Synthesis of (*R*)- and (*S*)-Acetoin (3-Hydroxybutan-2-one)

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Two synthetic routes to the enantiomers of acetoin (2) of high optical purity have been devised. One starting from (*S*)-3-methylbut-3-en-2-ol (9) led to (*S*)-(+)-acetoin (13). The other, starting from (2*R*,3*R*)-butane-2,3-diol gave (*R*)-(−)-acetoin (16).

Acetoin (3-hydroxybutan-2-one) (2) is a ubiquitous metabolite. Although best known as a product of microbial fermentations,[1] it is also produced by enzyme systems of animals [1d,2] and higher plants.[3] The Voges–Proskauer test [4] for the production of acetoin by bacteria is used as a basic taxonomic marker and is especially useful in classifying the *Enterobacteria*.[5] Although less important than its congener biacetyl (butane-2,3-dione), acetoin contributes to the aroma of beer [6] and of other foodstuffs.[7] Through its metabolic relationship with biacetyl it is also important in determining the aroma of butter and of milk fermentation products such as cheese.[8]

In spite of its widespread distribution, and although it is the simplest naturally occurring chiral ketone, acetoin has never been synthesised in optically pure form. Optically active acetoin has been isolated from many natural sources and reported specific rotations ($[\alpha]_D$) range from $-6.42°$ [9] to $-105°$.[10] Dextrorotatory acetoin with specific optical rotations falling between these extreme values has also been obtained.[3a] In none of the reported studies has experimental evidence been adduced for the optical purity of the acetoin and in most cases evidence of its chemical homogeneity is also lacking.

A specific optical rotation of $-84 \pm 2°$ for optically pure laevorotatory acetoin has been assumed, although the grounds for preferring this particular value over higher values were not given.[11] The uncertainty over the specific optical rotation of acetoin explains its absence from a recent comprehensive catalogue of chiral organic compounds.[12]

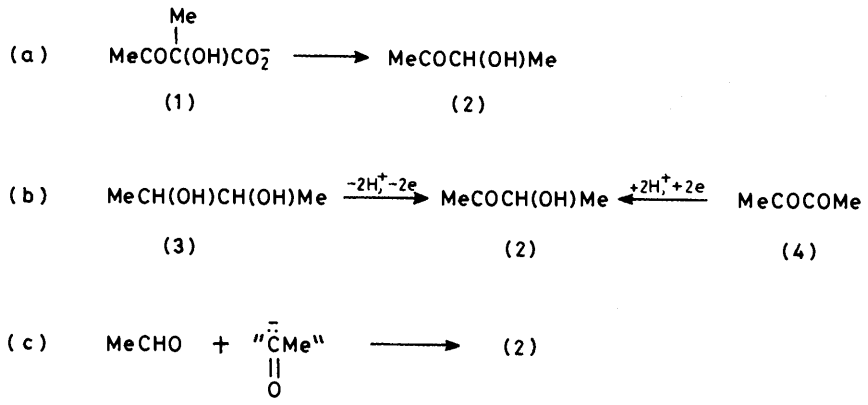
Acetoin may be produced enzymatically by the decarboxylation of α-acetolactate (2-hydroxy-2-methyl-3-oxobutanoate) (1), an intermediate in valine biosynthesis (Scheme 1a), by oxidation of butane-2,3-diol (3), by reduction of biacetyl (4) (Scheme 1b), and by the condensation of active acetaldehyde (formed by the decarboxylative addition of pyruvate to thiamin pyrophosphate) with acetaldehyde (Scheme 1c).[13] In connection with studies of branched-chain amino acid metabolism we wished to resolve the uncertainty regarding the specific optical rotation of acetoin. This has been accomplished through the two syntheses of optically pure acetoin described below.

Optically active acetoin undergoes racemisation at alkaline pH, although it is relatively stable in aqueous solution at *ca.* pH 4.5. Pure liquid monomeric acetoin crystallises to a dimer, a process reported to be accompanied by racemisation.[9] Accordingly, the syntheses described below were designed to give acetoin of high optical purity as solutions of the pure compound in water.

