Chemistry of Ketene Acetals. Part 9.† A Simple 'One-Pot' Synthesis of 4-Hydroxy-δ-lactones and 5,6-Dihydro-2-pyrones from 1,1-Dimethoxypropene and β-Oxy Aldehydes

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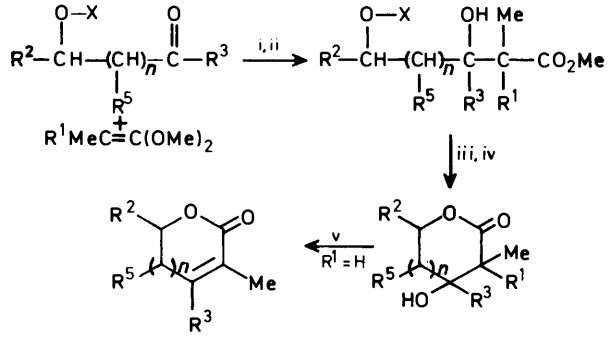
Protected β-oxy aldehydes react easily with 1,1-dimethoxypropene (**1a**) in the presence of $ZnCl_2$ to give 2,2-dimethoxyoxetanes. Hydrolysis of these oxetanes and deprotection of the latent hydroxy function in a one-pot procedure gives 4-hydroxy-δ-lactones in moderate to good yields. Starting with β-oxy aldehydes having an α-branched side chain and defined stereochemistry, δ-lactones with completely defined stereochemistry can be synthesized. Dehydration of the hydroxy lactones with concentrated sulphuric acid gives easy access to 5,6-dihydro-2-pyrones. The usefulness of this route is demonstrated in the synthesis of a simple, optically active 5,6-dihydro-2-pyrone (**37**).

δ-Lactones are versatile, synthetic intermediates and are widespread in Nature; γ-lactones occur preferentially in plants and δ-lactones in animal products.[1] Some δ-lactones are significant in insect behaviour[2] and recently there has been a lot of synthetic effort concerning the synthesis of these pheromones.[3–5] However, general synthetic routes to δ-lactones are relatively scarce and most syntheses that have been published use strongly basic conditions and yield 5,6-dihydro-2-pyrones.[6–9] A relatively mild, basic method was presented by Giese *et al.*,[10] who used radical C–C bond formation as the critical step. Paterson *et al.*[11] used the Lewis acid-catalysed reaction of ketene bis-trimethylsilyl acetals with α-chloro sulphides as the key reaction. However, the products of the latter procedure were also transformed into 5,6-dihydro-2-pyrones in order to reduce the number of diastereoisomeric products.

In previous work[12] we showed that hydroxy substituted γ-lactones can easily be obtained from ketene acetals (**1**) and α-oxygenated aldehydes or ketones (Scheme 1, $n = 0$, X = Ac). In order to extend this strategy we undertook an investigation into



Scheme 1. *Reagents:* i, cat; ii, H_3O^+; iii, deprotection of O–X; iv, H^+; v, dehydration

the synthetic applications of reactions between β-oxygenated carbonyl compounds and ketene acetals (**1**). These would give access to 4-hydroxy-δ-lactone derivatives. Elimination of the 4-hydroxy function might then allow the synthesis of substituted 5,6-dihydro-2-pyrones (Scheme 1, $n = 1$).

† Part 8. R. G. Hofstraat, H. W. Scheeren, and R. J. F. Nivard, *J. Chem. Soc., Perkin Trans. 1*, 1985, 561.

We now present a mild, acidic route to 4-hydroxy-3-methyl-δ-lactones and their corresponding 5,6-dihydro-2-pyrones based on readily available β-oxygenated aldehydes and ketene acetals.[13]

Synthesis of β-Oxygenated Aldehydes.—First, we concentrated on the synthesis of β-hydroxy aldehydes since we expected β-hydroxy ketones lacking an activating α-substituent to be unreactive.[13] Since β-hydroxy aldehydes are very labile compounds, readily dehydrating to the corresponding α,β-unsaturated aldehydes, most synthetic routes provide β-hydroxy aldehydes in a protected form. The protection of the hydroxy group is, moreover, necessary, in order to avoid reaction between the free hydroxy group and the ketene acetal (**1**). Two methods are known to us which deliver directly protected compounds in a one-step synthesis.

Tsumara *et al.*[14] described the synthesis of 3-acetoxypropanal (**2**) from propenal, acetic acid, and barium acetate *via* a Michael addition reaction. Reaction of propenal under the described conditions gave compound (**2**) in an overall yield of 43% after careful distillation. A further study of the method showed not only that sodium acetate could be used instead of barium acetate but also that the formyloxy- and propionyloxy-analogues of compound (**2**) could be similarly prepared from formic acid and propionic acid, respectively. This method enabled us to synthesize 3-acetoxybutanal (**3**) and the β-acetoxy ketone (**4**), in yields of 5 and 50—54%, respectively. 2-Methylpropenal was, however, entirely unreactive under these conditions. The low yield in the case of (**3**) and the non-reactivity of the methyl substituted propenal probably reflect the greater stability of a disubstituted over a monosubstituted double bond.

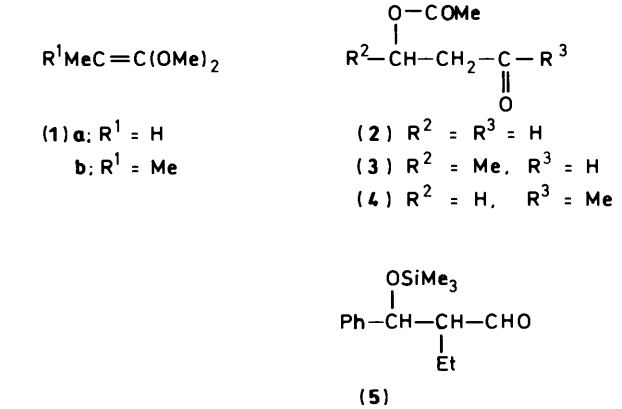
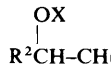
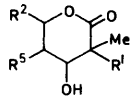
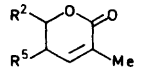


Table 1.







	R^2	R^5	X	Ketene acetal		R^1	R^2	R^5	Yield[a]	R^2	R^5	Yield[a]
(2)	H	H	Ac	(1a)	(21)	H	H	H	50	(22) H	H	30
(3)	Me	H	Ac	(1a)						(25) Me	H	28
(5)	Ph	Et	$SiMe_3$	(1a)						(27) Ph	Et	70[b]
(15)	Ph	Me	CH(Me)OEt	(1a)	(28)	H	Ph	Me	61[b]			
(15)	Ph	Me	CH(Me)OEt	(1b)	(31)	Me	Ph	Me	12[c]			
(16)	c-Hex	Me	CH(Me)OEt	(1a)	(29)	H	c-Hex	Me	40[c]			
(17)	Pr^i	Me	CH(Me)OEt	(1a)	(30)	H	Pr^i	Me	44[c]			
(35)	Me	H	CH(Me)OEt	(1a)						(37) Me	H	38

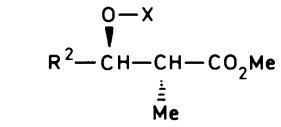
[a] Yield in % based on the aldehyde. [b] Diastereoisomeric mixture. [c] One diastereoisomer.

Yamamoto and co-workers[15] described a synthesis of β-silyloxy ketones from benzaldehyde or substituted benzaldehydes. Although the scope of this reaction is limited with respect to the starting aldehydes, it is still an attractive method since it delivers the products in a single step from the readily available silyl enol ethers of ketones. By this route, benzaldehyde and the silyl enol ether of butanal in acetonitrile were pressurised in the presence of $ZnCl_2$ to 12 kbar for 96 h at 50 °C to give a mixture containing *ca.* 75% of the β-silyloxy aldehyde (**5**). Bulb-to-bulb distillation afforded compound (**5**) in a yield of 30—35% based on benzaldehyde, as a 1:1 diastereoisomeric mixture. Attempts to synthesize an analogue of (**5**) using cinnamaldehyde as the starting compound failed.

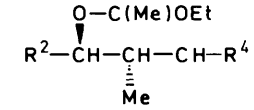
Since both direct methods had drawbacks, Tsumara's being of limited scope and Yamamoto's leading to 1:1 diastereoisomeric mixtures, we investigated others.

Four more laborious methods of potentially broader scope for the synthesis of (protected) β-hydroxy aldehydes have been published. First, the imine anion route as originally conceived by Wittig and co-workers[16] and second, an approach based on the chemistry of dihydrothiazoles as pursued by Meyers *et al.*[17] In our hands both these methods failed as a convenient synthesis of β-hydroxy aldehydes when we used simple aldehydes as starting compounds.* The third method for the synthesis of β-oxygenated aldehydes is based on the selective reduction of suitable, protected β-hydroxy esters as for instance demonstrated by Corey *et al.*[18] The fourth method is based on 1,3-dithiane chemistry as developed by Masamune and co-workers.[19]

We have concentrated on the third method since stereoselective methods for the synthesis of β-hydroxy esters have recently been described by us and others.[20,21] *A priori*, the use of these compounds implies the synthesis of δ-lactones with defined stereochemistry at the 5- and 6-position. Thus, *threo* β-hydroxy esters (**6**)—(**8**) were chosen as the starting compounds. Reduction of these esters gives aldehydes with an α-branched side-chain. Previous results suggested that reaction with a ketene acetal should give a *threo* configuration around the 3- and 4-positions of the product after hydrolysis.[21] Hence, δ-lactones with entirely defined stereochemistry might be synthesized.



(**6**) R^2 = Ph, X = H
(**7**) R^2 = c-Hex, X = H
(**8**) R^2 = Pr^i, X = H
(**9**) R^2 = Ph, X = CH(Me)OEt
(**10**) R^2 = c-Hex, X = CH(Me)OEt
(**11**) R^2 = Pr^i, X = CH(Me)OEt



(**12**) R^2 = Ph, R^4 = CH_2OH
(**13**) R^2 = c-Hex, R^4 = CH_2OH
(**14**) R^2 = Pr^i, R^4 = CH_2OH
(**15**) R^2 = Ph, R^4 = CHO
(**16**) R^2 = c-Hex, R^4 = CHO
(**17**) R^2 = Pr^i, R^4 = CHO

The pure *threo* compound (**6**) was isolated by crystallisation from light petroleum[22] of a 3:1 *threo–erythro* mixture.[21] Compounds (**7**) and (**8**) were obtained as 19:1 *threo–erythro* mixtures[21] and were used without further purification. The hydroxy function was protected as an acetal with ethyl vinyl ether according to the method of Tufariello.[23] This functionality appeared to be perfectly stable under the applied reaction conditions.

Reduction of the ester function in (**9**) with di-isobutylaluminium hydride (DIBAH) in dichloromethane at −78 °C according to the method of Keck *et al.*[24] gave a mixture containing starting material, the corresponding alcohol (**12**), and little of the desired aldehyde.† Scolastico and co-workers[24c] showed that reduction of an ester to the alcohol using $LiAlH_4$ followed by a Collins oxidation to afford the aldehyde delivers slightly better yields than selective reduction of the ester with DIBAH at −90 °C. Hence, we decided to circumvent the DIBAH reduction.

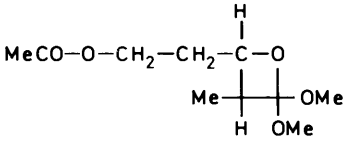
* Hydrolysis according to the method of Dauben[16b] of the β-hydroxy imine obtained from 2-methylpropanal and *N*-ethylidenecyclohexylamine resulted in a mixture of the starting hydroxy imine and the α,β-unsaturated aldehyde. By following the method of Meyers using butanal, we could isolate the MOM-protected β-hydroxy aldehyde, albeit in very low yield (*ca.* 10%); reduction of the dihydrothiazole to the thiazolidine with aluminium amalgam appeared in our hands not to be straightforward.

† Careful investigation of the literature indicated that reduction of an ester with DIBAH is a delicate reaction, for which various solvents, *e.g.* hexane, toluene, dichloromethane and various reaction temperatures, *e.g.* −78 °C, −90 °C, −100 °C are used; see ref. 24.

Reduction of compounds (**9**)—(**11**) with $LiAlH_4$ in ether was straightforward and gave the alcohols (**12**)—(**14**) in good yield. Oxidation of the alcohols to aldehydes (**15**)—(**17**) was investigated with the alcohol (**12**) both by a modification of the Collins oxidation[26] and by the dimethyl sulphoxide (DMSO)–oxalyl chloride oxidation as described by Swern.[27] Both methods gave the desired aldehyde (**15**) but since the Swern oxidation is easier to perform and gives slightly better yields we continued to use it. Aldehydes (**15**)—(**17**) were obtained in good yield *via* this method.

Synthesis of 4-Hydroxy-δ-lactones and 5,6-Dihydro-2-pyrones.—The protected aldehydes thus obtained were converted with the ketene acetals (**1a**) and (**1b**) into 4-hydroxy lactones and 5,6-dihydropyrones (see Scheme 1) and a survey of the results is given in Table 1.

A $ZnCl_2$ catalysed reaction of compound (**2**) with the ketene acetal (**1a**) in acetonitrile and at room temperature gave, instead of the expected products, rapid dimerisation of (**1a**): probably $ZnCl_2$ catalyses the elimination of acetic acid from (**2**), and (**1a**) dimerises readily under the influence of protonic acids. However, using bornyloxyaluminium dichloride (BAD)[28] and dichloromethane at low temperature, compound (**2**) was converted into a product which, when isolated at room temperature in the presence of the catalyst, appeared to be the 2,2-dimethoxytetrahydropyran (**19**): its ^1H n.m.r. spectrum



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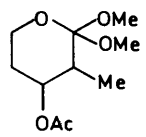
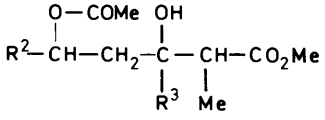
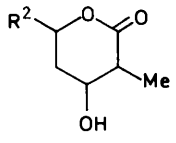


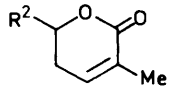
(**19**)



(**20**) $R^2 = R^3 = H$
(**23**) $R^2 = Me$, $R^3 = H$

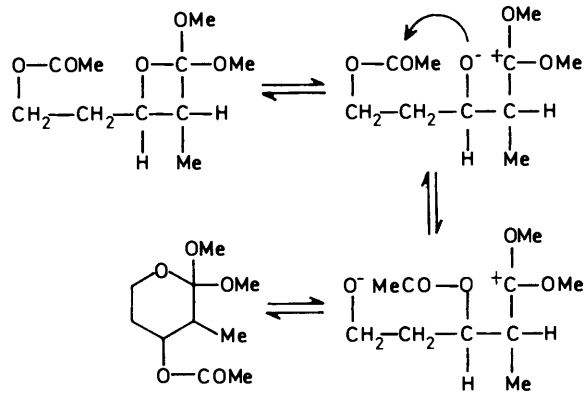


(**21**) R^2 = H
(**24**) $R^2 = Me$



(**22**) $R^2 = H$
(**25**) $R^2 = Me$

showed no signals characteristic of 3-H in 2,2-dialkoxyoxetanes in the range 2.5—2.9 p.p.m.[14] The formation of compound (**19**) may be explained by a shift of the acetoxy group, as already noted in the reactions of analogous α-acetoxy aldehydes[28c] with compound (**1a**) (Scheme 2). However, hydrolysis of the crude reaction product at −10 °C in a two-phase system, dichloromethane–water, gave compound (**20**) in good yield as an 8:1 *threo–erythro* mixture, indicating that the oxetane (**18**) is the initially formed product. Although compound (**20**) could be obtained analytically pure in small amounts *via* bulb-to-bulb distillation, purification is rather tricky since elimination of acetic acid and subsequent dehydration during distillation is a substantial problem. Consequently, in a further experiment we pursued the reaction route with the crude product (85—90%).



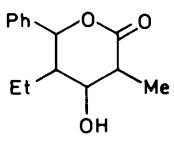
Scheme 2.

Saponification of the protecting acetoxy group and the methyl ester of compound (**20**) with 30% KOH proceeded with little elimination of the acetoxy group, and careful acidification with 30% sulphuric acid to pH < 2 gave the 4-hydroxy-δ-lactone (**21**) (75—80%) together with a very little of the 5,6-dihydropyrone (**22**).

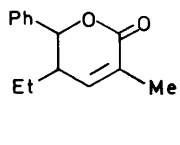
Reaction of compound (**3**) with ketene acetal (**1a**) under the same conditions as used in the reaction of (**2**) gave compound (**23**) in good yield. Since the crude product was sufficiently pure (*ca.* 90%), the deprotection was carried out without purification. After acidification (30% sulphuric acid) a mixture containing compounds (**24**) and (**25**) in a *ca.* 1:1 ratio was isolated. Since (**24**) could not be obtained completely free from (**25**), the mixture was dehydrated with sulphuric acid at 0 °C to give (**25**) in 55—60% yield after work-up and bulb-to-bulb distillation. Analogously, (**21**) afforded (**22**) in similar yield. As expected, compound (**4**) failed to react with compound (**1a**) both in refluxing acetonitrile and with $ZnCl_2$ catalysis.

Since reaction of the diastereoisomeric mixture (**5**) with (**1a**) and subsequent hydrolysis[21] gave a complex mixture of δ-lactones (**26**), dehydration was carried out directly in a Dean-Stark apparatus with benzene and toluene-*p*-sulphonic acid to give the 5,6-dihydropyrone (**27**) as a 1:1 diastereoisomeric mixture [60% yield based on (**5**)].

Reaction of the pure *threo* aldehyde (**15**) and the almost (95%) pure *threo* aldehydes (**16**) and (**17**) with (**1a**) in acetonitrile with $ZnCl_2$ catalysis and at room temperature gave the corresponding 2,2-dimethoxyoxetanes which were not isolated but directly hydrolysed[21] to the 4-hydroxy-δ-lactones

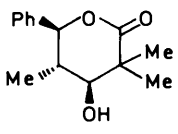


(**26**)



(**27**)

(**28**) R^1 = Ph
(**29**) R^1 = c-Hex
(**30**) R^1 = Pr^i

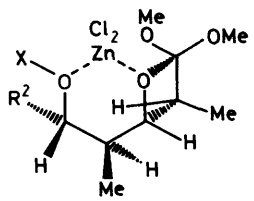


(**31**)

using THF and hydrochloric acid (18%) (Scheme 1, $n = 1$, $R^3 = H$, $R^5 = Me$). In this way compounds (**15**) and (**16**) gave a 4:1 diastereoisomeric mixture of δ-lactones. Crystallization of the lactones from hexane–ethyl acetate in the case of (**16**) afforded the major diastereoisomer (**29**) pure and in moderate yield. The main product from (**15**), the lactone (**28**), was obtained as a solid 4:1 mixture of diastereoisomers. Reaction of the aldehyde (**17**) with (**1a**) and subsequent hydrolysis gave the main diastereoisomer (**30**) by purification by m.p.l.c. from the 3:1 reaction mixture of diastereoisomers. Compound (**15**) reacted with (**1b**) in acetonitrile at 50 °C in the presence of $ZnCl_2$ to give, after hydrolysis and crystallization, (**31**) in low yield. The low yield of (**31**) compared with (**28**) possibly arises as a result of the lower reactivity of (**1b**) relative to (**1a**).

Structural assignments for the major isomers (**28**), (**29**), (**30**), and (**31**) were based on ^1H n.m.r. spectral results; they are in agreement with the stereochemical expectations based on oxetane formation.[29] For all these lactones the (~10 Hz) 5-H,6-H coupling constants indicate a *trans* axial disposition of these protons. This corresponds with the *threo* configuration present in the preceding aldehydes. The small 4-H, 5-H coupling constants for the lactones (**28**), (**29**), and (**30**) point to a *cis* equatorial disposition for 4-H. For the lactone (**31**) 4-H is expected to have a *trans* axial disposition as a result of strong coupling with 5-H ($J_{4,5} \sim 10$ Hz). Finally the small coupling constants for 3-H,4-H in the lactones (**28**), (**29**), and (**30**) allow no discrimination between a *trans* equatorial or a *cis* axial position for 3-H. On account of the expected stereochemistry in the reaction of the aldehydes (**15**), (**16**), and (**17**) with (**1a**) the major diastereoisomers of (**28**), (**29**), and (**30**) should have a *threo* configuration * at C-3 and C-4. Consequently, 3-H should have a *trans* equatorial disposition.

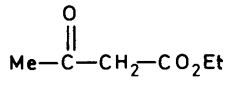
The observed steric relationship between 4-H and 5-H can be rationalised in terms of complexation of zinc chloride with the aldehyde oxygen and the oxygen of the β-oxy substituent in compounds (**15**), (**16**), and (**17**). As illustrated in (I), formation of the most stable *trans* oxetanes from such aldehydes and (**1a**) is



(**1**)

favoured from the *Re* side of the aldehydes. For the reaction of the ketene acetal (**1b**), having two methyl groups, it appears from models that oxetane formation from the *Re* side is less favourable than from the *Si* side since it leads to strong steric interaction between a methyl group of the ketene acetal and the bulky R^2 group. The oxetane formation with the ketene acetal (**1b**) is more difficult and needs stronger reaction conditions.

Synthesis of a Chiral 5,6-Dihydro-2-pyrone.—Finally we attempted the synthesis of optically active 5,6-dihydro-2-pyrones starting with a chiral β-hydroxy ester. Recently, Seebach and co-workers[28] described an enantioselective preparation of *S*-(+)-β-hydroxy esters from the corresponding β-keto esters by yeast reduction. We followed this method using the keto butyrate (**32**). Yeast reduction gave the optically active alcohol (**33**), as described, in a yield of 61% and with an e.e. of 84% $[\alpha]_D^{20}$ +36.6 (*c* 4.5, $CHCl_3$). Protection with ethyl vinyl ether and subsequent reduction with $LiAlH_4$ gave the protected diol (**34**) in good yield. Oxidation of (**34**) with DMSO and oxalyl chloride proceeded well and gave the aldehyde (**35**) in a yield of 75% based on (**33**). Reaction of (**35**) with (**1a**) in acetonitrile at room temperature with $ZnCl_2$ catalysis was complete within 0.5 h. The product of this reaction was not isolated but directly hydrolysed with THF and hydrochloric acid (18%) to give the 4-hydroxy lactone (**36**). This was dehydrated, without purification, with di-isopropyl ether and



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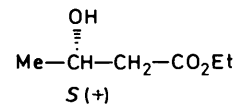

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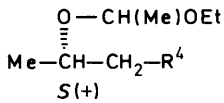
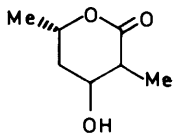
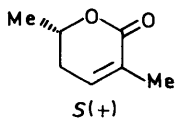


(**34**) $R^4 = CH_2OH$

(**35**) $R^4 = CHO$



(**36**)



(**37**)

toluene-*p*-sulphonic acid in a Dean-Stark apparatus to give a crude product containing *ca.* 50% of (**37**). It was isolated in a moderate yield after m.p.l.c. purification using cyclohexane–ethyl acetate (3:1). The specific rotation $[\alpha]_D^{20}$ was +160° (*c* 0.81, $CHCl_3$); the ^1H n.m.r. spectrum of (**37**) in the presence of an optically active shift reagent [Eu(hfc)$_3$] showed an e.e. of 80—85%. Although the method needs to be optimized, the synthesis of (**37**) shows that the route described has considerable potential in that the chirality present in the starting β-hydroxy ester is maintained during the formation of a 5,6-dihydro-2-pyrone (**37**).

Experimental

General Methods.—^1H N.m.r. spectra were recorded on a Varian T60 Mz, a Hitachi Perkin-Elmer R-24B 60 Mz or a Bruker WH90 Mz spectrometer and for compounds (**28**), (**29**), and (**30**) a Bruker WM 500 Mz spectrometer, using CCl_4 or $CDCl_3$ with THS as internal reference. Mass spectra were measured with a Varian SM1-B double focussing mass spectrometer or with a VG 7070E mass spectrometer. Elemental analyses were performed by Mr. P. van Galen (Microanalytical Department of our University). Other general methods were described previously.[13b,21] Compounds (**7**)—(**9**) were synthesized as reported.[21] The silyl enol ether of butanal was prepared as described by House *et al.*,[29] b.p. 42—52 °C/70 mmHg (lit.,[29] 52—62 °C/75 mmHg).

* It has been demonstrated that under the applied reaction conditions aldehydes having an α-branched side chain can be selectively converted into *trans* oxetanes with (**1a**). These *trans* oxetanes yield *threo* β-hydroxy esters after hydrolysis. See ref. 22.

3-*Acetoxypropanal* (**2**).—A mixture of propenal (56 g, 1.0 mol), glacial acetic acid (120 g, 2.0 mol), and sodium acetate (8.2 g, 0.1 mol) was stirred at room temperature for 16 h after which most of the residual acetic acid was removed under reduced pressure. The remaining oil was treated with ether (100 ml), the precipitate (sodium acetate) filtered off, and the filtrate concentrated under reduced pressure. The remaining oil was distilled at low pressure, to yield the title compound (**2**) (50.2 g, 43%), b.p. 35—40 °C/0.5 mmHg; $\delta_H(CCl_4)$ 1.98 (3 H, s, OCOMe), 2.67 (2 H, d t, *J* 6 and 1.5 Hz, 2-H), 4.22 (2 H, t, *J* 6 Hz, 3-H), and 9.60 (1 H, t, *J* 1.5 Hz, 1-H).

3-*Acetoxybutanal* (**3**).—A mixture of but-2-enal (70 g, 1.0 mol), glacial acetic acid (120 g, 2.0 mol), and sodium acetate (8.2 g, 0.1 mol) was stirred at 50 °C for 72 h. After cooling to room temperature the reaction mixture was treated as described for compound (**2**) to yield the title compound (**3**) (6.5 g, 5%), b.p. 45—50 °C/0.4 mmHg; $\delta_H(CCl_4)$ 1.30 (3 H, d, *J* 6 Hz, 4-H), 1.95 (3 H, s, OCOMe), 2.56 (2 H, d t, *J* 6 and 1.5 Hz, 2-H), 5.20 (1 H, br sextet, *J* 6 Hz, 3-H), and 9.52 (1 H, t, *J* 1.5 Hz, 1-H).

2-*Ethyl*-3-*phenyl*-3-*trimethylsilyloxypropan*-1-*al* (**5**).—$ZnCl_2$ (0.5 ml of a saturated solution in acetonitrile) was added to a mixture of benzaldehyde (1.90 g, 18 mmol) and 1-trimethylsilyloxybut-1-ene (3.20 g, 22 mmol) in acetonitrile (1.5 ml). The mixture was placed in a 7.5 ml Teflon ampoule, and acetonitrile (a few drops) was added to fill the ampoule completely. The closed ampoule was placed in a one-wall piston-in-cylinder high-pressure apparatus [30] and pressurised at 12 kbar and 50 °C for 96 h. After depressurising and cooling of the reaction mixture to room temperature triethylamine (TEA) (0.5 ml) was added and the solvent evaporated. Pentane (*ca.* 40 ml) was then added until a light precipitate formed. This was filtered off and the filtrate evaporated to give the crude product which upon bulb-to-bulb distillation afforded a (1:1) diastereoisomeric mixture of the *title compound* (**5**) (1.55 g, 34%), b.p. 95—105 °C/0.6 mmHg (Found: M^+ + 1, 251.1115; $C_{14}H_{22}O_2Si$ requires M + 1, 251.1108); *m/z* 251 (M + 1, 12%), 235 (M − Me, 16), 205 (18), 180 (22), 179 [M − CH(Et)CHO, 100], 177 (18), and 161 (M − $OSiMe_3$, 20); $\delta_H(CDCl_3)$ 0.04 (9 H, br s, $OSiMe_3$), 0.84 and 0.87 (3 H, 2 t, *J* 9 Hz, Me), 1.16—2.00 (2 H, m, CH_2Me), 2.36—2.67 (1 H, m, 2-H), 4.86 and 5.04 (1 H, 2 d, *J* 7 and 5 Hz, 3-H), 7.32 (5 H, br s, Ph), and 9.65 and 9.69 (1 H, 2 d, *J* 3 and 4 Hz, 1-H).

Synthesis of the Alcohols (**12**)—(**14**): *General Procedure.*—Trifluoroacetic acid (1 ml) was carefully added to a vigorously stirred mixture of ethyl vinyl ether (30 ml) and a β-hydroxy ester (40 mmol) cooled to 0 °C. The mixture was stirred at 0 °C for 2 h and then left at 5 °C for 16 h; TEA (7 ml) was then added and the excess of ethyl vinyl ether was evaporated. Di-isopropyl ether (100 ml) was added and the mixture was washed with water (2 × 30 ml) and brine (30 ml). The combined aqueous layers were extracted with di-isopropyl ether (25 ml) and the combined ethereal layers were dried (Na_2SO_4). After evaporation of the solvent crude products were isolated >92% pure by g.c. The crude products were dissolved in dry ether (40 ml) and dropped into a suspension of $LiAlH_4$ (1.6 g, 42 mmol) in dry ether (200 ml) at room temperature. After the addition was complete the mixture was refluxed for 4 h and allowed to come to room temperature. The excess of $LiAlH_4$ was then destroyed carefully by addition of water (*ca.* 3 ml) and potassium hydroxide (15% solution; *ca.* 4 ml). The resulting suspension was filtered and the remaining salts were washed with ether (2 × 15 ml). The combined filtrates were dried (Na_2SO_4) and evaporated to yield the crude products which upon distillation *via* a short Vigreux column (10 × 1 cm) or bulb-to-bulb distillation afforded the pure products as (1:1) diastereoisomeric mixtures. The following compounds were prepared in this way.

3-(1-*Ethoxyethoxy*)-2-*methyl*-3-*phenylpropan*-1-*ol* (**12**) (7.2 g, 76%), b.p. 100—110 °C/0.4 mmHg (Found: M^+ + 1, 239.1652. $C_{14}H_{22}O_3$ requires M + 1, 239.1647); *m/z* (c.i.) (M + 1, 1%), 221 (M − OH, 2), 193 (M − EtO, 3), 149 [M − OCH(Me)-OEt, 40], 131 [M − OCH(Me)OEt, $-H_2O$, 22], and 73 [C(Me)OEt^+, 100]; $\nu_{max.}(CHCl_3)$ 3 600—3 300 (OH), 3 140—2 860 (CH), 1 510—1 370 (CH), and 1 170—1 010 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.71 and 0.73 (3 H, 2d, *J* 7 Hz, 2-Me), 0.93 and 1.22 (3 H, 2t, *J* 7 Hz, OCH*Me*), 1.24 and 1.31 (3 H, 2d, *J* 7 Hz, OCH*Me*OEt), 1.78 (1 H, br s, OH), 1.76—2.31 (1 H, m, 2-H), 2.99—3.98 (4 H, m, OCH_2Me, 3-H), 4.22 and 4.45 (1 H, 2d, *J* 9 Hz, 1-H), 4.44 and 4.58 [1 H, 2q, *J* 5 Hz, O*CH*MeOEt], and 7.31 (5 H, br s, Ph).

3-*Cyclohexyl*-3-(1-*ethoxyethoxy*)-2-*methylpropan*-1-*ol* (**13**) (7.0 g, 72%), b.p. 120—130 °C/0.5 mmHg (Found: M^+ − OEt, 199.1699. $C_{12}H_{23}O_2$ requires 199.1698); *m/z* (c.i.) 245 (M^+ + 1, 1%), 199 (M − OEt, 74), 155 [M − OCH(Me)OEt, 100], 153 (18), and 137 (30); $\nu_{max.}(CHCl_3)$ 3 600—3 300 (OH), 3 020—2 860 (CH), 1 480—1 380 (CH), and 1 170—970 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.84—2.09 [21 H, m, c-Hex-H, 2-H, 2-Me, OCH(*Me*)OCH_2*Me*], 2.59 (1 H, br t, *J* 6 Hz, OH), 3.20—4.03 (5 H, m, 1-H, 3-H, OCH_2Me), and 4.60 and 4.72 [1 H, 2q, *J* 5 Hz, O*CH*(Me)OEt].

3-(1-*Ethoxyethoxy*)-2,4-*dimethylpentan*-1-*ol* (**14**) (5.95 g, 73%), b.p. 65—68 °C(0.5 mmHg (Found: M^+ + 18, 222.2084. $C_{11}H_{24}O_3$ requires M + 18, 222.2069); *m/z* (c.i., NH_3) 222 (M + 18, 6%), 176 (72), 159 (M − OEt, 81), 150 (100), and 133 (32); $\nu_{max.}$(NaCl) 3 610—3 160 (OH), 3 000—2 780 (CH), 1 450 (CH), 1 380 (CH), and 1 180—990 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.73—1.39 [15 H, m, 2,4-Me, 5-H, CH(*Me*)OCH_2*Me*], 1.56—2.09 (2 H, m, 2-H, 4-H), 2.49 (1 H, br s, OH), 3.21—3.73 (5 H, m, 1-H, 3-H, OCH_2-Me), and 4.62 and 4.73 (1 H, 2q, *J* 6 Hz, O*CH*Me).

Synthesis of the Aldehydes (**15**)—(**17**): *General Procedure.*—The aldehydes (**15**)—(**17**) were prepared as described by Swern *et al.*,[26] using DMSO and oxalyl chloride in dichloromethane; the procedure was executed on a 20 mmol scale. The following compounds were prepared in this way.

3-(1-*Ethoxyethoxy*)-2-*methyl*-3-*phenylpropan*-1-*al* (**15**) (4.1 g, 86%), b.p. 100—110 °C/0.5 mmHg; *m/z* (c.i.) 221 (M − Me, 2), 191 (M − OEt, 9), 147 [M − OCH(Me)OEt, 59], 135 (16), 119 (27), and 73 (100); $\nu_{max.}(CHCl_3)$ 3 100—2 810 (CH), 1 730 (CO), 1 500—1 370 (CH), and 1 170—1 000 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.86 and 0.87 (3 H, 2d, *J* 7 Hz, 2-Me), 0.91 and 1.19 (3 H, 2t, *J* 7 Hz, OCH_2*Me*), 1.23 and 1.25 (3 H, 2 d, *J* 7 Hz, OCH*Me*), 2.56—3.64 (3 H, m, 2-H, OCH_2Me), 4.39—4.84 (2 H, m, 1-H, O*CH*Me), 7.31 (5 H, br s, Ph), and 9.83 (1 H, d, *J* 3 Hz, *CH*O).

3-*Cyclohexyl*-3-(1-*ethoxyethoxy*)-2-*methylpropan*-1-*al* (**16**) (3.95 g, 81%), b.p. 100—110 °C/0.3 mmHg (Found: M^+ − OEt, 197.1537. $C_{12}H_{21}O_2$ requires 197.1542); *m/z* (c.i., NH_3) 260 (M + 18, 4%), 216 (11), 215 (20), 214 (44), 198 (13), 197 (M − OEt, 100), 196 (15), 188 (11), 170 (18), 153 [M − OCH-(Me)OEt, 31], and 73 (20); $\nu_{max.}(CHCl_3)$ 3 010—2 810 (CH), 1 725 (CO), 1 450 (CH), and 1 200—1 070 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.82—2.07 [20 H, m, c-Hex-H, 2-Me, OCH-(*Me*)OCH_2*Me*], 2.44—2.84 (1 H, m, 2-H), 3.33—3.76 (3 H, m, 1-H, OCH_2Me), 4.51—4.82 [1 H, m, O*CH*(Me), and 9.76 (1 H, d, *J* 2 Hz, CHO].

3-(1-*Ethoxyethoxy*)-2,4-*dimethylpentan*-1-*al* (**17**) (3.0 g, 74%), b.p. 72—76 °C/0.6 mmHg; (Found: M^+ + 18, 220.193. $C_{11}H_{22}O_3$ requires M + 18, 220.191); *m/z* (c.i., NH_3) 220 (M + 18, 19%), 174 (32), 157 (M − OEt, 100), 148 (36), and 131 (23); $\nu_{max.}(CHCl_3)$ 3 040—2 800 (CH), 2 710 (CH), 1 720 (CO), 1 460—1 380 (CH), and 1 130—1 010 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.76—1.40 [15 H, m, 5-H, 2-Me, 4-Me, OCH(*Me*)OCH_2*Me*], 1.53—2.05 (1 H, m, 4-H), 2.42—2.82 (1 H, m, 2-H), 3.24—3.73 (3

H, m, 3-H, OCH_2Me), 4.51—4.78 (1 H, m, OC*H*Me), and 9.73 (1 H, br d, *J* 1.8 Hz, CHO).

Methyl 5-Acetoxy-3-hydroxy-2-methylpentanoate (**20**).—BAD (0.55M solution in ether; 1.0 ml) was added to a stirred mixture of compounds (**2**) (4.65 g, 40 mmol) and (**1a**) (4.45 g, 44 mmol) in dry dichloromethane (15 ml) at −78 °C. After 30 min the mixture was allowed to warm to −10 °C when water (15 ml) was added. This mixture was stirred vigorously for 1 h at −10 °C and then allowed to come to room temperature. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined dichloromethane layers were dried (Na_2SO_4) and evaporated to yield a crude mixture containing *ca.* 90% of the *title compound* (**20**). Bulb-to-bulb distillation, using a container and receivers previously treated with base (TEA), afforded compound (**20**) as an 8:1 diastereoisomeric mixture (6.9 g, 84%), b.p. 90—100 °C/0.5 mmHg (Found: C, 52.85; H, 7.9. $C_9H_{16}O_5$ requires C, 52.93; H, 7.90%); $\nu_{max.}$(CCl_4) 3 660—3 220 (OH), 3 010—2 840 (CH), 1 750—1 710 (CO), 1 450 and 1 380 (CH), and 1 235 cm^{-1} (CO); δ_H(CCl_4) (major isomer) 1.20 (3 H, d, *J* 7 Hz, 2-Me), 1.73 (2 H, d t, *J* 6 and 6 Hz, 4-H), 2.05 (3 H, s, OCO*Me*), 2.30—2.77 (1 H, m, 2-H), 2.83 (1 H, br s, OH), 3.67 (3 H, br s, CO_2Me), 3.95 (1 H, d t, *J* 6 and 4 Hz, 3-H), and 4.18 (2 H, br t, *J* 6 Hz, 5-H).

Tetrahydro-4-hydroxy-3-methyl-2-pyrone (**21**).—Compound (**20**) (4.1 g, 20 mmol) was added to a vigorously stirred solution of KOH (30% solution; 15 ml) and the mixture was stirred at room temperature for 16 h. It was then carefully acidified to pH <1 with sulphuric acid (30% solution; *ca.* 14 ml) and its temperature allowed to rise >30 °C. After almost complete evaporation of the water the resulting mixture was extracted with dichloromethane (5 × 30 ml). The combined dichloromethane extracts were dried (Na_2SO_4) and evaporated to give a crude product which upon bulb-to-bulb distillation afforded the title compound (**21**) as an 8:1 diastereoisomeric mixture (1.56 g, 60%), b.p. 120—130 °C/0.3 mmHg; *m/z* (e.i.) 130 (M^+, 54%), 112 ($M - H_2O$, 65), 102 (M − CO, 14), 74 ($M - C_3H_4O$, 25), and 71 ($M - CO_2$Me 100); $\nu_{max.}$($CHCl_3$) 3 600 (OH), 3 650—3 250 (OH), 3 010—2 850 (CH), 1 730 (CO), 1 400 (CH), and 1 280—1 080 cm^{-1} (CO); δ_H($CDCl_3$) 1.30 and 1.36 (3 H, 2d, *J* 7 Hz, 3-Me), 1.58—2.71 (3 H, m, 5-H, 3-H), 3.49 (1 H, br s, OH), 3.71—3.94 (1 H, m, 4-H), and 4.09—4.64 (2 H, m, 6-H).

5,6-*Dihydro-3-methyl-2-pyrone* (**22**).—Compound (**21**) (1.3 g, 10 mmol) was added dropwise to concentrated sulphuric acid (5.0 g) at 0 °C to give after 10 min a dark brown mixture which was stirred for 45 min. It was then poured onto ice (50 g) and carefully neutralised with sodium hydrogen carbonate (8.5 g). Dichloromethane (20 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 ml) and the combined dichloromethane layers were dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation afforded the title compound (**22**) (0.71 g, 56%), b.p. 42—44 °C/2 mmHg; *m/z* (e.i.) 112 (*M*, 100%), 97 (M − Me, 5), 84 (M − CO, 18), and 68 ($M - CO_2$, 11); $\nu_{max.}$(CCl_4) 3 040—2 880 (CH), 1 730 (CO), 1 470—1 360 (CH), and 1 130 cm^{-1} (CO); δ_H($CDCl_3$) 1.91 (3 H, q, *J* 2 Hz, 3-Me), 2.21—2.61 (2 H, m, 5-H), 4.35 (2 H, t, *J* 6 Hz, 6-H), and 6.61 (1 H, m, 4-H).

5,6-*Dihydro-3,6-dimethyl-2-pyrone* (**25**).—BAD (0.55M solution in ether; 0.5 ml) was added to a stirred mixture of compounds (**3**) (2.0 g, 15.4 mmol) and (**1a**) (1.75 g, 17 mmol) in dichloromethane (5 ml) at −78 °C and the mixture was stirred for 30 min. It was then treated as described for compound (**20**). After work-up the product was directly saponified, cyclised, and dehydrated as described for compounds (**21**) and (**22**), respectively, without purification of the intermediate products. After final work-up the crude product (750 mg) was purified by bulb-to-bulb distillation to yield the title compound (**25**) (610 mg, 28%), b.p. 75—90 °C/ 0.6 mmHg (lit.,[4] 55—60 °C/0.2 mmHg, m.p. 31—33 °C) (Found: C, 65.85; H, 8.1. Calc. for $C_7H_{10}O_2$: C, 66.65; H, 7.99%); *m/z* (e.i.) 126 (M^+, 85%), 111 (M − Me, 10), 82 ($M - CO_2$, 100), and 54 (25); $\nu_{max.}$(CCl_4) 3 010—2 810 (CH), 1 720 (CO), 1 380—1 330 (C=C), and 1 250 and 1 120 cm^{-1} (CO); δ_H($CDCl_3$) 1.41 (3 H, d, *J* 6 Hz, 6-Me), 1.91 (3 H, q, *J* 1.8 Hz, 3-Me), 2.20—2.40 (2 H, m, 5-H), 4.52 (1 H, br sextet, *J* 6 Hz, 6-H), and 6.47—6.64 (1 H, m, 4-H).

5-*Ethyl-5,6-dihydro-3-methyl-6-phenyl-2-pyrone* (**27**).—$ZnCl_2$ (saturated solution in acetonitrile; 0.5 ml) was added to a stirred mixture of compounds (**5**) (1.15 g, 4.6 mmol) and (**1a**) (1.65 g, 16 mmol) in acetonitrile (5 ml) at room temperature. The mixture was stirred for 2 h and work-up was performed as previously described.[21] Toluene (100 ml) and toluene-*p*-sulphuric acid (*ca.* 100 mg) were added to the crude product and the mixture was refluxed for 16 h in a Dean-Stark apparatus. After cooling, the mixture was extracted with water (2 × 25 ml) and brine (25 ml). The combined aqueous layers were extracted with toluene (25 ml) and the combined organic layers were dried (Na_2SO_4), and evaporated to yield a crude product (1.4 g). M.p.l.c. of a part of the crude product (500 mg) using silica gel and hexane–di-isopropyl ether (5:3) afforded a 1:1 diastereoisomeric mixture of the *title compound* (**27**) (250 mg, 70%), b.p. 125—145 °C/0.4 mmHg (Found: M^+ + 1, 217.1231. $C_{14}H_{16}O_2$ requires M + 1, 217.1228); *m/z* (c.i.) 217 (M + 1, 100%), 199 (M − 17, 24), 171 (M − 45, 13), 139 (M − Ph, 16), and 110 (M − Ph, − Et, 30); $\nu_{max.}$(CCl_4) 3 100—2 840 (CH), 1 725 (CO), 1 610—1 480 (CH), and 1 280—1 200 cm^{-1} (CO); δ_H-($CDCl_3$) 0.68—1.53 (5 H, m, Et), 1.99 (3 H, q, *J* 1.5 Hz, Me), 2.27—2.82 (1 H, m, 5-H), 5.09 and 5.58 (1 H, 2d, *J* 10 and 4 Hz, 6-H), 6.56 and 6.87 (1 H, 2dq, *J* 2.5 and 1.5 Hz, *J* 6 and 1.5 Hz, 4-H), and 7.36 (5 H, br s, Ph).

Synthesis of 4-Hydroxy-3-methyl-δ-lactones (**28**)—(**30**): *General Procedure.*—$ZnCl_2$ (saturated solution in acetonitrile; 0.5 ml) was added to a stirred mixture of the appropriate aldehyde, (**15**)—(**17**), (2 mmol) and ketene acetal (**1a**) (310 mg, 3 mmol) in acetonitrile (1 ml) at room temperature. The mixture was stirred for 1 h and TEA (0.5 ml) and THF (15 ml) were added. The mixture was cooled to −78 °C and a solution of toluene-*p*-sulphonic acid (15 mg) in MeOH (1.5 ml) was added. The mixture was kept at −78 °C for 0.5 h and then allowed to warm to room temperature. Hydrochloric acid (18.5% solution; 10 ml) was added and the mixture was stirred for 36 h. Brine (20 ml) was then added and the ethereal layer was separated. The aqueous layer was extracted with ether (4 × 25 ml) and the combined ethereal layers were washed with brine (25 ml), dried (Na_2SO_4), and evaporated. The resulting faint yellow oils in the case of compounds (**28**) and (**29**) contained a 4:1 diastereoisomeric mixture of δ-lactones according to capillary g.c. Crystallisation from hexane–di-isopropyl ether–ethyl acetate afforded the major diastereoisomer in the case of compound (**29**) in pure form. In the case of compound (**30**) the resulting oil contained a 3:1 diastereoisomeric mixture of δ-lactones and the major isomer was purified *via* m.p.l.c. using silica gel and cyclohexane–ethyl acetate (3:1). The following compounds were prepared in this way.

3,4,5,6-*Tetrahydro-4-hydroxy-3,5-dimethyl-6-phenyl-2-pyrone* (**28**). A 4:1 diastereoisomeric mixture (270 mg, 61%), m.p. 134—137 °C (hexane–ethyl acetate) (Found: C, 70.5; H, 7.3%; M^+, 220.1097. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%; *M*, 220.1099); *m/z* (e.i.) 220 (*M*, 2%), 118 (16), 117 (12), and 107 (PhCHOH, 100); $\nu_{max.}$($CHCl_3$) 3 600 (OH), 3 620—3 300 (OH), 3 110—2 860 (CH), 1 735 (CO), 1 470 (CH), and 1 370 cm^{-1} (CH); δ_H

(500 Mz, $CDCl_3$) 0.92 and 0.97 (3 H, 2d, *J* 7 Hz, 5-Me), 1.36 and 1.41 (3 H, 2d, *J* 7 and 7.2 Hz, 3-Me), 2.02 (1 H, d, *J* 4.3 Hz, OH), 2.10—2.20 (1 H, m, 5-H), 2.76 (1 H, dq, *J* 7.2 and 2.7 Hz, 3-H), 2.87 (1 H, dq, *J* 7 and 4.2 Hz, 3-H), 3.92 (1 H, ddd, *J* 4.2, 4.3 and 3.6 Hz, 4-H), 3.99 (1 H, br, 4-H), 4.74 and 5.27 (1 H, 2d, *J* 11 Hz, 6-H), and 7.36 (5 H, m, Ph).

6-*Cyclohexyl*-3,4,5,6-*tetrahydro*-4-*hydroxy*-3,5-*dimethyl*-2-*pyrone* (**29**). (182 mg, 40%), m.p. 124—126 °C (hexane–ethyl acetate) (Found: C, 68.65; H, 9.75%; $M^+ + 1$, 227.1648. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%; $M + 1$, 227.1647); *m/z* (c.i.) 227 ($M + 1$, 23%), 209 ($M - OH$, 13), 191 (12), 153 ($M - C_3H_4O_2$, 100), 143 (M – c-Hex, 13), and 135 (20); $\nu_{max.}$($CHCl_3$) 3 640—3 300 (OH), 3 020—2 860 (CH), 1 740 (CO), 1 450 (CH), 1 400—1 370 (CH), and 1 260—1 180 cm^{-1} (CO); δ_H(500 Mz, $CDCl_3$) 1.06 (3 H, d, *J* 7 Hz, 5-Me), 1.27 (3 H, d, *J* 7 Hz, 3-Me), 1.10—1.90 (11 H, complex, c-Hex-H), 1.85 (1 H, d, *J* 4.3 Hz, OH), 2.00 (1 H, ddq, *J* 3.1, 10.1 and 7 Hz, 5-H), 2.68 (1 H, dq, *J* 3.8 and 7 Hz, 3-H), 3.70 (1 H, d with fine spl, *J* 10.1 Hz, 6-H), and 3.76 (1 H, dd after exch. OH with CD_3OD, *J* 3.1 and 3.8 Hz, 4-H).

3,4,5,6-*Tetrahydro*-4-*hydroxy*-6-*isopropyl*-3,5-*dimethyl*-2-*pyrone* (**30**). (165 mg, 44%), m.p. 67—69 °C (hexane–ethyl acetate) (Found: C, 64.35; H, 9.7%; $M^+ + 1$, 187.1330. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%; $M + 1$, 187.1334); *m/z* (c.i.) 187 ($M + 1$, 24%), 169 ($M - OH$, 12), 143 ($M - Pr^i$, 8), 126 ($M - OH$, $-Pr^i$, 15), 113 ($M - Pr^i$, −2 Me, 100), and 69 (15); δ_H(500 Mz, $CDCl_3$) 0.97, 1.06, and 1.09 (9 H, 3d, *J* 6.9 Hz, Pr^i and 5-Me), 1.29 (3 H, d, *J* 6.9 Hz, 3-Me), 1.88—1.98 (2 H, m, $CHMe_2$, 5-H), 1.97 (1 H, d, *J* 4.8 Hz, OH), 2.69 (1 H, dq, *J* 6.9 and 3.9 Hz, 3-H), 3.74 (1 H, dd, *J* 2.2 and 10.2 Hz, 6-H), and 3.77 (1 H, dd after exch. OH with CD_3OD, *J* 3.8 and 3.9 Hz, 4-H).

3,4,5,6-*Tetrahydro*-4-*hydroxy*-3,3,5-*trimethyl*-6-*phenyl*-2-*pyrone* (**31**).—$ZnCl_2$ (saturated solution in acetonitrile; 0.5 ml) was added to a stirred mixture of compounds (**15**) (475 mg, 2 mmol) and (**1b**) (465 mg, 4 mmol) in acetonitrile (2 ml), and the mixture was heated at 50 °C for 16 h. TEA (0.5 ml) was added and the temperature was allowed to come to room temperature. The mixture was treated as described for compounds (**30**)—(**32**). The crude product was crystallized using hexane–di-isopropyl ether–ethyl acetate to yield the *title compound* (**31**) (55 mg, 12%), m.p. 152—154 °C (hexane–ethyl acetate) (Found: C, 71.85; H, 7.8%; $M^+ + 1$, 235.1332. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%; $M + 1$, 235.1334); *m/z* 235 ($M + 1$, 6%), 217 ($M - OH$), 7), 171 (M – 3Me, $-H_2O$, 16), 145 (13), 139 (M – Ph, $-H_2O$, 25), 119 (78), 118 (22), and 117 (100); $\nu_{max.}$($CHCl_3$) 3 700 (OH), 3 600 (OH), 3 580—3 360 (OH), 3 140—2 860 (CH), 1 725 (CO), 1 530 (CH), 1 430 (CH), and 1 280—1 160 cm^{-1} (CO); δ_H($CDCl_3$) 0.93 (3 H, d, *J* 6 Hz, 5-Me), 1.40 and 1.46 (6 H, 2s, 3-Me), 1.83 (1 H, br d, *J* 5 Hz, OH), 2.04—2.38 (1 H, m, 5-H), 3.61 (1 H, dd, *J* 11 and 6 Hz, 4-H), 4.74 (1 H, d, *J* 11 Hz, 6-H), and 7.36 (5 H, br s, Ph).

(S)-(+)-5,6-*Dihydro*-3,6-*dimethyl*-2-*pyrone* (**37**).—The pyrone (**37**) was synthesized from the 3-hydroxybutanoate (**33**) which was prepared by yeast reduction of the corresponding β-keto butanoate (**32**) as described by Seebach *et al.*,[28] yield 61%, b.p. 74—76 °C/15 mmHg, $[\alpha]_D^{21}$ +36.6° (*c* 4.1 in $CHCl_3$) (lit.,[28] b.p. 71—73 °C/12 mmHg, $[\alpha]_D^{25}$ +37.2° (*c* 1.3 in $CHCl_3$). The alcohol (**34**) and the aldehyde (**35**) were synthesized as described for compounds (**12**) and (**15**). The products were distilled and identified on the basis of their ^1H n.m.r. spectra:

3-(1-*Ethoxyethoxy*)*butan*-1-*ol* (**34**) (86%), b.p. 98—100 °C/15 mmHg; δ_H($CDCl_3$) 1.09—1.37 [9 H, m, 4-H, OCH(*Me*)OCH_2-*Me*], 1.58—1.83 (2 H, m, 2-H), 2.29 and 2.96 (1 H, br t, *J* 6 Hz, OH), 3.31—4.16 (5 H, m, 1-H, 3-H, OCH_2Me), and 4.69 and 4.73 (1 H, 2q, *J* 5 Hz, OCHOEt).

3-(1-*Ethoxyethoxy*)*butan*-1-*al* (**35**) (82%), b.p. 95—105 °C/14 mmHg; δ_H($CDCl_3$) 1.09—1.37 [9 H, m, 4-H, OCH(*Me*)OCH_2-*Me*], 2.49—2.69 (2 H, m, 2-H), 3.32—3.78 (2 H, m, OCH_2Me), 4.24 (1 H, br septet, Me*CH*CH_2), and 4.77 [1 H, br q, O*CH*(Me)OEt].

The aldehyde (**35**) was allowed to react with the ketene acetal (**1a**) as described for compound (**15**). The crude product was refluxed with di-isopropyl ether (50 ml) and toluene-*p*-sulphuric acid (100 mg) in a Dean-Stark apparatus for 16 h. After cooling to room temperature the di-isopropyl ether solution was washed with brine (3 × 20 ml), dried (Na_2SO_4), and evaporated to afford the crude product [500 mg, prepared from 5 mmol of (**35**)]. This was purified by m.p.l.c. using silica gel and cyclohexane–ethyl acetate (3:1) to yield the pyrone (**37**) as a colourless oil (240 mg, 38%), $[\alpha]_D^{21}$ + 160° (*c* 0.8 in $CHCl_3$). A ^1H n.m.r. spectrum in the presence of Eu(hfc)$_3$ showed an e.e. of 80—85% (6-Me signal) indicating that the chirality was maintained during the reaction sequence. ^1H N.m.r., mass, and i.r. spectra were identical with those of compound (**25**).

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