 3.96 (6 H, s), 6.86 (1 H, t, *J* 7 Hz), and 8.00 (2 H, d, *J* 7 Hz).

5-(Chloromethylene)hept-3-en-2-one (15).—Diethyl 2-oxopropylphosphonate (1.2 g) in 1,2-dimethoxyethane (1 ml) was added with stirring to sodium hydride (50% in oil; 305 mg) in 1,2-dimethoxyethane (3 ml). When hydrogen evolution ceased the mixture was added to 2-(chloromethylene)butanal (4b) (720 mg) in 1,2-dimethoxyethane (1 ml). After stirring overnight the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with brine, dried, and evaporated, and the residue separated by p.l.c. (diethyl ether–light petroleum 1 : 4) to give *3,9-bischloromethyleneundeca-4,7-dien-6-one* (16) (237 mg, 24%), m.p. 80—81°; $\nu_{max.}$ 2 940, 2 880, 1 740, 1 700, 1 605, 1 320, and 980 cm^{-1}; $\lambda_{max.}$ (EtOH) 313 nm (ε 6 300); δ 1.06 (6 H, t, *J* 7 Hz), 2.46 (4 H, q, *J* 7 Hz), 6.4 (2 H, s, CHCl), 6.41 (2 H, d, *J* 16 Hz), and 7.66 (2 H, d, *J* 16 Hz); *m/z* 258 (M^+) and 223 (100%) (Found: C, 60.25; H, 6.4. $C_{13}H_{16}Cl_2O$ requires C, 60.25; H, 6.2%); and *5-(chloromethylene)hept-3-en-2-one* (15) (200 mg, 20%), b.p. 50° at 0.5 mmHg; $\lambda_{max.}$ (EtOH) 276 nm (ε 11 700); δ 1.07 (3 H, t, *J* 7 Hz), 2.3 (3 H, s), 2.46 (2 H, q, *J* 7 Hz), 6.17 (1 H, d, *J* 16 Hz), 6.47 (1 H, s, CHCl), and 7.03 (1 H, d, *J* 16 Hz); *m/z* 158 (M^+) and 123 (100%) (Found: C, 60.3; H, 7.1; Cl, 22.6. $C_8H_{11}ClO$ requires C, 60.55; H, 7.0; Cl, 22.35%). When the reaction was repeated with the addition of the aldehyde (4b) (700 mg) to the phosphonate salt (1.34 g), the dienone (15) (678 mg, 62%) was obtained.

1-Chloro-1-formyloxybutane (5).—n-Butanal (3.6 g) in dichloromethane (5 ml) was added to *N*-chloromethylene-*N,N*-dimethylammonium chloride (2a) [from *N,N*-dimethylformamide (5.84 g) and phosgene] in dichloromethane (40 ml). After 2 h reflux and then cooling, aqueous potassium carbonate (20%; 30 ml) and ice were added. The aqueous phase was saturated with potassium carbonate (15 g) and extracted with diethyl ether. Evaporation of the combined organic phases and distillation gave an oil, possibly 1-chloro-1-formyloxybutane (5) (4.1 g, 61%), b.p. 60° at 10 mmHg; $\nu_{max.}$ 3 415, 2 824, 1 735, 1 682, and 1 355 cm^{-1}; δ 1.0 (3 H, t, *J* 6 Hz), 1.16—2.33 (4 H, m), 6.53 (1 H, t, *J* 6 Hz), and 8.06 (1 H, s); *m/z* 101 (M^+ − 35/37), 90, 73, 65, and 55 (100%).

2-(2-Chloroethoxymethylene)butanal (4e).—The acetal (17a) [9] (3.92 g) was slowly added to *N*-chloromethylene-*N,N*-dimethylammonium chloride (2a) [from *N,N*-dimethylformamide (5.84 g) and phosgene] in dichloromethane (40 ml), and the mixture refluxed overnight. After cooling the mixture was added to pH 9 buffer. The aqueous phase was saturated with potassium carbonate and extracted with diethyl ether. The combined organic phase was washed with brine, dried, and evaporated, and the residue was distilled (×2) to give *2-(2-chloroethoxymethylene)butanal* (4e) (3.5 g, 64%), b.p. 110° at 1.5 mmHg; $\lambda_{max.}$ (EtOH) 248 nm (ε 18 400); δ 1.0 (3 H, t, *J* 7 Hz), 2.25 (2 H, q, *J* 7

Hz), 3.76 (2 H, t, *J* 6 Hz), 4.4 (2 H, t, *J* 6 Hz), 6.96 (1 H, s), and 9.16 (1 H, s); *m/z* 164/162 (M^+) and 99 (100%) (Found: C, 51.55; H, 6.9. $C_7H_{11}ClO_2$ requires C, 51.7; H, 6.8%).

2-(*Piperidinomethylene*)*butanal* (4g).—Piperidine (225 mg) and 2-(2-chloroethoxymethylene)butanal (4e) (410 mg) in pyridine (1 ml) were refluxed for 2 h; the mixture was then cooled and evaporated. P.l.c. (diethyl ether–light petroleum 9 : 1) of the residue gave 2-(*piperidinomethylene*)*butanal* (4g) (344 mg, 84%) as an oil, b.p. 82—84° at 0.1 mmHg; $\nu_{max.}$ 2 952, 2 948, 2 750, and 1 594 cm^{-1}; $\lambda_{max.}$ (EtOH) 292 nm (ε 31 400); δ 1.0 (3 H, t, *J* 7 Hz), 1.66 (6 H, m), 2.38 (2 H, q, *J* 7 Hz), 3.43 (4 H, m), 6.4 (1 H, s), and 8.83 (1 H, s); *m/z* 167 (M^+) and 152 (100%) (Found: C, 71.65; H, 10.35; N, 8.2. $C_{10}H_{17}NO$ requires C, 71.85; H, 10.25; N, 8.35%).

2-(1,3-*Dithiolan*-2-*yl*)*butanal* (18a).—2-Propyl-1,3-dithiolan [11] (17b) (7.5 g) was added slowly to *N*-chloromethylene-*N*,*N*-dimethylammonium chloride (2a) [from *N*,*N*-dimethylformamide (9.17 g) and phosgene] in dichloromethane (100 ml). Subsequently anhydrous toluene-4-sulphonic acid (860 mg) was added and the mixture refluxed for 12 h. After cooling, saturated aqueous sodium hydrogen carbonate and ice were added. The organic phase was washed with brine, dried, and evaporated. Distillation gave 2-(1,3-*dithiolan*-2-*yl*)*butanal* (18a) (6.8 g, 77%), b.p. 93—95° at 0.1 mmHg; $\nu_{max.}$ 2 904, 2 828, 2 820, 1 713, 1 390, 1 140, and 980 cm^{-1}; δ 0.95 (3 H, t, *J* 7 Hz), 1.76 (2 H, m), 2.33—2.83 (1 H, m), 3.2 (4 H, s), 4.66 (1 H, d, *J* 7 Hz), and 0.73 (1 H, d, *J* 2 Hz); *m/z* 176 (M^+) and 105 (100%) (Found: C, 47.7; H, 7.0; S, 36.6. $C_7H_{12}OS_2$ requires C, 47.7; H, 6.85; S, 36.35%).

Ethyl 4-(1,3-*Dithiolan*-2-*yl*)*hex*-2-*enoate* (18b).—Propylene oxide (329 mg) in THF (1 ml) and, after 3 h, the dithiolan (18a) (500 mg) in THF (2 ml) were added with stirring to ethoxycarbonylmethyltriphenylphosphonium bromide (1.2 g) in THF (4 ml). After 2 days at room temperature the mixture was filtered and the filtrate evaporated. P.l.c. (diethyl ether–light petroleum 1 : 4) and distillation gave *ethyl* 4-(1,3-*dithiolan*-2-*yl*)*hex*-2-*enoate* (18b) (520 mg, 74%), b.p. 88—90° at 0.2 mmHg; $\nu_{max.}$ 2 924, 1 714, 1 654, 1 458, 970, and 853 cm^{-1}; δ 0.9 (3 H, t, *J* 7 Hz), 1.3 (3 H, t, *J* 7 Hz), 1.43—2.23 (3 H, m), 3.18 (4 H, s), 4.2 (2 H, q, *J* 7 Hz), 4.57 (1 H, d, *J* 7 Hz), 5.87 (1 H, d, *J* 16 Hz), and 6.83 (1 H, dd, *J* 16 and 7 Hz); *m/z* 246 (M^+) and 176 (100%) (Found: C, 53.45; H, 7.2; S, 25.95. $C_{11}H_{18}O_2S_2$ requires C, 53.6; H, 7.35; S, 26.0%).

2-(2-*Hydroxyethylthiomethylene*)*butanal* (4f).—2-Propyl-1,3-oxathiolan [11] (17c) (1.5 g) was slowly added to *N*-chloromethylene-*N*,*N*-dimethylammonium chloride (2a) [from *N*,*N*-dimethylformamide (2.04 g) and phosgene] in dichloromethane (20 ml). After 12 h at reflux the mixture was cooled and added to saturated aqueous sodium hydrogen carbonate and ice. The organic phase was washed with brine, dried, evaporated, and separated by p.l.c. (ethyl acetate–light petroleum 4 : 1) to give 2-(2-*hydroxyethylthiomethylene*)*butanal* (4f) (918 mg, 52%), m.p. 50—52° (from benzene and light petroleum); $\nu_{max.}$ 3 400, 2 940, 2 880, 2 820, 1 648, and 1 580 cm^{-1}; δ 1.0 (3 H, t, *J* 7 Hz), 2.28 (2 H, q, *J* 7 Hz), 3.06 (2 H, t, *J* 6 Hz), 3.88 (2 H, t, *J* 6 Hz), 7.31 (1 H, s), and 9.26 (1 H, s); *m/z* 160 (M^+) and 115 (100%) (Found: C, 52.45; H, 7.5; S, 20.0. $C_7H_{12}O_2S$ requires C, 52.45; H, 7.55; S, 20.0%). Acetylation with acetic anhydride in pyridine gave 2-(2-*acetoxyethylthiomethylene*)*butanal* (4h) (84%), b.p. 110° at 0.8 mmHg; $\nu_{max.}$ 2 980, 2 948, 1 742, 1 670, 1 588, 1 082, and 913 cm^{-1}; δ 1.0 (3 H, t, *J* 7 Hz), 2.1 (3 H, s), 2.17 (2 H, q, *J* 7 Hz), 3.13 (2 H, t, *J* 6 Hz), 4.32 (2 H, t, *J* 6 Hz), 7.23 (1 H, s), and 9.28 (1 H, s); *m/z* 202 (M^+) and 115 (100%) (Found: C, 53.7; H, 7.15; S, 15.65. $C_9H_{14}O_3S$ requires C, 53.45; H, 6.95; S, 15.85%).

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