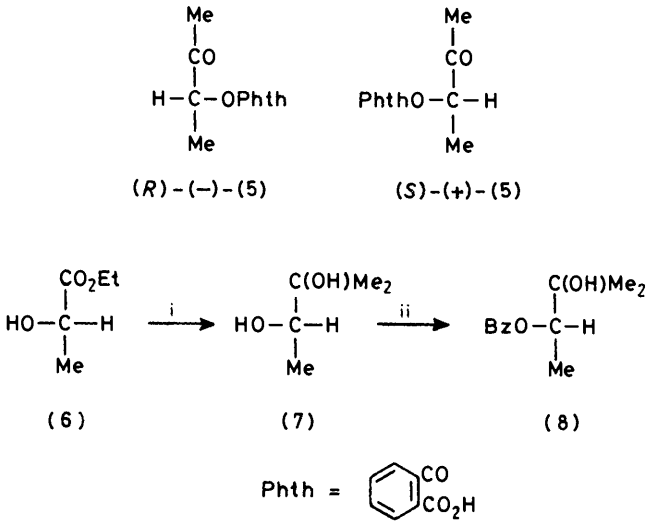
Before attempting a synthesis of optically active acetoin, the direct resolution of a derivative of acetoin itself was attempted. The hydrogen phthalate of acetoin (5) (Scheme 2) was obtained as a solid which crystallised with difficulty but which gave a nicely crystalline dicyclohexylammonium salt. A crystalline sample of the derivative could not be obtained with either quinine or brucine. However, with (*R*)-1-phenylethylamine, a crystalline salt was obtained of constant melting point (112 °C) and rotation (−1.3°). The recovered hydrogen phthalate had $[\alpha]_D$ $-10 \pm 1°$. The enantiomeric salt with (*S*)-1-phenylethylamine of constant melting point 112 °C was also obtained, the hydrogen phthalate recovered from which had $[\alpha]_D$ $+11.7 \pm 1°$. In spite of the constancy of the melting points and optical rotations of the enantiomeric 1-phenylethylammonium salts of the hydrogen phthalates of acetoin, and of their close complementarity, the following evidence showed that these materials were only partly resolved. Thus, in order to determine the absolute configurations of the apparently optically pure hydrogen phthalates of acetoin, they were converted into the corresponding 2-methylbutane-2,3-diols [as (7)] by treatment with methylmagnesium iodide. To permit correlation with standard material by n.m.r. spectroscopy in the presence of chiral shift reagent, optically pure (*S*)-2-methylbutane-2,3-diol (7) was prepared from ethyl (*S*)-lactate (6) by treatment with methylmagnesium iodide (Scheme 2). When the n.m.r. spectrum of 2-methylbutane-2,3-diol was determined in the presence of tris[3-trifluoroacetyl-(+)-camphorato]europium(III), no enantiomeric chemical shift differences, but only a broadening of the shifted n.m.r. signals was observed. However, in the n.m.r. spectrum of the corresponding benzoyl derivative determined in the presence of chiral shift reagent, separate signals were observed for the geminal methyl groups. Each of these signals showed enantiomeric chemical shift differences, the lower field signal with baseline resolution. From the corresponding spectrum of the (*S*)-diol benzoate (8) derived from ethyl (*S*)-lactate, it was found that the downfield components of the enantiomerically split geminal methyl signals could be attributed to the (*S*)-isomer. This assignment was confirmed by redetermination of the spectrum after the addition of a small amount of racemic material.

When the diol benzoates derived from the attempted resolution of the hydrogen phthalate of acetoin (2) with (*R*)- and (*S*)-1-phenylethylamine were examined in the same way, it was found that the laevorotatory material ($[\alpha]_D$ $-10.1 \pm 1°$) consisted of a 60 : 40 mixture of isomers and the dextrorotatory material ($[\alpha]_D$ $+11.7 \pm 1°$) of a 30 : 70 mixture. The (+)-hydrogen phthalate gave rise to a diol benzoate [as (8)] enriched in the isomer giving the downfield components of the enantiomerically split geminal methyl signals, and the (−)-isomer a diol benzoate enriched in the isomer giving the corresponding upfield components. These observations permitted the assignments of the (*S*)-configuration to the (+)-hydrogen phthalate of acetoin and the (*R*)-configuration to the (−)-hydrogen phthalate (Scheme 2).

The possibility of partial racemisation during reaction of the resolved hydrogen phthalates of acetoin with methylmagnesium iodide was ruled out by re-examination of the n.m.r. spectra of the methyl esters of the hydrogen phthalates determined in the presence of chiral shift reagent. Initial experiments at ambient temperature showed no enantiomeric chemical-shift differences. However, at lower temperatures, such splitting was observed, reaching an optimum at −20 °C, below which broadening of the signals with loss of resolution occurred. When the methyl esters of the resolved hydrogen



Scheme 1.



Scheme 2. *Reagents:* i, MeMgI; ii, PhCOCl

phthalates of acetoin were examined, it was found that these consisted of mixtures of enantiomers with compositions corresponding closely to those of the derived diol benzoates [as (8)]. The possibility of racemisation during reaction of the hydrogen phthalates (5) with the Grignard reagent was thereby ruled out. It was also possible to assign the downfield and upfield components of the signal due to the enantiomerically split ester methyl groups to the (*S*)- and (*R*)-isomers, and the downfield and upfield components of the enantiomerically split signal due to the acetyl methyl group to the (*R*)- and (*S*)-isomers respectively.

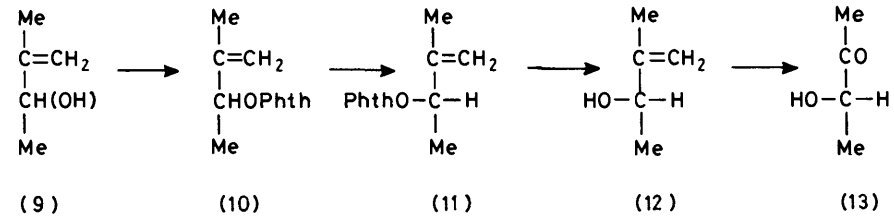
Conversion of the partly resolved hydrogen phthalates of acetoin into the corresponding dicyclohexylammonium salts, followed by repeated recrystallisation, produced crystalline material which was of lower optical purity than the starting material. The mother liquors were of correspondingly higher optical purity, but the greatest enrichment obtained was to an 88 : 12 mixture. These results suggested that the dicyclohexylammonium salt formed a racemic compound and that a 70 : 30 mixture of the enantiomeric salts was of an enantiomeric purity lower than that of the eutectic (assuming that the ternary phase diagram for the system was of the usual kind [14]). The assumption of the formation of a racemic compound was supported by the higher melting point (145 °C) of the racemic material compared with that of the optically pure material (135 °C, see below). Further support came from the corresponding i.r. spectra (KBr disc) which showed marked differences.

The first successful synthesis of optically pure (*i.e.* >96% optical purity, corresponding to an isomer ratio of >98 : 2) was achieved by the route shown in Scheme 3. 3-Methylbut-3-en-2-ol (9) was converted into the corresponding hydrogen phthalate (10). This was resolved by the Pope and Peachey method [15] using brucine and triethylamine. A brucine salt of constant melting point was obtained. Recovery of the dextrorotatory hydrogen phthalate (11) and hydrolysis to the laevorotatory unsaturated alcohol (12) followed by determination of the n.m.r. spectrum in the presence of chiral shift reagent, using the downfield of the vinyl proton signals as the indicator signal, indicated an optical purity of >96%. The sensitivity of this procedure was estimated by the addition of 8% racemic material, followed by redetermination of the n.m.r. spectrum. The size of the signal produced by the added 4% enantiomeric impurity was readily observed and showed that the presence of 2% of the minor enantiomer in the original material easily could have been detected. This isomer [having the (*S*)-configuration, see below] gave rise to the downfield components of the enantiomerically split vinyl proton signals in the n.m.r. spectrum.

Ozonolysis of the unsaturated alcohol (12) in chloroform followed by extraction into water gave a solution of (*S*)-acetoin of 100% purity by g.l.c. The concentration of the acetoin was determined by g.l.c. using 2-methoxyethanol as internal standard. The specific rotation ($[\alpha]_D^{25}$ +82 ± 3°) of the acetoin solution showed that it had the (*S*)-configuration (13). To confirm the optical purity of the acetoin, it was converted into the hydrogen phthalate. N.m.r. examination of the corresponding methyl ester in the presence of chiral shift reagent as before indicated an optical purity of >96%. This result both confirmed the optical purity of the acetoin and showed that the procedure for conversion into the hydrogen phthalate did not cause racemisation. The dextrorotation of the acetoin showed that both the unsaturated alcohol (12) and the corresponding hydrogen phthalate (11) had the (*S*)-configuration.

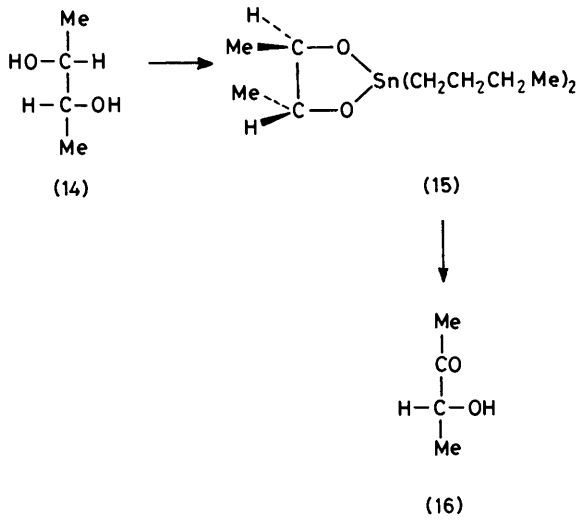
Attempts to isolate the hydrogen phthalate of the (*S*)-(−)-alcohol from mother liquors enriched in this enantiomer, by means of the brucine, dicyclohexylammonium, or 1-phenylethylammonium salts, were uniformly unsuccessful.

The second synthesis of optically pure acetoin started from butane-2,3-diol. Since both enantiomers of this compound are available, this synthesis, in principle, can give both enantiomers of acetoin. However, in order to illustrate the method, the (2*R*,3*R*)-isomer (14) was chosen, since this led to the enantiomer of the acetoin produced by the route described above.



(9) (10) (11) (12) (13)

Scheme 3.



(14) (15) (16)

Scheme 4.

David [16] has shown that 2,1,3-stannadioxolanes (cyclic stannylenes) formed by condensation of 1,2-diols with dibutyltin oxide, are readily oxidised by bromine to α-ketols. Since this reaction occurs under mildly acidic conditions, it seemed likely that any optically active acetoin produced by this method might resist racemisation. The crystalline cyclic stannylene (15) was prepared from (2*R*,3*R*)-butane-2,3-diol (14) and dibutyltin oxide. Oxidation of the derivative in dichloromethane solution, followed by extraction with water gave a solution of (*R*)-acetoin (16), pure (g.l.c.) except for a small impurity of butane-2,3-diol. Separation of the acetoin from the diol was readily effected by distillation, a process not expected to cause racemisation. The absence of racemisation was indicated by boiling a solution of acetoin under reflux in D_2O followed by determination of the ^{13}C n.m.r. spectrum. A 1 : 1 : 1 triplet, which would have been clearly evident in the signal due to the carbinol carbon in deuteriated material produced by exchange accompanying racemisation, was entirely absent. The specific rotation of the (*R*)-acetoin produced ($[\alpha]_D^{23}$ $-84 \pm 3°$) closely complemented that of the dextrorotatory isomer produced by the previous route.

Circular dichroism data for acetoin and for some of the other derivatives produced during this investigation, are given in Table 1.

Experimental

M.p.s were determined in open capillaries and are corrected. Optical rotations were measured using a Thorn Automation-NPL Type 243 Automatic Polarimeter. N.m.r. spectra were determined using either JEOL MH-100, Hitachi-Perkin-Elmer R600 or JEOL PS-100 spectrometers. Spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard unless otherwise indicated. Sodium 3-trimethylsilylpropanesulphonate was used as internal standard for spectra recorded in water. The chiral shift reagent used throughout was tris[3-trifluoroacetyl-(+)-camphorato]europium(III). I.r. spectra were recorded on a Perkin-Elmer 398 spectrometer as either liquid films or KBr discs. G.l.c. analyses were performed using a Pye Unicam GCD chromatograph fitted with a flame ionisation detector. The columns used were as follows: (1) 2.7 m × 3 mm (i.d.) glass column packed with OV 17 on Chromosorb W (100—200 mesh); (2) 1.6 m × 3 mm (i.d.) glass column packed with 15% Carbowax 20M on Chromosorb W (80—100 mesh). The carrier gas (N_2) flow rate was 30 ml min^{-1}. G.l.c. peak areas were determined using either a Pye Unicam DP88 integrator or a Laboratory Data Control 308 computing integrator. Bulb-tube distillations were carried out using a bulb-tube oven model GKR 50 (Buchi AG, Flawil, Switzerland). (2*R*,3*R*)-Butane-2,3-diol (Fluka) had $[\alpha]_D$ $-15 \pm 1°$ (neat), $[\alpha]_D$ $-13.6°$ (*c* 0.5, water). Ether refers to diethyl ether throughout.

1-*Methyl*-2-*oxopropyl Hydrogen Phthalate* (5).—Acetoin (8.8 g, 0.1 mol) and phthalic anhydride (14.8 g, 0.1 mmol) were dissolved in anhydrous pyridine (250 ml) and the solution was kept at room temperature for 5 days. The pyridine was removed at 25 °C under reduced pressure and the oily residue was dissolved in ether (200 ml); the solution was washed with sulphuric acid (1M; 100 ml) and water (2 × 100 ml) and the ether was removed under reduced pressure. The residual oil was dissolved in chloroform (100 ml) and dried (Na_2SO_4). The chloroform was removed under reduced pressure to give 1-*methyl*-2-*oxopropyl hydrogen phthalate* (5) as a pale yellow oil which slowly crystallised (20.9 g, 89%), m.p. 71 °C [after recrystallisation from EtOAc–light petroleum (b.p. 60—80 °C)], δ_H 1.47 (3 H, d, *Me*CH), 2.27 (3 H, s, MeCO), 5.16 (1 H, q, MeC*H*), 7.2—7.8 (4 H, m, Ar), and 10.51 (1 H, s, CO_2H), $\nu_{max.}$ 1 695, 1 730, and 1 745 cm^{-1} (CO) (Found: C, 60.9; H, 5.1. $C_{12}H_{12}O_5$ requires C, 61.02; H, 5.12%). Dicyclohexylammonium salt, m.p. 145 °C (acetone), $\nu_{max.}$ 1 380, 1 630 (CO_2^-), 1 720, and 1 730 cm^{-1} (CO) (Found: C, 68.6; H, 8.5; N, 3.4. $C_{24}H_{35}NO_5$ requires C, 69.04; H, 8.45; N, 3.36%).

Methyl 1-*Methyl*-2-*oxopropyl Phthalate*.–To a solution of the hydrogen phthalate of acetoin (0.5 g) in ether (10 ml) at 0 °C was added an excess of an ethereal solution of diazomethane. The ether was removed to give the methyl ester (100%) homogeneous by t.l.c. [Kieselgel F_{254}, benzene–ether (1 : 1), R_F 0.41]. Final purification was effected by bulb-tube distillation (150 °C, 0.01 mmHg), >98% pure by g.l.c. (column 1), $\nu_{max.}$ 1 720 cm^{-1} (CO); δ_H 1.58 (3 H, d, *Me*CH), 2.34 (3 H, s, MeCO), 4.06 (3 H, s, CO_2Me), 5.56 (1 H, q, MeC*H*), and 7.8—8.2 (4 H, m, Ar) (Found: C, 62.5; H, 5.55. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64%).

Table 1. Circular dichroism data

Compound	Solvent [a]	λ/nm (Δε)
Dicyclohexylammonium salt of the hydrogen phthalate of (*S*)-3-methylbut-3-en-2-ol (11)	A	204 (+6.3), 239 (+3.6)
	B	201 (+6.8), 241 (+3.2)
Dicyclohexylammonium salt of the hydrogen phthalate of (*S*)-acetoin (5) [b]	A	238 (+2.45), 278 (+1.13)
	B	242 (+3.39), 277 (+0.97)
(*S*)-Acetoin (2)	C	276 (−0.56)

[a] Solvents: A = MeOH; B = MeOH–HCl; C = water. [b] D. H. G. Crout, J. Littlechild, and S. M. Morrey, to be published.

Table 2. Attempted resolution of the hydrogen phthalate (5) of acetoin. Yields and m.p.s of 1-phenylethylammonium salts, optical rotations of the corresponding hydrogen phthalates, and m.p.s and optical rotations of the dicyclohexylammonium salts of the corresponding hydrogen phthalates

	1-Phenylethylammonium salt		Hydrogen phthalate	Dicyclohexylammonium salt of hydrogen phthalate	
Cryst. no.	Yield (g)	M.p. (°C)	$[\alpha]_D$ (EtOH)	M.p. (°C)	$[\alpha]_D$ (EtOH)
1	17.7	111—112	−9.9°	142	−1.7°
2	10.8	112.5	−10.6°	142	−1.8°
3	8.4	112	−9.4°	143	−1.3°

Attempted Resolution of the Hydrogen Phthalate of Acetoin (5).—(*a*) To the hydrogen phthalate (5) (23.6 g, 0.1 mol) in ether (250 ml) was slowly added a solution of (+)-1-phenylethylamine (12.1 g, 0.1 mol) in ether (100 ml) with stirring. The resulting solid was recrystallised to constant m.p. (acetone, 3×). The salt (6.4 g) had m.p. 112 °C (Found: C, 67.35; H, 6.6; N, 4.0. $C_{20}H_{23}NO_5$ requires C, 67.21; H, 6.49; N, 3.92%). After each recrystallisation, the free acid was isolated from a portion (500 mg) of the salt by passage of an aqueous solution (10 ml) through a column of Dowex 50WX8 ion-exchange resin (5 ml bed volume, 20—50 mesh, H^+ form) followed by elution with water (10 ml). The aqueous eluate was extracted with ether (3 × 20 ml) and the combined ethereal extracts were dried and evaporated to give an almost quantitative recovery of the hydrogen phthalate (5). This was converted into the dicyclohexylammonium salt which was recrystallised (acetone). The optical rotation and melting point of the salt were determined. The m.p.s of the 1-phenylethylammonium salt, the rotations of the corresponding hydrogen phthalate, and the m.p.s and optical rotations of the corresponding dicyclohexylammonium salt are given in Table 2. (*b*) The (−)-1-phenylethylammonium salt of the hydrogen phthalate (5) was prepared as above, m.p. 112 °C, $[\alpha]_D^{23}$ (for the recovered hydrogen phthalate) +11.7° (*c* 3.3, EtOH) (Found: C, 67.5; H, 6.6; N, 4.0. $C_{20}H_{23}NO_5$ requires C, 67.21; H, 6.49; N, 3.92%).

(RS)-2-*Methylbutane*-2,3-*diol*.—A solution of (*RS*)-acetoin (8.8 g, 0.1 mol) in ether (50 ml) was added slowly with stirring to a solution of methylmagnesium iodide (2M; 100 ml) at 0 °C. The mixture was boiled under reflux for 1.5 h and cooled. Hydrochloric acid (2M; 100 ml) was added slowly. The mixture was shaken and the aqueous solution was saturated with sodium chloride and extracted continuously with ether for 18 h. The ethereal extract was dried ($MgSO_4$) and stirred with mercury to remove iodine. The ether was evaporated to give a pale yellow oil which was distilled (bulb-tube) at 120 °C, 15 mmHg (lit.,[17] b.p. 93—95 °C, 24 mmHg) to give (*RS*)-2-methylbutane-2,3-diol (5.8 g, 56%), >95% pure by g.l.c. (column 2, 135 °C), $\nu_{max.}$ 3 400br cm^{-1} (OH); δ_H 1.15 (3 H, d, *Me*CH), 1.16, 1.21 (each 3 H, s, Me_2C), 2.96br (2 H, s, OH), and 3.61 (1 H, q, Me*CH*).

(RS)-2-*Hydroxy*-1,2-*dimethylpropyl Benzoate*.—To a solution of 2-methylbutane-2,3-diol (104 mg, 1 mmol) in dry pyridine (1 ml), benzoyl chloride (141 mg, 1 mmol) was added and the mixture was kept overnight; ether (50 ml) was then added and the resulting solution was washed with hydrochloric acid (1M; 50 ml). The acidic solution was re-extracted with ether (2 × 50 ml) and the combined ethereal solutions were dried ($MgSO_4$) and evaporated. The residue was distilled (bulb-tube, 120 °C, 0.01 mmHg) to give (*RS*)-2-hydroxy-1,2-dimethylpropyl benzoate [as (8)] >90% pure by g.l.c. (column 2, 200 °C), $\nu_{max.}$ 1 720 (CO) and 3 500 cm^{-1} (OH); δ_H 1.3 (6 H, s, Me_2C), 1.35 (3 H, d, *Me*CH), 2.98br (1 H, s, OH), 5.13 (1 H, q, Me*CH*), and 7.5—7.8 (3 H, m, Ar) (Found: C, 69.2; H, 8.0. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%). The n.m.r. spectrum was also determined in the presence of chiral shift reagent (molar ratio benzoate : chiral shift reagent 2 : 1) to give the results described in the text.

(S)-2-*Methylbutane*-2,3-*diol from Ethyl* (S)-*Lactate*.—To a solution of methylmagnesium iodide (60 mmol) in ether (30 ml) at 0 °C a solution of ethyl (*S*)-lactate (2.36 g, 20 mmol) in ether (10 ml) was added slowly, with stirring. The mixture was boiled under reflux for 1.5 h and cooled. Sulphuric acid (2M; 50 ml) was added slowly and the product was isolated as above and distilled [bulb-tube, 120 °C, 15 mmHg (lit.,[18] b.p. 85 °C, 19 mmHg)]. The n.m.r. spectrum was identical with that of the racemic material prepared from acetoin (above).

2-*Methylbutane*-2,3-*diol from the Partially Resolved Hydrogen Phthalate of Acetoin*.—In a typical procedure, a solution of the partially resolved hydrogen phthalate (above) (217 mg, 0.9 mmol), enriched in the (−)-isomer) in ether (3 ml) was added with stirring to a solution of methylmagnesium iodide (4 mmol) in ether (6 ml) at 0 °C. The mixture was boiled under reflux for 1.5 h. The product was isolated as described above for the racemic material. The corresponding hydrogen phthalate enriched in the (+)-isomer was treated similarly. Both products were benzoylated as described above for the racemic material and the n.m.r. spectra were determined in the presence of chiral shift reagent to give the results described in the text. The methyl esters of the racemic and partially resolved hydrogen phthalates of acetoin were prepared as described

above. The n.m.r. spectra were determined in the presence of chiral shift reagent (molar ratio chiral shift reagent : methyl ester 1 : 2) at −20 °C to give the results described in the text.

(RS)-3-*Methylbut*-3-*en*-2-*ol* (9).—A solution of freshly distilled 2-methylprop-2-enal (148 g, 2.11 mol) in ether (500 ml) was slowly added to a solution of methylmagnesium iodide (2.54 mol) in ether (500 ml) at 0 °C with stirring. The mixture was allowed to warm to room temperature and was then stirred for a further 3 h. The mixture was cooled and a saturated solution of ammonium chloride (500 ml) was added with stirring. The ethereal layer was separated, the aqueous solution was extracted with ether (2 × 250 ml), and the combined ethereal solutions were dried ($MgSO_4$) and evaporated. The residue was distilled to give (*RS*)-3-methylbut-3-en-2-ol (9) (103 g, 56%), b.p. 113—114 °C (lit.,[19] b.p. 116—117 °C), >98% pure by g.l.c. (column 2, 90 °C), δ_H 1.22 (3 H, d, *Me*CH), 1.68 (3 H, m, MeC:C), 2.11 (1 H, s, OH), 4.12 (1 H, q, *Me*CH), and 4.65 and 4.83 (each 1 H, m, CH_2:C). The n.m.r. spectrum was determined in the presence of chiral shift reagent (molar ratio chiral shift reagent : alcohol 1 : 2) to give the results described in the text.

Hydrogen Phthalate (10) *of* (RS)-3-*Methylbut*-3-*en*-2-*ol*.—A mixture of (*RS*)-3-methylbut-3-en-2-ol (9) (43 g, 0.5 mol) and phthalic anhydride (74 g, 0.5 mol) in dry pyridine (30 ml) was heated on a steam-bath for 5 h. The cooled mixture was mixed with ether (200 ml) and the solution was washed with hydrochloric acid (2M; 250 ml); the washings were then extracted with ether (3 × 200 ml). The combined ethereal extracts were dried ($MgSO_4$) and the ether was evaporated. The residue was dissolved in chloroform (200 ml), dried ($MgSO_4$), and the chloroform removed under reduced pressure. The last traces of solvent were removed by stirring and warming the residual oil at 0.1 mmHg and 50 °C for 4 h, to give the hydrogen phthalate of (*RS*)-3-methylbut-3-en-2-ol (10) (110.4 g, 94%) essentially pure by n.m.r. The compound did not crystallise even when kept for several months, $\nu_{max.}$ 1 700 and 1 720 cm^{-1} (CO); δ_H 1.44 (3 H, d, *Me*CH), 1.77 (3 H, s, MeC:C), 4.89 and 5.03br (each 1 H, s, CH_2:C), 5.55 (1 H, q, MeC*H*), 7.4—8.0 (4 H, m, Ar), and 10.2 (1 H, s, OH). The dicyclohexylamine salt crystallised (acetone) and had m.p. 161 °C, $\nu_{max.}$ 1 635 (CO_2) and 1 725 cm^{-1} (CO) (Found: C, 72.3; H, 9.1; N, 3.15. $C_{25}N_{37}NO_4$ requires C, 72.2; H, 8.97; N, 3.37%). The methyl ester was prepared by treating a solution of the hydrogen phthalate (10) in ether (10 ml) at 0 °C with an excess of ethereal diazomethane. A quantitative yield was obtained of the ester of the hydrogen phthalate of 3-methylbut-3-en-2-ol, pure by t.l.c. [Kieselgel F_{254}, benzene–ether (1 : 1), R_F 0.55]. The ester was distilled (bulb-tube, 110 °C, 0.01 mmHg) to give a product 99% pure by g.l.c. (column 1, 225 °C), $\nu_{max.}$ 1 725 cm^{-1} (CO); δ_H 1.39 (3 H, d, *Me*CH), 1.75 (3 H, s, MeC:C), 3.80 (3 H, s, CO_2Me), 4.84, 4.98br (each 1 H, s, CH_2:C), 5.44 (1 H, q, MeC*H*), and 7.3—7.7 (4 H, m, Ar) (Found: C, 67.4; H, 6.4. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%).

Resolution of the Hydrogen Phthalate of (RS)-3-*Methylbut*-3-*en*-2-*ol* (10).—To a solution of the hydrogen phthalate (10) of the racemic alcohol (9) (85.7 g, 0.336 mol) and triethylamine (18.5 g, 0.183 mol) in methanol (100 ml), was added slowly a solution of brucine (78.9 g, 0.183 mol) in methanol (500 ml); the methanol was removed under reduced pressure. Acetone was added and removed under reduced pressure several times to eliminate traces of methanol. Three crystallisations of the residue from acetone gave the brucine salt of the (*S*)-hydrogen phthalate of 3-methylbut-3-en-2-ol (11) (37.1 g, 31%), m.p. 148 °C, $\nu_{max.}$ 1 665 and 1 715 cm^{-1} (CO) (Found: C, 68.6; H, 6.25; N, 4.35. $C_{36}H_{40}N_2O_8$ requires C, 68.77; H, 6.41; N, 4.46%). The hydrogen phthalate was recovered by suspending the brucine salt (37.1 g) in ether (200 ml) and shaking the suspension with hydrochloric acid (2M; 200 ml). The aqueous layer was extracted with ether (2 × 200 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated, finally at 0.1 mmHg for 2 h, to give the (*S*)-hydrogen phthalate (11) of 3-methylbut-3-en-2-ol (12.7 g), $[\alpha]_D^{25}$ +33 ± 2° (*c* 3, acetone). Hydrolysis to the alcohol followed by n.m.r. determination in the presence of chiral shift reagent showed the alcohol to be of >96% optical purity. The dicyclohexylammonium salt crystallised from acetone, m.p. 163 °C (Found: C, 72.75; H, 9.2; N, 3.4. $C_{25}H_{37}NO_4$ requires C, 72.26; H, 8.97; N, 3.37%). The i.r. spectrum (HBr disc) was identical with that of racemic material.

(S)-3-*Methylbut*-3-*en*-2-*ol* (12).—A solution of the (+)-hydrogen phthalate (11) of 3-methylbut-3-en-2-ol (5.4 g, 23 mmol) in sodium hydroxide solution (2M; 40 ml) was heated on a stream-bath for 2 h. The cooled solution was extracted with ether (3 × 40 ml) and the ethereal extracts were dried ($MgSO_4$) and concentrated by distillation. The residue was distilled (bulb-tube, 130 °C), to give (*S*)-3-methylbut-3-en-2-ol (12) (965 mg, 40%, >95% pure by n.m.r.), $[\alpha]_D^{21}$ −5.6 ± 1° (c 8, chloroform). N.m.r. determination in the presence of chiral shift reagent gave the results described in the text.

(S)-*Acetoin* (13).—A solution of (*S*)-3-methylbut-3-en-2-ol (12) (250 mg) in chloroform (10 ml) was ozonized at −10 °C for 45 min. The solution was shaken with a suspension of manganese dioxide (100 mg) in water (5 ml). The organic layer was re-extracted with water (2 × 5 ml). The combined aqueous solutions were filtered to give a solution of (*S*)-acetoin, pure by g.l.c. (column 2, 120 °C). The concentration of acetoin was determined by g.l.c. using a calibration curve determined with authentic material against 2-methoxyethanol as internal standard. The yield of acetoin was 40%, $[\alpha]_D^{25}$ +82 ± 3° (*c* 0.5, H_2O). The optical purity of the acetoin was confirmed as follows. The aqueous solution (15 ml, 80 mg acetoin) was saturated with sodium chloride and extracted continuously with ether for 18 h. The ethereal extract was dried ($MgSO_4$) and the bulk of the ether was removed by distillation under nitrogen through a 40 cm column packed with glass helices (bath temperature 45 °C). The residual solution (*ca.* 3 ml) was mixed with dry pyridine (4 ml) and phthalic anhydride (200 mg), and 4A molecular sieve (750 mg) was added. The mixture was left at room temperature for 7 days after which ether (40 ml) was added, and the solution was washed with hydrochloric acid (2M; 40 ml). The acidic washings were re-extracted with ether (2 × 40 ml) and the combined ethereal solutions were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was methylated (diazomethane) as before and purified by preparative t.l.c. [Kieselgel F_{254}, benzene–ether (1 : 1), R_F = 0.4] to give the methyl ester of the hydrogen phthalate of (*S*)-acetoin as a colourless oil (34 mg). N.m.r. determination in the presence of chiral shift reagent indicated an optical purity of >96%.

2,2-*Dibutyl*-4,5-*dimethyl*-2,1,3-*stannadioxolane* (15).—A mixture of dibutyltin oxide (8.34 g, 33.5 mmol) and (*R,R*)-butane-2,3-diol (14) (3 ml, 3.02 g, 33.5 mmol) in benzene (50 ml) was boiled under reflux. Water was removed using a Dean and Stark trap. A constant volume (*ca.* 1 ml) of water had been collected after 1 h, but boiling was continued overnight. The benzene was removed under reduced pressure and the residual solid was recrystallised three times from benzene to give 2,2-dibutyl-4,5-dimethyl-2,1,3-stannadioxo-

lane (15) (8.3 g, 77%), m.p. 134—136 °C (lit.,[20] m.p. of the corresponding derivative of *meso*-butane-2,3-diol = 124—126 °C) (Found: C, 44.8; H, 8.4. $C_{12}H_{26}O_2Sn$ requires C, 44.9; H, 8.16%).

(R)-*Acetoin* (16).—To a solution of the stannadioxolane (15) (321 mg, 1 mmol) in dichloromethane (6 ml), a solution of bromine (160 mg, 1 mmol) in dichloromethane (2 ml) was added dropwise with stirring. The solution was extracted with (3 × 3 ml) and the combined solutions were filtered. The resulting solution contained, in addition to acetoin, a small quantity of butane-2,3-diol (g.l.c.). The latter was readily separated from the acetoin by distillation of the aqueous solution. The acetoin distilled with the water and the butane-2,3-diol was concentrated in the boiler. The concentration of (*R*)-acetoin (16) was determined by g.l.c. as before, $[\alpha]_D^{23}$ $-84 \pm 3°$ (*c* 0.6, H_2O).

Acknowledgements

We thank Dr. P. M. Scopes for c.d. determinations.

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Received 20*th April* 1983; *Paper* 3/632