Stereochemistry of Addition to the Carbonyl Group. Part 17.[1] Study of the Factors affecting Asymmetric Induction in Condensation Reactions of Methyl- and Phenyl-magnesium Bromide with Chiral Carbonyl Compounds

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The dependence of the stereoselectivity upon the nature of the chiral carbonyl compound [2-methyl-3-phenylpropanal (1), 2,3,3-trimethylbutanal (2), 4,4-dimethyl-3-phenylpentanal (3), 3-phenylbutanone (4), and 2-phenylpropanal (5)], the solvent, and the concentration of the reactive species for various condensation reactions of phenyl- and methyl-magnesium bromide at 30° is reported. The stereochemical results have been interpreted on the basis of the generalized Curtin–Hammett principle and according to a trigonal-type transition state (Pérez-Ossorio model). No effect of the concentration of the reactive species on the product ratio was observed. An unexpected influence of the solvent was observed in the condensation of (4) with phenylmagnesium bromide. A good linear correlation between stereoselectivity and the E_T parameter of the solvent was obtained. The explanation offered here takes into account the steric selection of the transition states and a further differentiating effect of the solvent polarity on them. A slight influence of solvent polarity on reactions of (5) with Grignard reagents was also noticed.

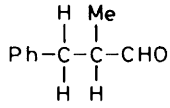
RESEARCH on the stereochemical study of addition reactions of complex metal hydrides and organometallic compounds to chiral acyclic carbonyl derivatives follow two major lines. The first defines theoretical models which eventually allow predictions of stereoselectivity related to the structure of the reacting system. The second deals with an investigation of the experimental conditions which influence the extent of asymmetric induction for a particular substrate. The aim of these theoretical and experimental approaches is to control the factors affecting reactivity in order to obtain as high a proportion as possible of one diastereoisomeric carbinol in a mixture.

This is important since stereochemical control of the addition of complex metal hydrides and organometallic compounds to the carbonyl group is often a key step in the synthesis of a great variety of compounds. In addition, finding a correlation between the structure of the reacting system and the stereochemical results provides a valuable tool for the configurational assignment of the diastereoisomeric carbinols obtained in this way. This in itself is an important aim as may be concluded from the wide applications of such empirical correlations as Horeau's method,[2] Prelog's generalization,[3] Barton's rule,[4] *etc.*

In this paper we report the results on the study of assymmetric induction in the condensation reactions of phenylmagnesium bromide with 2-methyl-3-phenylpropanal (1), 2,3,3-trimethylbutanal (2), 4,4-dimethyl-3-phenylpentanal (3), and 3-phenylbutanone (4), in ethyl ether and tetrahydrofuran at various concentrations. In the first solvent, changes in the concentration of the organometallic compound may modify the position of the Schlenk equilibrium (1),[5] and the competition among the different reactive species in solution may produce changes in stereoselectivity, as postulated in previous reports.[6]

$$R_2Mg + MgBr_2 \rightleftharpoons 2\ RMgBr \rightleftharpoons (RMgBr)_2 \rightleftharpoons (RMgBr)_n \quad (1)$$

The influence of solvent (Et_2O and THF) in modifying the nature of the reactive species has also been studied in the condensation reactions of phenylmagnesium bromide with (1)—(3) and, more thoroughly [ethyl



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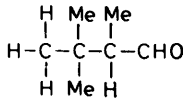

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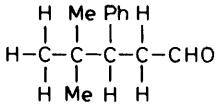

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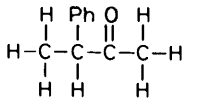

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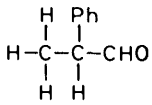


(5)

ether, tetrahydrofuran (THF), dimethoxyethane, triethylamine, 1,4-dioxan, di-isopropyl ether, and diglyme] in the reaction of this reagent with (4) and with 2-phenylpropanal (5) as well as in that of methylmagnesium bromide with (5).

Effect of the Concentration of Phenylmagnesium Bromide in Ethyl Ether and Tetrahydrofuran.—The results of the condensation reactions of (1)—(4) with phenylmagnesium bromide at different concentrations in Et_2O and THF are summarized in Table 1.

For reactions in ethyl ether the concentration of the Grignard reagent does not affect the stereoselectivity. In this solvent, organomagnesium compounds are well described by the Schlenk equilibrium (1) and it has been shown that phenylmagnesium bromide exists as a monomer only at concentrations below 0.1M.[5] The fact that the product ratio is not altered with concentration changes may be explained by assuming that although all the species in the equilibrium compete they have about the same steric requirements in their approach to the substrate. It may also be assumed that only one reactive species is present in solution.

TABLE 1

Observed stereoselectivity (% *RS*,*SR*-β-isomer) in the condensation of PhMgBr at 30° in Et_2O and THF with (1)—(4)

No.	Solvent	Conc.(M)	(1)		(2)	(3)	(4)	
			a	*b*	*a*	*b*	*a*	*b*
1	Et_2O	2.4	51	49	98	65	42	41
2	Et_2O	2.0				66		
3	Et_2O	0.7	51	53	98		41	37
4	Et_2O	0.6				68		
5	Et_2O	0.2				67		
6	Et_2O	0.15	52	52	98		38	37
7	Et_2O	5×10^{-2}				66		
8	Et_2O	3.3×10^{-2}	49	53	98		40	37
9	Et_2O	8×10^{-3}				66		
10	Et_2O	5×10^{-3}	50	51	98		49	48
11	THF	1.2	51	49	98	68	60	56
12	THF	0.14	53	48	98	67	65	61
13	THF	3.6×10^{-2}	51	52	98	68	66	66

[a] Evaluated by ^1H n.m.r. (±3%). See Experimental section. [b] Evaluated by g.l.c. (±3%). See Experimental section.

According to Ashby,[7] this species is the monomer, whether phenylmagnesium bromide or diphenylmagnesium.

Likewise a similar change in the concentration of phenylmagnesium bromide in THF has no effect on the stereochemical results. This is in accord with the fact that organomagnesium compounds exist always as monomers in THF.[5] A slight alteration in the distribution of products with increasing dilution is observed in the reaction of (4). Although this effect may be significant, it is too small and isolated to merit an explanation for the moment.

Effect of Solvent.—Stereoselectivity changes upon changing the solvent have been previously reported for the condensation of phenylmagnesium bromide with (4).[8] A satisfactory linear correlation with the $E_T(30)$ parameter of the solvent has been found [equation (2)].

$$\ln (RS/RR) = 0.34E_T(30) - 12.47 \qquad (2)$$

On the other hand, as shown in Table 2, there is no significant effect of the solvent upon the stereoselectivity for the condensation of (5) with either phenyl- or methylmagnesium bromide. This effect is also absent in going from ethyl ether to tetrahydrofuran in the condensation reactions of (1)—(3) with phenylmagnesium bromide (Table 1). The effect of solvent seems to be related to the presence of a phenyl group in the induction centre. However, a rationalization of these facts requires a discussion of the stereochemical results observed in ethyl ether from which a selection among the competing transition states for each case could be made.

Steric Control of Approach.—Nearly every theory dealing with the stereoselectivity observed for addition reactions of complex metallic hydrides and organometallic compounds to cyclic and acyclic ketones postulates that the nucleophile approaches the carbonyl group at right angles to the plane m (Figure 1). Thus stereoselectivity in this type of reactions, which are carried out under kinetic control, will be defined by the difference in steric hindrance to the attack on each face of the functional group, a and b (steric control of approach).

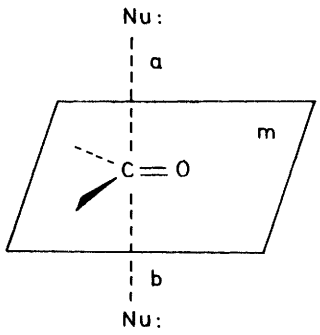


FIGURE 1 Modes of approach for nucleophiles attacking carbonyl groups

On this basis and assuming a reactant-like transition state several authors have proposed theoretical models for predicting the stereoselectivity.[9-11] Figure 2 shows the geometrical features of the transition states for models defined by Karabatsos (K‡),[9] