Baker's Yeast-mediated Preparation of Optically Active Aryl Alcohols and Diols for the Synthesis of Chiral Hydroxy Acids

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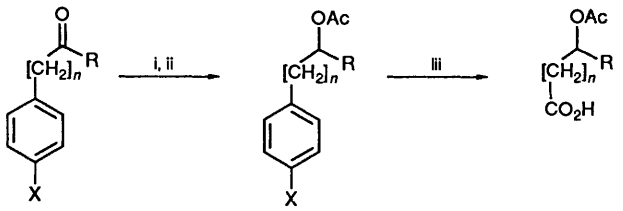
Baker's yeast reduction of 1-(4-methoxyphenyl)propan-2-one, 4-phenylbutan-2-one, and 2-hydroxy-1-(4-methoxyphenyl)ethanone (*p*-methoxyphenacyl alcohol), afforded in good yield and high optical purity the corresponding (*S*)-alcohols and the (*R*)-diol, but only after careful investigation of incubation conditions. Protection of the above hydroxy compounds, and ruthenium tetraoxide oxidation of their acetates, afforded the corresponding acetoxy acids in good yield and high optical purity. (*S*)-1-(*p*-Methoxyphenyl)ethane-1,2-diol could be prepared either by baker's yeast incubation of the acetate of *p*-methoxyphenacyl alcohol or 2-acetoxy-1-(4-methoxyphenyl)ethanone (24% yield, 82% ee) or from its (*R*)-enantiomer *via* a Mitsonobu reaction on its mono t-butyldimethylsilyl ether.

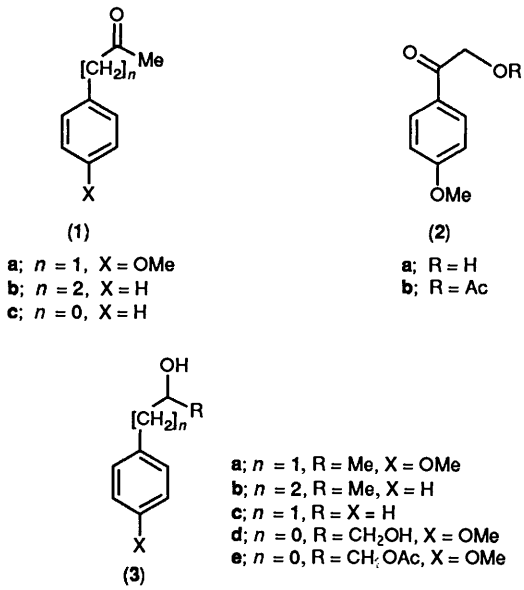
Many bioactive natural products contain a carbon framework derived from chiral hydroxy acids which are currently available by chemical and biochemical methods.[1] Among the biochemical approaches, the recently reported enzymatic resolution of acyloxyalkanoates is a useful method.[2] The reduction of keto esters[3] and keto acids[4] by *Saccharomyces cerevisiae* or other micro-organisms[5] is equally feasible and generally leads to the corresponding hydroxy acids or lactones in good to excellent enantiomeric excess (ee). We now report on our studies of the preparation of a few chiral hydroxy acids, starting from aryl ketones and using baker's yeast as biocatalyst. The aryl moiety of the aryl alcohols or diols prepared by this route can be cleaved by the ruthenium tetraoxide methodology developed by Sharpless and co-workers[6] (Scheme 1).



Scheme 1. *Reagents:* i, Baker's yeast; ii, Ac_2O, pyridine; iii, $RuCl_3$, $NaIO_4$.

We have examined two commercially available aryl ketones, namely 1-(4-methoxyphenyl)propan-2-one (*p*-methoxyphenylacetone) (**1a**), and 4-phenylbutan-2-one (**1b**), and one α-hydroxy ketone, 2-hydroxy-1-(4-methoxyphenyl)ethanone (*p*-methoxyphenacyl alcohol) (**2a**). Although baker's yeast has been successfully applied to the reduction of a large number of structurally different ketones,[7] several failures have also been reported.[8] Simple aryl ketones seem to fall into this unfortunate category, since acetophenone (**1c**) was reduced in only 12% yield, although with high ee (95%).[5] Low yields and modest enantioselectivity were also reported for the biotransformation of aryl ketones (**1a**) and (**1b**).[9] The case of α-hydroxy ketones is more favourable, and also a reversed enantioselectivity has been observed for the reduction of esters of phenacyl alcohol.[10]

Baker's Yeast Reduction of Aryl Ketones.—With the above considerations in mind, we attempted baker's yeast-mediated bioreduction of aryl ketones (**1a**) and (**1b**) and α-hydroxy ketone (**2a**) and its acetate (**2b**). The two aryl ketones (**1a**) and (**1b**) were reduced to the corresponding alcohols (**3a**) and (**3b**) only under appropriate conditions, found after much experimentation. The results are collected in the Table 1 and show that, depending on the substrate, different amounts of yeast were needed to give good yields, the higher yeast/substrate ratio being necessary for acceptable biotransformation of the aryl ketones. Also, addition of several portions of fermenting yeast at intervals gave better results than did addition of the substrate to the full amount of yeast all at once. The ee of the hydroxy derivatives (**3a**) and (**3b**) was established from analysis of the 500 MHz ^1H NMR spectrum of their (*R*)-MTPA esters.†[11]



It should be noted that the two ketones (**1a**) and (**1b**) show a similar pattern of reduction, because the highest ee value (98%) in the case of alcohol (**3a**) corresponds to a low conversion (20%), and for complete reduction 95% optically pure alcohol (**3a**) can be obtained. Similarly, the alcohol (**3b**)

† MTPA = α-methoxy-α-trifluoromethyl-α-phenylacetic acid (β,β,β-trifluoro-α-methoxy-α-phenylpropionic acid).

Table 1. Baker's yeast reduction of aryl ketones (**1a**) and (**1b**).

Product[a]	Yeast/substrate quotient (g mmol^{-1})	Incubation time (days)	Yield[b] (%)	$[\alpha]_D$[c] (°)	ee[d] (%)
(**3a**)	10	1	15	+28	98
(**3a**)	30	5	80	+27	95
(**3b**)	10	1	12	+15	95
(**3b**)	25[e]	5	82	+14	90

[a] The alcohols were in the (*S*) configuration. [b] Yields refer to pure, isolated product. [c] Recorded for solutions in chloroform. [d] As (*R*)-(+)-MTPA ester by 200 MHz NMR spectroscopy. [e] Portionwise addition of fermenting yeast.

Table 2. Baker's yeast reduction of aryl ketones (**2a**) and (**2b**).

Product[a]	Yeast/substrate quotient (g mmol^{-1})	Incubation time (days)	Yield[b] (%)	$[\alpha]_D$[c] (°)	ee[d] (%)
(**3d**)	20	1	25	−35	95
(**3d**)	20	5	70	−29	78
(**3d**)[e]	20	3	85	−36	98
(**3e**)	10	1	25	+24	82
(**3e**)[e]	20	2	25	+21	72

[a] The diol (**3d**) was in the (*R*) and the acetate (**3e**) in the (*S*) configuration. [b] Yields refer to pure, isolated product. [c] Recorded for solutions in ethanol for (**3d**) or acetone for (**3e**). [d] As (*R*)-(+)-MTPA diester for (**3d**) and monoester for (**3e**) by 500 MHz ^{1}H NMR spectroscopy. [e] Under nitrogen.

exhibits a lower ee (90%) when the transformation of (**1b**) is practically complete and the highest optical purity (95% ee) was observed when the reduction was only 15–20% complete. We also found that incubation of the ketone (**1b**) afforded a 5–10% yield of 2-phenylethanol (**3c**). This alcohol probably arose from a Baeyer–Villiger-type reaction on the parent ketone (**1b**), since other oxidations in this reaction medium have been observed by Fujisawa and collaborators.[12] In all cases, the configuration of the isolated alcohols was (*S*), in agreement with Prelog's rule,[13] which generally applies to the micro-organism-mediated reduction of ketones.

4-Methoxyphenacyl alcohol (**2a**) and its acetate (**2b**) were also good substrates and yields of the hydroxy derivatives (**3d**) and (**3e**) were satisfactory to good, depending on the conditions adopted for the incubation experiments (Table 2). The ee of the products was established by 500 ^{1}H NMR spectroscopy of the most suitable derivative, *i.e.* the diester of diol (**3d**) with (*R*)-(+)-MTPA chloride and the (*R*)-(+)-MTPA ester of the acetate (**3e**). Under fermenting conditions, the maximum ee-value (95%) of the (*R*)-diol (**3d**) was observed only for limited conversion of starting aryl ketone (**2a**). If the biotransformation period was prolonged, the yields of this product were improved, but the ee was lowered (78%). Under controlled anaerobic conditions (nitrogen atmosphere), we could attain a quantitative transformation of the substrate and we obtained the diol (**3d**) in 85% yield and 98% ee. The reduction of the acetate (**2b**) was less clean and the best results were obtained for a 25% yield of the (*S*)-monoacetate (**3e**) with 82% ee. Again, for the α-hydroxy ketone (**2a**) and its acetate (**2b**), we confirmed our previous observation that simple protection of the alcohol function(s) is sufficient to reverse the stereochemical outcome of baker's yeast bioreduction.[10] However, compared with the reported reduction of phenacyl alcohol and its acetate (92 and 94% ee),[10] the results obtained with the diol (**3d**) and the acetate (**3e**) showed that the ee-value of monoacetate (**3e**) was not as satisfactory as that for the unsubstituted diol monoacetate. This fact is probably connected with the nature of the *para*-substituent, a similar observation having been reported for baker's yeast reduction of 4-substituted acetophenones.[14] We are currently investigating the effect of other electron-donating or -withdrawing groups on the bioreduction of substituted aromatic α-hydroxy ketones.

Synthesis of Hydroxy Acids.—The transformation of the alcohols (**3a**) and (**3b**) and diol (**3d**) was efficiently carried out by periodate oxidation, catalysed by ruthenium tetraoxide,[6] of the corresponding acetates (**4**), in accord with the results of Kasai and Ziffer.[15] In order to exploit the synthetic potential of the hydroxy acids which could be obtained from the chiral hydroxy derivatives (**3**), especially the diol (**3d**), a protection regimen different from our acetate one might be desirable. The acetal was cleared and the diol oxidized to benzoic acid; thus the acetal protection was not convenient and acetate remains a more suitable protecting group in the RuO_4 oxidation of the aromatic ring. Therefore, these oxidations were carried on acetate (**4**) and the results are collected in Table 3.

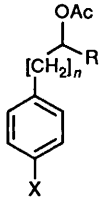
The preparation of the acetoxy acids (**5a–c**), their utility as chiral intermediates, and their optical purity deserve a few comments.

3-*Acetoxybutanoic acid* (**5a**). The acetoxy acid (**5a**) can be prepared optically pure from chiral 3-hydroxybutanoic acid by acetylation and can itself be used as a chiral synthon. This is generally the case of (*R*)-(−)-(**5a**), as illustrated by a few examples reported in the literature.[16] Starting from 98% optically pure acetoxy alcohol (**4a**), we could prepare (*S*)-3-acetoxybutanoic acid (**5a**) in good yield (80%) and with an optical rotation (+3.7°) which is among the highest reported [+3.4° for the (*S*)- and −4.0° for the (*R*)-isomer].[17] The methyl ester corresponding to a sample of acid (+)-(**5a**) had been already prepared and showed $[\alpha]_D$ +0.5° (neat),[18] and from acid (−)-(**5a**) the corresponding methyl ester, $[\alpha]_D$ −0.51° (neat), has been recorded.[19] On the other hand, it has also been reported that acetylation of a sample of (*S*)-(−)-methyl 3-hydroxybutanoate yielded a methyl acetoxy ester of $[\alpha]_D$ +0.79.[20] In order to clarify this confused situation, acid (*S*)-(+)-(**5a**) was transformed with ethereal diazomethane into its methyl ester, which showed an optical rotation −1.7° (*c* 4, $CHCl_3$). This confirms that the acid (**5a**) and its ester have opposite optical rotations. Furthermore, acetylation of optically pure (*R*)-(−)-3-hydroxybutanoate, in our hands, led to a sample of methyl acetoxy ester with $[\alpha]_D$ +0.5°, showing that this simple operation may lead to considerable racemization, different from the results of the esterification of the acetoxy acid (**5a**). Finally, in order to check the optical

Table 3. Ruthenium tetraoxide oxidation of acetates (**4a–c**).[a]

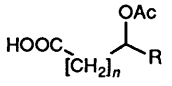
Product[a]	Time (h)	Yield[b] (%)	$[\alpha]_D$[c] (°)	ee[d] (%)	Configuration
(**5a**)	2	82	+3.7	98	*S*
(**5b**)	5	74	+6.6	90	*S*
(**5c**)	3	65	−12.5	98	*S*

[a] Sodium periodate–$RuCl_3$–substrate molar proportions 21:0.2:1. [b] Yields refer to pure, isolated product. [c] Recorded for solutions in ethanol for (**5a**), dichloromethane for (**5b**), and chloroform for (**5c**) (as methyl ester). [d] By 500 MHz ^1H NMR spectral analysis of derivatives (**6a–c**).



(4)

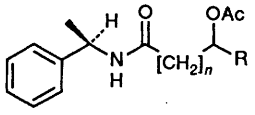
a; *n* = 1, R = Me, X = OMe
b; *n* = 2, R = Me, X = H
c; *n* = 0, R = CH_2OAc, X = OMe



(5)

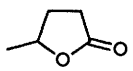
a; *n* = 1, R = Me
b; *n* = 2, R = Me
c; *n* = 0, R = CH_2OAc

purity of our sample of acid (**5a**), we prepared its chloride and the corresponding amide (**6a**) with (*R*)-1-phenylethylamine. The 500 MHz ^1H NMR spectrum of compound (**6a**) established that our sample of acetoxy acid (**5a**) ($[\alpha]_D$ +3.7°) was 98% optically pure and the same optical purity should be assumed for its methyl ester ($[\alpha]_D$ −1.7°).

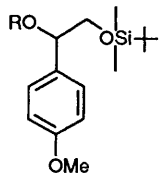


(6)

a; *n* = 1, R = Me
b; *n* = 2, R = Me
c; *n* = 0, R = CH_2OAc



(7)



(8)

a; R = H
b; R = COPh

Our method for the preparation of acid (**5a**), although not competitive with the classical procedure for the preparation of (*S*)-alkyl 3-hydroxybutanoates,[21] can give access to a nearly optically pure acetoxy ester of acid (**5a**).

4-*Acetoxypentanoic acid* (**5b**). The acetoxy acid (**5b**) itself could be used as a chiral synthon or alternatively it could be cyclized to (*S*)-γ-methylbutanolactone [5-methyl-4,5-dihydrofuran-2(3*H*)-one] (**7**), which can itself serve as a valuable chiron, as shown by Mori[22] who used this compound for a chemical synthesis of (*R*)- and (*S*)-sulcatol, the aggregation pheromone in the scolytid beetle, *Gnathotrichus sulcatus*. More recently, another chemical synthesis of lactone (**7**) and its use as a chiron for the synthesis of geodiamolide A have been reported.[23] In addition, two enzymatic syntheses of the lactone (**7**) have been reported, a lipase-catalysed lactonization of methyl 4-hydroxypentanoate[24] and a bioreduction of ethyl laevulinate and cyclization of the thus formed 4-hydroxy ester.[3] It should be mentioned that the optical purity of the lactone (**7**) was always established by measurement of the optical rotation and, for this compound, only indirect evidence is available to correlate optical rotation and ee. The configuration of the acetoxy acid (**5b**) was easily assessed by comparison with reported literature data on the lactone (**7**),[22] thus establishing that the bioreduction of the aromatic ketone (**1b**) proceeds according to Prelog's rule.[13] The overall yield of the lactone (**7**) from the alcohol (**3b**) was 46% (isolated yield) and the optical rotation of −29.5° (*c* 1.3, CH_2Cl_2) recorded for our sample was nearly identical with the highest rotation recorded in the literature[22] ($[\alpha]_D$ −29.6°, *c* 1.29, CH_2Cl_2). The optical purity of the lactone (**7**) was 90% as established by 500 MHz ^1H NMR spectroscopy of the diastereoisomeric derivative (**6b**), obtained by acetylation of the hydroxy amide formed after reaction of lactone (**7**) with (*R*)-1-phenylethylamine.

2,3-*Diacetoxypropanoic acid* (**5c**). From the diacetylated diol (**4c**), (*S*)-(−)-diacetoxypropanoic acid (**5c**) was obtained with $[\alpha]_D$ −12.5° (*c* 1, $CHCl_3$), a value which is superior to the highest rotation recorded in the literature.[25] Examination of the 500 MHz ^1H NMR spectrum of diastereoisomeric amide (**6c**) allowed us to establish that our sample of acid (**5c**) was 98% optically pure and could be used as chiral synthon, as has been shown previously.[26]

One of our initial goals was to have access to both (*R*)- and (*S*)-diol (**3d**) with high ee, in order to prepare both (*R*)- and (*S*)-glyceric acids (**5c**). However, reduction of the acetate (**2b**) was less satisfactory and from the (*S*)-monoacetate (**3e**) we could prepare (*S*)-diacetate (**4c**) of only 82% ee [25% yield from α-hydroxy ketone acetate (**2b**)]. We tried to prepare chemically the (*S*)-diol from (*R*)-(**3d**), using the methodology described by Takano[27] for the preparation of (*S*)-1-benzylglycerol from the (*R*)-enantiomer. However, when this procedure was applied to optically active diol (**3d**), a nearly racemic mixture of the corresponding diacetate (**4c**) was obtained. We then turned to the Mitsonobu procedure,[28] which we decided to apply to the mono t-butyldimethylsilyl ether (**8a**). This was prepared selectively from (*R*)-diol (**3d**) in 94% yield, and it reacted with benzoic acid in the presence triphenylphosphine and diethyl azodicarboxylate (DEAD).[28] The (*S*)-benzoate (**8b**) was obtained in 92% yield with >95% inversion, as shown by comparison with the optical rotation of the benzoate prepared from the alcohol (*R*)-(**8a**).

Conclusions.—We have shown that the bioreduction of aryl ketones (**1a**) and (**1b**) and α-hydroxy ketone (**2a**) can be efficiently achieved with fermenting baker's yeast after careful study of the incubation conditions. The hydroxy derivatives (**3a**), (**3b**), and (**3d**) so obtained exhibit high optical purity and, suitably protected as the acetate, can constitute the starting material for the preparation of chiral hydroxy acids (**5a–c**) of synthetic utility. When the biocatalytic process was not completely satisfactory in reversing the stereochemical outcome of the reduction, as in the case of the α-acetoxy ketone (**2b**), a well documented chemical method could be successfully used for the purpose.

Experimental

Bakers' yeast was purchased from Eridania (Italy) and chemicals from Fluka (Switzerland). The 60 MHz ^1H NMR spectra were recorded on a Varian 360 L spectrometer; Bruker spectrometers AC 200 and AM 500 were used for the 200 and 500 MHz ^1H NMR spectra, respectively. All the NMR spectra were recorded for $CDCl_3$ solutions ($SiMe_4$ internal or external standard). Optical rotations were measured on a Perkin-Elmer

Model 141 Polarimeter. Distillations for analytical purposes were performed with a Büchi GKR-50 glass tube (Kugelrohr) oven. TLC analyses were carried out on Merck 60 F_{254} silica gel plates.

Baker's Yeast-mediated Preparation of (S)-(+)-1-(4-*Methoxyphenyl*)*propan-2-ol* (**3a**) *and* (S)-(+)-4-*Phenylbutan-2-ol* (**3b**).—To a vigorously stirred solution of sucrose (70 g) in water (0.9 l) was added bakers' yeast (140 g). The suspension was kept at 30 °C for 0.5 h then the appropriate carbonyl compound (**1a**) or (**1b**) (12 mmol) was added. Three portions of fermenting baker's yeast [70 g in a solution of sucrose (35 g) in water (225 ml)] were added during 5 days. The suspension was filtered through a Celite pad and, after extraction with diethyl ether (4 × 0.5 l), drying with sodium sulphate, and careful evaporation of the solvent, a residue was obtained which was purified by silica gel column chromatography.

The alcohol (**3a**) (1.6 g, 80%) was obtained by elution with hexane–ethyl acetate (8:2); b.p. 200 °C (12 mmHg) (Found: C, 72.4; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.29; H, 8.43%); $[\alpha]_D$ +27° (*c*, 4.4 in $CHCl_3$); δ_H(60 MHz) 1.15 (3 H, d, *J* 7 Hz, Me), 2.0–2.2 (1 H, m, exchangeable with D_2O), 2.6 (2 H, d, *J* 7 Hz, CH_2), 3.75 (3 H, s, OMe), 3.7–4.0 (1 H, m, CHO), 6.8 (2 H, d, *J* 10 Hz, ArH), and 7.15 (2 H, d, *J* 10 Hz, ArH). A 95% ee for the (*S*)-alcohol (**3a**) was established by ^{1}H NMR (200 MHz) analysis of its (*R*)-(+)-MTPA ester, by integration of signals of the two singlets corresponding to the OMe signal for (*R*)- and (*S*)-(**3a**) at δ_H 3.80 and 3.82, respectively.

The alcohol (**3b**) (1.48 g, 82%) was obtained by elution with hexane–ethyl acetate (8:2); b.p. 130–132 °C/18 mbar* (lit.,[29] 132 °C/14 mmHg) (Found: C, 80.1; H, 9.5. Calc. for $C_{10}H_{14}O$: C, 79.96; H, 9.39%); $[\alpha]_D$ +14° (*c*, 2.75 in $CHCl_3$) (lit.,[29] +14.74°, neat); δ_H(60 MHz) 1.25 (3 H, d, *J* 7 Hz, Me), 1.55–2.0 (2 H, m, CH_2), 2.65–2.95 (2 H, d, *J* 7 Hz, CH_2), 3.0 (1 H, exchangeable with D_2O), 3.5–4.0 (1 H, m, CHO), and 7.15–7.5 (5 H, m, Ph). A 90% ee for the (*S*)-alcohol (**3b**) was established by ^{1}H NMR (200 MHz) analysis of its (*R*)-MTPA ester, by integration of signals of the two doublets corresponding to the Me signal for (*R*)- and (*S*)-(**3b**) centred at δ_H 1.325 and 1.395, respectively.

Baker's Yeast Preparation of (R)-(−)-1-(4-*Methoxyphenyl*)-*ethane*-1,2-*diol* (**3d**) *under Anaerobic Conditions*.—The *p*-methoxyphenacyl alcohol (**2a**) was prepared from commercially available *p*-methoxyphenacyl bromide and sodium formate according to ref. 10 (85% yield). To a solution of sucrose (135 g) in water (1.5 l) was added bakers' yeast (135 g). The suspension was stirred at 30 °C for 0.5 h, then kept under nitrogen while the α-hydroxy ketone (**2a**) (1 g, 6 mmol) was added and the suspension was vigorously stirred. After complete conversion of the substrate (24 h), the suspension was filtered through a Celite pad. After extraction with diethyl ether (3 × 0.5 l), drying with sodium sulphate, and careful evaporation of the solvent, a residue (1.25 g) was obtained, which was purified by silica gel column chromatography. The product (**3d**) (0.86 g, 85%) was obtained by elution with hexane–ethyl acetate (1:1); m.p. 93–95 °C (lit.,[30] 94–95 °C) (Found: C, 64.4; H, 7.2. Calc. for $C_9H_{12}O_3$: C, 64.28; H, 7.14%); $[\alpha]_D$ −35° and $[\alpha]_{546}$ −41.6° (*c*, 1 in EtOH) {lit.,[30] $[\alpha]_{546}$ −41.2° for the (*R*)-isomer, *c* 0.5–1.5 in EtOH}; δ_H(60 MHz) 3.7 (2 H, d, *J* 6 Hz, CH_2O), 3.8 (3 H, s, OMe), 4.0–4.3 (2 H, m, exchangeable with D_2O), 4.7 (1 H, t, CHO), 6.95 (2 H, d, *J* 8 Hz, ArH), and 7.4 (2 H, d, *J* 8 Hz, ArH). A 98% ee for the (*S*)-diol (**3d**) was established by ^{1}H NMR (500 MHz) analysis of its (*R*)-(+)-MTPA diester, by integration of signals of the two singlets corresponding to the OMe signals for (*R*)-and (*S*)-(**3d**) centred at δ_H 3.785 and 3.795, respectively.

Preparation of Acetates (**4a–c**).—The alcohols (**3a**), (**3b**), and (**3d**) (10 mmol) were dissolved in pyridine (15 ml) and acetic anhydride (3.15 ml, 33.3 mmol) was added. After 5 h at room temperature the mixture was treated with water (20 ml) and extracted with dichloromethane (3 × 20 ml). The extract was washed with water (3 × 15 ml), dried, and evaporated under reduced pressure. Yields of the acetates were 92–98% and the products were used directly without further purification.

Ruthenium(III)-*catalysed Periodate Oxidation of Acetates* (**4a–c**).—The acetate (10 mmol) was dissolved in a mixture of acetonitrile (40 ml) and tetrachloromethane (40 ml), then water (100 ml), sodium periodate (45.6 g, 0.212 mol), and ruthenium(III) chloride (0.41 g, 2 mmol) were added. The mixture was kept at 70 °C for 3 h and the progress of the reaction was monitored by TLC [toluene–ethyl acetate (8:2)] until complete disappearance of the starting material. The mixture was filtered through a Celite pad, dichloromethane (45 ml) was added, the organic phase was separated, and the aqueous phase was extracted withh dichloromethane (2 × 40 ml). After usual work-up, the residue from the combined organic phases was treated with diethyl ether (25 ml) and inorganic salts were removed by filtration. Evaporation of the filtrate afforded the acetoxy acids (**5a–c**).

3-*Acetoxybutanoic acid* (**5a**).—Yield 1.2 g (82%). The physicochemical characteristics were in agreement with those described;[18] $[\alpha]_D$ +3.7° (*c*, 2.3 in EtOH) (lit.,[17] +3.4°, same conditions); δ_H(60 MHz) 1.35 (3 H, d, *J* 7 Hz, Me), 2.05 (3 H, s, MeCO), 2.65 (2 H, d, *J* 7 Hz, CH_2CO), 5.1–5.5 (1 H, m, CHO), and 7.4 (1 H, br, exchangeable with D_2O).

For analytical purposes, a sample of the methyl ester of acid (**5a**) was prepared by treatment, with ethereal diazomethane, of an ethereal solution of the acid. The physicochemical characteristics of the ester were in agreement with those described;[19] $[\alpha]_D$ −1.7° (*c*, 4 in $CHCl_3$) (lit., [18] +0.5°, neat); δ_H(60 MHz) 1.35 (3 H, d, *J* 7 Hz, Me), 2.05 (3 H, s, MeCO), 2.65 (2 H, dd, *J* 7 Hz, CH_2CO), 3.75 (3 H, s, OMe), and 5.1–5.5 (1 H, m, CHO).

4-*Acetoxypentanoic acid* (**5b**).—Yield 1.18 g (74%); δ_H(60 MHz) 1.2 (3 H, d, *J* 7 Hz, Me), 1.8–2.6 (7 H, s + m, MeCO and CH_2CO), 4.8–5.3 (1 H, m, CHO), and 10.2–10.6 (1 H, br, exchangeable with D_2O).

For analytical purposes, a sample of the methyl ester of acid (**5b**) was prepared by treatment of an ethereal solution of the acid with ethereal diazomethane. The physicochemical characteristics were in agreement with those described;[31] $[\alpha]_D$ +6.6° (*c*, 3 in CH_2Cl_2); δ_H(60 MHz) 1.25 (3 H, d, *J* 7 Hz, Me), 1.8–2.8 (7 H, s + m, MeCO and CH_2CO), 3.7 (3 H, s, OMe), and 4.8–5.2 (1 H, m, CHO).

(S)-(−)-5-*Methyl*-4,5-*dihydrofuran*-2(3H)-*one* (**7**).—To a solution of the acid (**5b**) (0.37 g, 2.3 mmol) in methanol (42 ml) was added potassium carbonate (2.1 g, 15.2 mmol) and the mixture was refluxed for 3 h. The progress of the reaction was monitored by TLC [$CHCl_3$–MeOH (7:3)] and when the hydrolysis was complete the solvent was evaporated off under reduced pressure. Water (20 ml) was added, and the mixture was cooled to 0 °C and treated with 6M-hydrochloric acid to pH 3. Extraction with dichloromethane (3 × 15 ml) and usual work-up afforded the lactone (**7**) (0.194 g, 84%); b.p. 170 °C (16 mmHg) (lit.,[22] 110 °C/39 mmHg) (Found: C, 60.1; H, 8.15. Calc. for $C_5H_8O_2$: C, 60.0; H, 8.05%); $[\alpha]_D$ −29.5° (*c*, 1.3 in CH_2Cl_2) (lit.,[22] −29.6°; *c*, 1.29 in CH_2Cl_2); δ_H(60 MHz) 1.4 (3 H, d, *J* 6 Hz, Me), 1.6–2.7 (4 H, m, CH_2), and 4.4–4.9 (1 H, m, CHO).

* 1 bar = 10^5 Pa.

2,3-*Diacetoxypropanoic acid* (**5c**). Yield 1.235 g (65%). For analytical purposes, a sample of the methyl ester of acid (**5c**) was prepared as for the esters of acids (**5a**) and (**5b**). The physicochemical characteristics were in agreement with those described;[25] $[\alpha]_D$ −12.5° (*c*, 1 in $CHCl_3$) (lit.,[25] +11.3°, same conditions); δ_H(60 MHz) 2.1 (3 H, s, MeCO), 2.2 (3 H, s, MeCO), 3.8 (3 H, s, OMe), 4.5 (2 H, d, *J* 4 Hz, CH_2CO), and 5.4 (1 H, t, *J* 4 Hz, CHO).

Derivatives (**6a–c**) *from Acids* (**5a–c**), *for* 500 MHz ^{1}H *NMR Analysis*.—A solution of the acetoxy acid (0.1 mmol) in anhydrous dichloromethane (0.5 ml) was treated with oxalyl dichloride (0.0165 g, 0.13 mmol), in the presence of dimethylformamide (20 μl), at 0 °C. After 1 h, the solution was evaporated under nitrogen and a solution of (*R*)-(+)-1-phenylethylamine (52 μl, 0.4 mmol) was added. After evaporation of the solvent, ethyl acetate (2 ml) was added and the solution was washed successively with 6M-hydrochloric acid and water, and was then dried.

For the 500 MHz ^{1}H NMR analysis, the resonances of the (*R*)- and (*S*)-Me groups of C-1, or the MeCO group were first established from spectra of the racemic acids (**5a–c**), then were compared with those of derivatives (**6a–c**) from chiral material. In the amide (**6a**) from racemic (**5a**), the resonances of (*R*)- and (*S*)-Me were observed at δ_H 1.27 and 1.29, and those of MeCO at δ_H 1.90 and 1.98. From the (*S*)-acetoxy acid (**5a**) a 1:21 ratio of these signals was observed.

In the case of derivative (**6b**), this could be prepared directly from (*S*)-(−)-γ-valerolactone (**7**) (30 mg, 0.3 mmol) with (*R*)-(+)-1-phenylethylamine (100 μl, 0.79 mmol) in tetrahydrofuran (THF) (1.2 ml) at 60 °C for 6 h in a screw-cap test tube. After evaporation of the solvent, ethyl acetate (2 ml) was added and the solution was washed successively with 6M-hydrochloric acid and water, and was then dried. The crude mixture recovered after evaporation of the solvent was directly acetylated with acetic anhydride in pyridine to afford the desired product (**6b**), pure by TLC and GLC (30 mg). In the 500 MHz ^{1}H NMR spectrum, the resonances of the (*R*)- and (*S*)-Me groups in a spectrum of the same derivative (**6b**) prepared from racemic lactone (**7**) were doublets (*J* 6.28 Hz) centred at δ 1.205 and 1.225. In derivative (**6b**) from the (*S*)-acetoxy acid (**5b**) a 1:18.5 ratio of these signals was observed.

In the amide (**6c**) from racemic (**5c**), the resonances of (*R*)- and (*S*)- the diastereoisomer's COMe groups were at δ_H 1.94 and 2.03, and δ_H 2.12 and 2.14, respectively. From the (*S*)-diacetoxy acid (**5c**), a 1:20 ratio of these signals was observed.

(R)-2-(*t-Butyldimethylsiloxy*)-1-(4-*methoxyphenyl*)*ethanol* (**8a**).—To a solution of (*R*)-diol (**3d**) (0.55 g, 3.27 mmol) in anhydrous THF (6.5 ml), were added sequentially t-butyldimethylsilyl chloride (0.59 g, 3.92 mmol) and imidazole (0.53 g, 7.84 mmol). The mixture was kept at 40 °C for 5 h, the solvent was evaporated off, water (3 ml) was added, and the product was extracted with dichloromethane (3 × 3 ml). The crude product was purified by silica gel chromatography, and elution with hexane–ethyl acetate (9:1) afforded pure *silyl ether* (**8a**) (0.87 g, 94%) (Found: C, 63.95; H, 9.35. $C_{15}H_{26}O_3Si$ requires C, 63.83; H, 9.22%); $[\alpha]_D$ −40.5° (*c*, 1.2 in CH_2Cl_2); δ_H(60 MHz) 0.1 (6 H, s, $SiMe_2$), 0.9 (9 H, s, (Bu^t), 3.6–3.9 (5 H, s + m, CH_2O and OMe), 4.8–5.0 (1 H, m, CHO), 7.1 (2 H, d, *J* 10 Hz, ArH), and 7.5 (2 H, d, *J* 10 Hz, ArH).

(S)-2-(*t-Butyldimethylsiloxy*)-1-(4-*methoxyphenyl*)*ethyl Benzoate* (**8b**).—A solution of (*R*)-silyl ether (**8a**) (0.85 g, 3 mmol) and triphenylphosphine (0.525 g, 2 mmol) in anhydrous diethyl ether (2 ml) was added dropwise to a solution of diethyl azodicarboxylate (0.35 g, 2 mmol) and benzoic acid (0.245 g, 2 mmol) in anhydrous diethyl ether (2 ml). The mixture was kept overnight at room temperature and then the white precipitate was filtered off, the solvent was evaporated off and the crude mixture was purified by silica gel chromatography. Elution with hexane afforded pure *benzoate* (**8b**) (0.7 g, 92%) (Found: C, 68.5; H, 7.9. $C_{22}H_{30}O_4Si$ requires C, 68.39; H, 7.77%); $[\alpha]_D$ −8.2° (*c*, 1.5 in CH_2Cl_2); δ_H(60 MHz) 0.1 (6 H, s, $SiMe_2$), 0.9 (9 H, s, Bu^t), 3.9 (3 H, s, OMe), 3.95–4.2 (2 H, m, CH_2O), 6.25 (1 H, t, *J* 7 Hz, CHO), 7.1 (2 H, d, *J* 10 Hz, ArH), 7.5–7.8 (5 H, m, Ph), and 8.2–8.4 (2 H, m, ArH).

A sample of the (*R*)-silyl ether (**8a**) (0.1 g, 0.35 mmol) was treated with a solution of benzoyl chloride (0.06 g, 0.43 mmol) in pyridine (2 ml) at room temperature overnight. After usual work-up, the (*R*)-benzoate (**8b**) was purified by silica gel chromatography as previously described; $[\alpha]_D$ +8.9° (*c*, 1.5 in CH_2Cl_2).

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