Double Stereoselection in the Aldol-type Synthesis of γ-Methyl and γ-Alkoxy β-Hydroxy Ketones Mediated by α-Sulphinyl Hydrazones

Rita Annunziata, Mauro Cinquini,* Franco Cozzi, and Amilcare Gilardi
Centro C.N.R. and Istituto di Chimica Industriale dell'Università, Via Golgi 19, 20133 Milano, Italy
Silvia Cardani, Giovanni Poli, and Carlo Scolastico *
Centro C.N.R. and Istituto di Chimica Organica dell'Università, Via Venezian 21, 20133 Milano, Italy

Optically active γ-methyl-β-hydroxy and γ-alkoxy-β-hydroxy ketones have been obtained by condensing chiral racemic aldehydes with chiral α-sulphinyl hydrazones. Good to excellent enantioselectivity and diastereoselectivity, both strongly dependent on the nature of the substrates and the reaction conditions, were achieved. The absolute and relative configuration of some of the ketols have been established, and a model to account for the stereochemical outcome of this reaction is discussed.

Stereoselective aldol-type condensations [1] are a powerful tool in the construction of acyclic molecules in which a number of stereocentres having definite relative and absolute configurations must be created. While simple diastereoselection can now be achieved through a variety of approaches,[1] the problem of diastereofacial discrimination,[2] met with when either, or both, the enolate and the carbonyl compound are chiral, is still a challenge, notwithstanding the impressive work especially by Heathcock,[2] Masamune,[1] and Evans.[1]

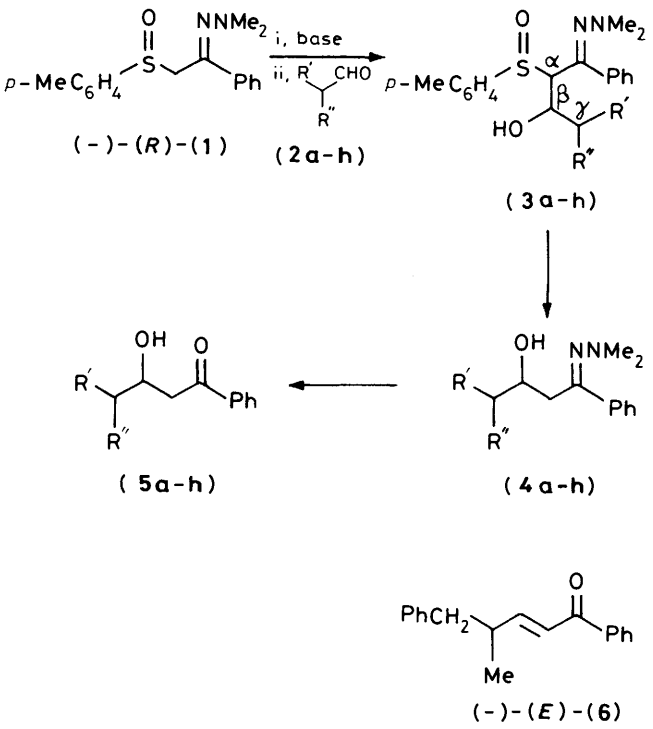
We have recently described an aldol-type asymmetric synthesis of β-hydroxy hydrazones and ketones,[3] in enantiomeric excess (e.e.) up to 88%, by reaction of aldehydes with the chiral enolate equivalents α-sulphinyl *N,N*-dimethylhydrazones.[4] We report here that this route proved to be effective when enantio- and diastereo-selectivity had simultaneously to be achieved.

Metallation of (−)-(*R*)-α-(*p*-tolylsulphinyl)acetophenone *N,N*-dimethylhydrazone (**1**) with Bu^{n}Li in the presence of HMPA (hexamethylphosphoric triamide), followed by addition of an excess of racemic, α-methyl or α-alkoxy aldehydes (**2a—h**) afforded a diastereoisomeric mixture of adducts (**3a—h**). In order to prevent stereoisomeric enrichment, isolation of intermediate products was avoided. Therefore, crude derivatives (**3a—h**) were directly converted by reductive desulphurization [3] into β-hydroxy hydrazones (**4a—h**), and cupric ion-promoted hydrolysis of the latter led to the ketols (**5a—h**); the latter were isolated by column chromatography on silica gel (Scheme 1).

The extent of diastereoselectivity was determined on compounds (**5a—h**) by h.p.l.c. and/or ^{1}H n.m.r. spectroscopy. Subsequently the spectra were recorded in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), Eu(hfc)$_3$, and the e.e.'s were evaluated. The results are reported in Tables 1 and 2.

These results show that both asymmetric induction and kinetic resolution are at work in the synthesis of (**5a—h**). In the formation of the adduct (**3**) the relative stereochemistry at the α and β carbons should mainly be affected by the geometry of the enolate,[1] the chirality of which determines the sense of the stereoselective C–C bond formation. At the same time, the relative stereochemistry at the β and γ carbons (*i.e.* the Cram *vs.* anti-Cram attack, see below) depends on the double stereodifferentiation, and therefore on the combination of the inherent diastereofacial selectivity of the two partners, the enolate and the aldehyde.

In the case of α-methyl aldehydes (**2a—d**) (see Table 1) diastereoisomeric ratios are related to relative size of R′ *vs.* methyl group, and excellent diastereoselectivities were only achieved when R′ is sterically demanding,† to the point that only one diastereoisomer was detectable when R′ is phenyl.



(**2a—5a**)	R′ = Et	R″ = Me
(**2b—5b**)	R′ = Pr^i	R″ = Me
(**2c—5c**)	R′ = $PhCH_2$	R″ = Me
(**2d—5d**)	R′ = Ph	R″ = Me
(**2e—5e**)	R′ = n-C_6H_{13}	R″ = OMe
(**2f—5f**)	R′ = Ph	R″ = OMe
(**2g—5g**)	R′ = Me	R″ = OCH_2OCH_2Ph
(**2h—5h**)	R′ = Ph	R″ = OCH_2OCH_2Ph

Scheme 1.

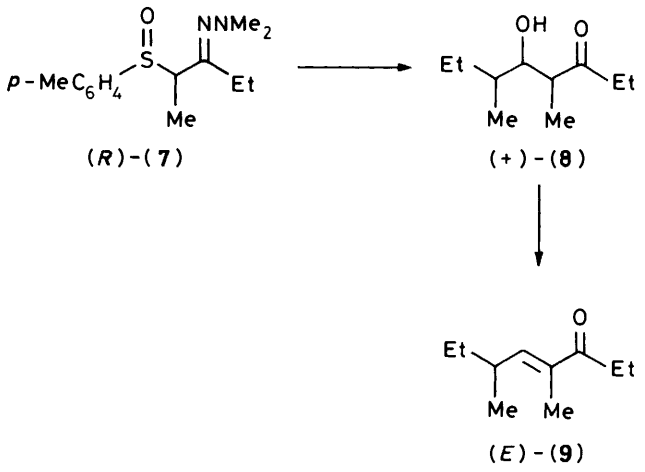
Furthermore, within each group of diastereoisomers one of the enantiomers was largely predominant, as expected on the basis of the excellent degree of enantioselectivity (e.e. 88%) observed in the condensation of (−)-(*R*)-(**1**) with isobutyraldehyde,[3] an achiral equivalent of (**2a—d**).

Double stereodifferentiation [2,6] was virtually complete in the

† An analogous observation was made in the diastereoselective addition of halogenomethyl anions to α-branching aldehydes.[5]

reaction of (−)-(*R*)-(**1**) with 2-phenylpropanal (**2d**), one out of the four possible stereoisomers of (**5d**) being produced.

To further demonstrate the large degree of stereoselective C–C bond formation always obtained, in comparison with the kinetic resolution which is only efficient in the case of bulky R′ groups, the ketol (−)-(**5c**) was converted (toluene-*p*-sulphonic acid and benzene) into the α,β-unsaturated ketone (−)-(*E*)-(**6**), $[\alpha]_D^{20}$ −4.7° (*c* 1.2, CH_2Cl_2), the e.e. of which was shown to be 11% by ^1H n.m.r. spectroscopy with the aid of Eu(hfc)$_3$. A similar situation was met with in the synthesis of manicone (**9**), one of the alarm pheromones of *Manica mutica* and *Manica bradleyi*.[7,8]



Scheme 2. *Reagents:* i, base; ii, (**2a**), iii, Na–Hg; iv, Cu^{2+}; v, toluene-*p*-sulphonic acid, benzene

Indeed, starting from the sulphoxide (**7**) the usual synthetic approach led to the ketol (+)-(**8**), consisting of a 5:3:2 mixture of three diastereoisomers.

^1H N.m.r. analysis allowed the assignment of the *syn*[9] (*erythro*) configuration at C(4)–C(5) of the major one and the *anti* (*threo*) configuration at C(4)–C(5) of the minor ones. Acid-catalyzed dehydration of (+)-(**8**) afforded virtually racemic (4*E*)-4,6-dimethyloct-4-en-3-one (**9**), in 40% overall yield starting from (**7**), thus showing the low extent of kinetic resolution of the aldehyde (**2a**).

As mentioned above aldol condensations of (**1**) were carried out with an excess of aldehydes (see Experimental section). This allowed recovery of high boiling (**2c**) and (**2d**) both in optically active form (e.e. 13 and 1% respectively),* [10] so that, on the basis of the sign of their optical rotations, the (*S*) absolute configurations could be assigned to unchanged (+)-(**2c**) and (+)-(**2d**).[10]

A large body of evidence indicates that nucleophilic attack on chiral aldehydes can be predicted following Cram's or related rules.[1,2] Thus the prevailing diastereoisomer in compounds (**5a—d**) should feature *syn*† relative configuration. Therefore, the (*R,R*) absolute configuration could be assigned to the major stereoisomer of (**5c**) and (**5d**) and, by extension, to (**5a**) and (**5b**) as well. The proposed transition state is depicted in Figure 1.

It should be noted that reaction of the aldehydes (**2a—d**) with the lithium enolate derived from acetophenone *N,N*-dimethylhydrazone (see Experimental section) leads to racemic β-ketols

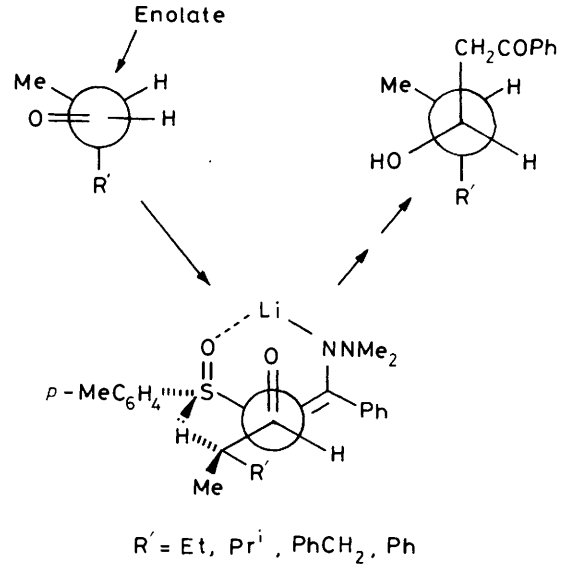
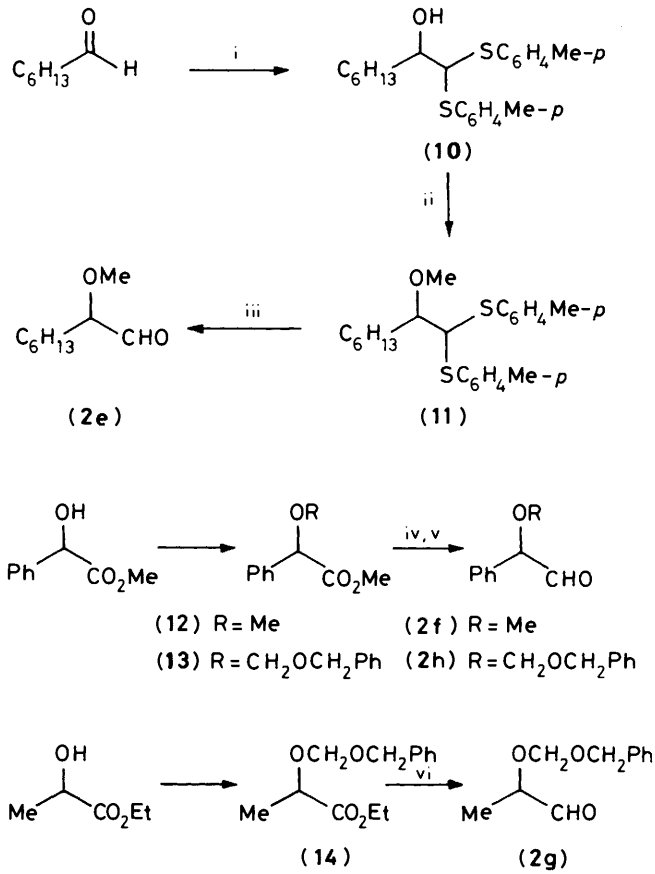


Figure 1.

(**5a—d**) in 1.3:1, 1.7:1, 1:1, and 1.8:1 diastereoisomeric ratios, respectively. Thus a substantial increase of diastereoselectivity was achieved by using the sulphinyl hydrazone (**1**) only when the bulkiness of R′ and methyl are very different.

In the case of α-alkoxy aldehydes (**2e—h**) (Table 2) synthesized according to Scheme (**3**), good to excellent degrees of



Scheme 3. *Reagents:* i, $(p\text{-}MeC_6H_4S)_2CH^-Li^+$; ii, NaH, MeI; iii, I_2, $NaHCO_3$, THF, H_2O; iv. $LiAlH_4$; v, $(COCl)_2$, DMSO, NEt_3; vi, DIBAL-H

* The strongly basic medium of the condensation reaction very likely favours a racemization process of the aldehyde (**2d**).

† ^1H N.m.r. data reported[2] by Heathcock for closely related compounds nicely agree with ours.

enantioselectivity were observed, at least in those cases in which e.e. determination was successful. They generally increased with increasing condensation temperatures. Thus, the α-sulphinyl hydrazone (**1**) proved to be an effective chiral enolate equivalent in aldol-type condensations.

It is generally assumed that in the addition of non-chelating lithium enolates to α-alkoxy-aldehydes, the diastereofacial discrimination is predictable on the basis of Felkin's model with the assumption that the alkoxy substituent ranks as 'large' among the groups bonded to the carbon atom α to the carbonyl.[1,6,11,12] In line with this, condensation of the lithium enolate derived from (**1**) with α-alkyl α-alkoxy aldehydes (**2e**) and (**2g**) should predominantly afford, if kinetically controlled, the 'Cram products' (Figure 2). The diastereoisomeric ratios

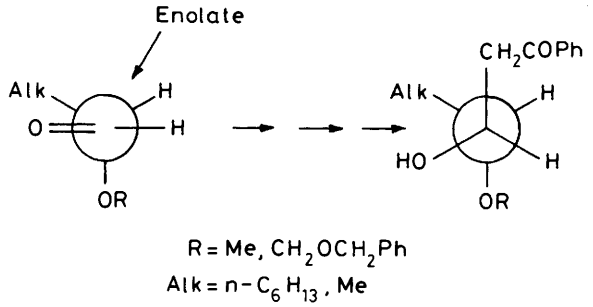


Figure 2.

(d.r.) reported in Table 2 for the condensation of (**2e**) and (**2g**) at −90 °C, 3.8:1 and 5.9:1, respectively, can accordingly be interpreted. A more efficient discrimination in the latter case was expected on the basis of the lower basicity of the (benzyloxy)methoxy group with respect to the methoxy one.[11]

Higher condensation temperatures, which are likely to shift the reaction toward thermodynamic control, resulted in different diastereoselectivities, to the extent that a marked reversal in the sense of selectivity was observed in the case of (**2e**) by working at −20 °C (d.r. 1:2.6).*

More balanced diastereoisomeric ratios were achieved for the α-phenyl- and α-alkoxy-aldehydes (**2f**) and (**2h**) (see Table 2). The temperature variation effect was maintained and reverse diastereoselectivity was observed in the case of (**2h**), on a change in the temperature from −90 °C up to 0 °C.

All chemical attempts to convert (**5e—h**) into the corresponding diols were fruitless and, therefore, it is not possible to assign the relative configuration at the two stereocentres in (**5e—h**). However, the chromatographic behaviour of (**5e—h**) and ^{1}H n.m.r. spectral pattern for (**5e—h**) (see Experimental section) seem to indicate that the first eluted isomers display the same relative stereochemistry at C_β and C_γ. On the basis of this hypothesis a reversal in Cram/anti-Cram selectivity occurs on passing from α-alkyl-α-alkoxy to α-aryl-α-alkoxy aldehydes: it is possible that in this aldol condensation alkoxy groups act as being larger than alkyl groups but not 'larger' than aryl groups.†‡ In other words, as Anh has pointed out, Felkin's model crucially relies on substituent ranking and, therefore, must be applied cautiously.[14]

Table 1. Enantio- and diastereo-selectivity in the synthesis of (−)-(**5a—d**) from (−)-(*R*)-(**1**)

Ketol	Yield[b] (%)	D.r.	E.e. (%)	$[\alpha]_D^{20c}$
(**5a**)	40	1.2:1	≥80[d]	−60.5
(**5b**)	40	3.0:1	60[e]	−40.5
(**5b**)	42	10:1	50[e]	−26.4
(**5c**)	46	1.2:1	≥90[d]	−28.4
(**5d**)	38	≥30:1	100[e]	−39.5

[a] Reactions carried out −90 °C unless otherwise stated; metallation time 1 h, condensation time 3 h. [b] Overall isolated yield of (**5a—d**) starting from (**1**). [c] *c* 1, $CHCl_3$. [d] As determined on both diastereoisomers. [e] As determined on the major diastereoisomer. [f] Condensation temperature −40 °C.

Table 2. Enantio- and diastereo-selectivity in the synthesis of (**5e—h**) from (−)-(*R*)-(**1**)

Entry	Ketol	Condensation temp. (°C)/ time (min)	D.r.[a]	E.e.[b] (%)	E.e.[c] (%)	% Yield[d]
1	(**5e**)	−90/3	3.8:1	28	62	43
2	(**5e**)	−90/180	3.8:1	42	69	45
3	(**5e**)	−50/3	1:1.2	72	82	43
4	(**5e**)	−50/180	1:1.7	73	92	43
5	(**5e**)	−20/3	1:2.6	80	83	40
6	(**5f**)	−90/180	1:1.5	79	*e*	41
7	(**5f**)	−50/180	1:1.3	83	*e*	39
8	(**5f**)	0/180	1:1.1	*e*	*e*	36
9	(**5g**)[f]	−90/60[g]	5.9:1	*e*	*e*	56
10	(**5g**)	−50/60	2.6:1	*e*	*e*	40
11	(**5h**)	−90/60	1:1.4	*e*	*e*	44
12	(**5h**)	−50/60	1:1.3	*e*	*e*	45
13	(**5h**)	0/60	1.5:1	*e*	*e*	30

[a] As determined by h.p.l.c. Ratio between first and second eluted diastereoisomers. [b] E.e. of the diastereoisomer eluted first. [c] E.e. of the diastereoisomer eluted second. [d] Overall yield of (**5e—h**) from (**1**). [e] E.e. not determined. [f] Unchanged (**2g**) was laevorotatory. [g] Very similar results were obtained with a condensation time of 180 min.

Experimental

^{1}H and ^{13}C N.m.r. spectra were recorded on Varian XL 200 or a Bruker WP 80 instrument, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. I.r. spectra were recorded with a Perkin-Elmer 457 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical, preparative, and column chromatography. H.p.l.c. analyses were performed on a Varian 5000 liquid chromatograph with a LiChrosorb SI 100 10 μm column using a Hewlett-Packard 3390 A integrator.

Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. 'Dry' solvents were distilled under dry N_2 atmosphere before use: tetrahydrofuran (THF) was distilled from sodium (in the presence of benzophenone ketide as indicator), hexamethylphosphoric triamide (HMPA) and di-isopropylamine from CaH_2, methanol from Mg turnings. All reactions employing 'dry' solvent were run under an inert atmosphere. Enantiomeric excesses (e.e.) were evaluated by ^{1}H n.m.r. spectroscopy in $CDCl_3$ with the aid of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) Eu(hfc)$_3$ under

* More puzzling is the increase in diastereoselectivity found in the condensation of (**1**) with (**2b**). A large amount of retro-aldol process prevent an extensive investigation on the effect of a temperature increase in the reaction to which Table 1 refers.

† To the best of our knowledge aldol-type condensations have been performed only on chiral α-alkyl-α-alkoxy aldehydes.[1,6,11,12]

‡ Our observation is not unprecedented: indeed α-phenyl- and α-cyclohexyl-propionaldehyde exhibit behaviour which is opposite in the sense of Cram *vs.* anti Cram selectivity.[1,13]

conditions pre-established on the corresponding racemic samples.

The α-sulphinyl hydrazones (**1**) and (**7**) were prepared as previously described.[3]

Synthesis of the Aldehydes (**2a—h**).—Compounds (**2a**) and (**2d**) were commercial products. Aldehydes (**2b**) and (**2c**) were prepared according to the method of Stork;[15] (**2b**) had b.p. 115 °C, n_D^{23} 1.4081 (lit.,[16] b.p. 69—72 °C at 160 mmHg, n_D^{25} = 1.4029); (**2c**) was purified by flash chromatography (silica gel, ether–hexane) and had ^{1}H n.m.r. and i.r. data in agreement with those reported.[10,17] For aldehydes (**2e—h**) see Scheme 3.

1,1′-*Di*-p-*tolylthio-octan*-2-*ol* (**10**).—To a solution of di-*p*-tolylthiomethane[18] (38.7 g, 0.140 mol) in anhydrous THF (300 ml), was slowly added at 0 °C, a 1.63M-solution of Bu^{n}Li in n-hexane (100 ml; 0.163 mol). The resulting solution was stirred for 1 h at 0 °C, cooled to −78 °C, treated with freshly distilled n-heptanal (25 ml, 179 mmol), stirred for 30 min at the same temperature, and finally quenched with saturated aqueous ammonium chloride. After extraction with ether, the organic phases were evaporated to dryness to give a crude product which was purified by silica gel (700 g) chromatography (n-hexane–ethyl acetate) to give pure (**10**) as an oil (54.1 g, 98%); δ_H 7.38 and 7.36 (2 × 2 H, 2 d, H *meta* to Me-Ar), 7.12 (4 H, d, H *ortho* to Me-Ar), 4.35 (1 H, d, SCHS), 3.77 (1 H, q, C*H*OH), 2.75 (1 H, br s, OH), 2.35 (6 H, s, *Me*Ar), 1.70—1.05 (10 H, m, CH_2), and 0.85 (3 H, t, *Me*CH_2) (Found: C, 70.9; H, 8.3. $C_{22}H_{30}OS_2$ requires C, 70.59; H, 8.07%).

2-*Methoxy*-1,1′-*di*-p-*tolylthio-octane* (**11**).—NaH (55% dispersion in mineral oil) (1.855 g, 43 mmol) was washed three times, by decantation, with anhydrous n-hexane. A solution of (**10**) (10.6 g, 28 mmol) in anhydrous dimethylformamide (280 ml) was then added at 0 °C and the resulting mixture stirred for 30 min at room temperature; it was then treated with methyl iodide (3.53 ml, 56.7 mmol), and stirred for a further 10 min. After quenching of the reaction mixture with water and extraction with ether, the crude product was purified by silica gel chromatography (n-hexane–ether) (10.7 g, 100%); δ_H 7.43—7.00 (8 H, m, ArH), 4.40 (1 H, d, SCHS), 3.85—3.50 (1 H, m, C*H*OMe), 3.30 (3 H, s, MeO), 2.26 (3 H, s, *Me*Ar), 1.49—0.99 [10 H, m, $(CH_2)_5$], and 0.83 (3 H, t, *Me*CH_2) (Found: C, 70.8; H, 8.45. $C_{23}H_{32}OS_2$ requires C, 71.08; H, 8.30%).

2-*Methoxyoctan*-1-*al* (**2e**).—A solution of (**11**) (9 g, 23 mmol) in THF–H_2O (85:15; 200 ml) was treated with iodine (11.8 g, 46 mmol) and $NaHCO_3$ (3.5 g, 42 mmol). The reaction was stirred for 30 min and then a second portion of iodine (11.8 g) and $NaHCO_3$ (3.5 g) was added. The treatment was repeated again after 30 min and the reaction stirred for a further 1 h, diluted with water, and extracted with CH_2Cl_2. Evaporation to dryness under reduced pressure of the extracts gave an oil which was purified by bulb-to-bulb distillation (40 °C at 0.1 mmHg) to give pure (**2e**) (3.09 g, 85%); δ_H 9.63 (1 H, d, CHO), 3.63—3.48 (1 H, m, MeOC*H*), 3.48 (3 H, s, MeO), 1.85—1.06 [10 H, m, $(CH_2)_5$], and 0.93 (3 H, t, *Me*CH_2) (Found: C, 68.25; H, 11.4. $C_9H_{18}O_2$ requires C, 68.31; H, 11.46%).

Methyl O-*Methyl*(*phenyl*)*glycolate* (**12**).[19]—A mixture of methyl phenylglycolate (7.6 g, 45.8 mmol), iodomethane (33 ml, 543.9 mmol), silver oxide (12.8 g, 54.96 mmol), and calcium chloride (6.86 g, 61.83 mmol) was refluxed overnight. Chloroform (30 ml) was then added and the mixture passed through a Celite pad. The filtrate was evaporated under reduced pressure to afford pure (**12**) (8 g, 97%); δ_H 7.2—7.5 (5 H, m, C_6H_5), 4.73 (1 H, s, CH), 3.65 (3 H, s, MeOC=O), and 3.35 (3 H, s, *Me*OCH) (Found: C, 66.7; H, 6.7. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.7%).

Methyl O-*Benzyloxymethyl*(*phenyl*)*glycolate* (**13**).—Methyl phenylglycolate was *O*-benzyloxymethylated according to a literature procedure[21] to afford the crude product that was purified by silica gel column chromatography (n-hexane–AcOEt 85:15 as eluant) (83% yield); δ 7.30 (10 H, m, 2 × C_6H_5), 5.24 (1 H, s, CH), 4.89—4.86 (2 H, d, OCH_2O), 4.66—4.63 (2 H, d, CH_2Ar), and 3.68 (3 H, s, MeO) (Found C, 71.3; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%).

O-*Methyl*(*phenyl*)*glycolaldehyde* (**2f**) *and* O-*Benzyloxymethyl*(*phenyl*)*glycolaldehyde* (**2h**).—The ester (**12**) or (**13**) was quantitatively reduced to the corresponding alcohol with lithium aluminium hydride and then submitted to Swern[21] oxidation under standard conditions to give (**2f**) or (**2h**). Crude (**2f**) or (**2h**) was purified by silica gel column chromatography (methylene chloride or n-hexane–ethyl acetate respectively). The aldehyde (**2f**) [66% overall yield from (**12**)] had δ_H 9.66 (1 H, d, CHO), 7.56—7.33 (5 H, m, C_6H_5), 4.70 (1 H, d, CH), and 3.9 (3 H, s, MeO) (Found: C, 71.95; H, 6.7. $C_9H_{10}O_2$ requires C, 71.98; H, 6.71). The aldehyde (**2h**) [93% overall yield from (**13**)] had δ_H 9.61 (1 H, d, CHO), 7.5—7.20 (5 H, m, C_6H_5), 5.12 (1 H, d, C*H*CHO), 4.95 (2 H, s, OCH_2O), and 5.9 (2 H, s, CH_2Ar) (Found: C, 74.9; H, 6.3. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%).

Ethyl 2-*Benzyloxymethoxypropanoate* (**14**).—A solution of ethyl lactate (19.5 ml, 0.165 mol) in anhydrous CH_2Cl_2 (100 ml) was treated at 0 °C with chloromethylbenzyl ether (27 ml, 0.19 mol) and di-isopropylethylamine (44 ml, 0.24 mol). The solution was stirred overnight at room temperature and then evaporated under reduced pressure to give an oil which was purified by silica gel chromatography (n-hexane–ether) to give pure (**14**) as a colourless liquid (22.6 g, 56%); δ_H 7.33 (5 H, s, C_6H_5), 4.85 (2 H, s, OCH_2O), 4.65 (2 H, s, CH_2Ar), 4.30 (1 H, q, C*H*Me), 4.18 (2 H, q, CH_2Me), 1.45 (3 H, d, *Me*CH), and 1.24 (3 H, t, *Me*CH_2) (Found: C, 65.8; H, 7.9. $C_{13}H_{18}O_4$ requires C, 65.51; H, 7.62%).

O-*Benzyloxymethyl-lactaldehyde* (**2g**).—A solution of (**14**) (2.84 g, 11.90 mmol) in anhydrous n-hexane (45 ml) was treated at −90 °C with a solution of 20% di-isobutylaluminium hydride in n-hexane (12.1 ml, 12.1 mmol). After 10 min the reaction was quenched with saturated aqueous NH_4Cl, diluted with ether, and filtered through a Celite cake. The organic phase was separated and evaporated under reduced pressure to give a crude product which was purified by flash chromatography (n-hexane–AcOEt) (2.26 g, 80%); δ_H 9.63 (1 H, d, CH=O), 7.30 (5 H, s, C_6H_5), 4.78 (2 H, s, OCH_2O), 4.60 (2 H, s, CH_2Ar), 4.05 (1 H, dq, CHO), and 1.23 (3 H, d, MeCH) (Found: C, 67.65; H, 7.35. $C_{11}H_{14}O_3$ requires C, 68.00; H, 7.27%).

General Procedure for the Synthesis of Compounds (**5a—h**).—To a stirred solution of α-sulphinyl hydrazone (2.0 mmol) in THF (50 ml) at −90 °C, Bu^{n}Li in hexane (3.0 mmol) was added, followed, after 30 min, by HMPA (6 mmol). After a further 30 min of stirring, aldehyde was added (6.0 mmol) and the mixture stirred for the time and the temperature described in Tables 1 and 2. The reaction mixture was quenched with saturated aqueous ammonium chloride and worked up as described.[3b] Reductive desulphurization and hydrazone hydrolysis were performed as described[3b] on the crude adducts. β-Ketols (**5a—d**) were purified by column chromatography (silica gel, ether–hexane as eluant) and isolated as diastereoisomeric mixtures. Each diastereoisomer of the β-ketols (**5e—h**) was isolated by flash chromatography (silica gel, ethyl acetate–hexane as eluant). In order to establish the conditions necessary to determine enantiomeric excess racemic compounds (**5a—h**) were prepared by an independent synthesis. The lithium enolate

of acetophenone *N,N*-dimethylhydrazone (Bu^{n}Li at −78 °C) was condensed with aldehydes (**5a—h**) and the β-hydroxy hydrazones were converted into the corresponding ketones.[22] Optically active and racemic (**5a—h**) displayed analogous i.r. and ^{1}H n.m.r. spectral data, in full agreement with the proposed structures. Some selected ^{1}H n.m.r. data are reported here.

3-*Hydroxy*-4-*methyl*-1-*phenylhexan*-1-*one* (**5a**) was obtained as a 1.2:1 mixture of diastereoisomers, $[\alpha]_D^{20}$ −60.5° (*c* 1, $CHCl_3$). Major isomer δ_H 4.05 (1 H, m, C*H*OH), 1.25 (1 H, m, C*H*Me), and 0.96 (3 H, d, *Me*CH). Minor isomer, δ_H 4.05 (1 H, m, C*H*OH), 1.05 (1 H, m, C*H*Me), and 0.93 (3 H, d, *Me*CH). Racemic (**5a**) was a 1.3:1 mixture of diastereoisomers (Found: C, 75.8; H, 8.85. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%).

3-*Hydroxy*-4,5-*dimethyl*-1-*phenylhexan*-1-*one* (**5b**) was obtained as a 3:1 or as 10:1 mixture of diastereoisomers, $[\alpha]_D^{20}$ = −40.5° and $[\alpha]_D^{20}$ = −26.4° (*c* 1, $CHCl_3$) respectively (see Table 1). Major isomer δ_H 4.27 (1 H, m, C*H*OH), 1.30 (1 H, m, C*H*CHOH), and 0.96 (3 H, d, *Me*CH). Minor isomer δ_H 4.12 (1 H, m, C*H*OH), 1.55 (1 H, m, C*H*CHOH), and 0.83 (3 H, d, *Me*CH). Racemic (**5b**) was a 1.7:1 mixture of diastereoisomers (Found: C, 76.2; H, 9.2. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%).

3-*Hydroxy*-4-*methyl*-1,5-*diphenylpentan*-1-*one* (**5c**) was obtained as a 1.2:1 mixture of diastereoisomers, $[\alpha]_D^{20}$ −28.4° (*c* 1, $CHCl_3$). Major isomer δ_H 4.22 (1 H, m, C*H*OH), 1.98 (1 H, m, C*H*CHOH), and 1.00 (3 H, d, *Me*). Minor isomer δ_H 4.15 (1 H, m, C*H*OH), 1.93 (1 H, m, C*H*CHOH), and 0.93 (3 H, d, *Me*). Racemic (**5c**) was a 1:1 mixture of diastereoisomers (Found: C, 80.6; H, 7.4. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).

3-*Hydroxy*-1,4-*diphenylpentan*-1-*one* (**5d**) was a single stereoisomer within experimental error. It had $[\alpha]_D^{20}$ −39.5° (*c* 1, $CHCl_3$). Racemic (**5d**) was a 1.8:1 mixture of diastereoisomers. Major isomer δ_H 4.23 (1 H, m, C*H*OH) and 1.40 (3 H, d, Me). Minor isomer δ_H 4.37 (1 H, m, C*H*OH) and 1.34 (3 H, d, Me). Optically active (**5d**) gave an ^{1}H n.m.r. spectrum identical with that of the major isomer of racemic (**5d**) (Found: C, 80.2; H, 7.1. $C_{17}H_{18}O_2$ requires C, 80.2; H, 7.1%). The signals exploited for e.e. determination in (**5a—d**) were those of the methyl groups.

The products (**5e—h**) were obtained as mixtures of diastereoisomers as described in Table 2. Racemic compounds (**5e—h**) were always obtained as 1:1 mixtures of diastereoisomers.

3-*Hydroxy*-4-*methoxy*-1-*phenyldecan*-1-*one* (**5e**) The first eluted isomer had δ_H 4.44—4.19 (1 H, m, C*H*OH), 3.48 (3 H, s, MeO), 3.22 (3 H, bd, $CH_2C{=}O$ and C*H*OMe). Compound (**5e**) from entry (2) Table 2 had $[\alpha]_D^{20}$ −11.5° (*c* 1, $CHCl_3$). The second eluted isomer had δ_H 4.49—4.23 (1 H, m, C*H*OH), 3.46 (3 H, s, MeO), 3.22 (3 H, br d, $CH_2C{=}O$ and C*H*OMe). Compound (**5e**) from entry (5) Table 2 had $[\alpha]_D^{20}$ −21.3 (*c* 1, $CHCl_3$) (Found: C, 73.2; H, 9.4. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.4%).

3-*Hydroxy*-4-*methoxy*-1,4-*diphenylbutan*-1-*one* (**5f**). The first eluted isomer δ_H 4.35—4.27 (2 H, m, C*H*OH and OH), 3.33 (3 H, s, MeO), 3.21 (3 H, d, $CH_2C{=}O$ and C*H*OMe). Compound (**5f**) from entry (7) Table 2 had $[\alpha]_D^{20}$ −40° (*c* 1, $CHCl_3$). The second eluted isomer had δ_H 4.48—4.17 (2 H, m, C*H*OH and O*H*), 3.27 (3 H, s, *Me*O), 3.13 (1 H, br d, C*H*OMe), and 3.03—2.93 (2 H, m, $CH_2C{=}O$). Compound (**5f**) from entry (7) Table 2 had $[\alpha]_D^{20}$ −3.1° (*c* 1, $CHCl_3$) (Found: C, 75.5; H, 6.8. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%).

4-*Benzyloxymethoxy*-3-*hydroxy*-1-*phenylpentan*-1-*one* (**5g**). The first eluted isomer had δ_H 4.85 (2 H, s, OCH_2O), 4.65 (2 H, s, CH_2Ar), 4.31—4.15 (1 H, m, C*H*OH), 4.04—3.84 (1 H, m, $CHOCH_2$), 3.28 (1 H, d, OH), 3.37—3.26 (2 H, m, $CH_2C{=}O$), 1.27 (3 H, d, *Me*CH). Compound (**5g**) from entry (9) Table 2 had $[\alpha]_D^{20}$ −1.8° (*c* 1, $CHCl_3$). The second eluted isomer had δ_H 4.83 (2 H, s, OCH_2O), 4.61 (2 H, s, CH_2Ar), 4.27—4.13 (1 H, m, C*H*OH), 3.89—3.77 (1 H, m, $CHOCH_2$), 3.19 (3 H, bd, $CH_2C{=}O$ and OH), and 1.26 (2 H, d, *Me*CH) (Found: C, 72.5; H, 7.1. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.1%).

4-*Benzyloxymethoxy*-3-*hydroxy*-1,4-*diphenylbutan*-1-*one* (**5h**).—The first eluted isomer had δ_H 4.95—4.37 (6 H, m, CH_2Ar, CH_2O, C*H*Ar and C*H*OH) and 3.18 (3 H, br d, $CH_2C{=}O$ and OH). The second eluted isomer had δ_H 4.86—4.46 (6 H, CH_2Ar, CH_2O, C*H*Ar and C*H*OH) and 3.22 (3 H, br d, $CH_2C{=}O$ and OH) (Found: C, 76.7; H, 6.3. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%).

Synthesis of (E)-4,6-*Dimethyloct*-4-*en*-3-*one* (**9**).—This compound was prepared in 40% overall yield starting from (**7**). The β-ketol (**8**) was obtained as described above in 47% yield. As a mixture of diastereoisomers it had $[\alpha]_D^{20}$ +0.9° (*c* 2, CH_2Cl_2). It was converted into manicone (**9**) by toluene-*p*-sulphonic acid-catalysed dehydration in refluxing benzene as described. Compound (**9**) had ^{1}H n.m.r. characteristics in agreement with those reported.

Synthesis of (E)-4-*Methyl*-1,5-*diphenylpent*-3-*en*-1-*one* (**6**).—This compound was prepared by toluene-*p*-sulphonic acid-catalyzed dehydration of (**5c**) in benzene at room temperature in 83% yield. It had $[\alpha]_D^{20}$ −4.7° (*c* 1.2, CH_2Cl_2); δ_H 7.90—7.10 (10 H, m, 2 × C_6H_5), 6.98 (1 H, dd, CH–C*H*=CH), 6.71 (1 H, d, CH=C*H*CO, J_{trans} 16 Hz), 2.85—2.60 (3 H, m, CH_2Ar and C*H*Me), and 1.12 (3 H, d, *Me*CH, *J* 6.8 Hz) (Found: C, 86.3; H, 7.2. $C_{18}H_{18}O$ requires C, 86.4; H, 7.25%).

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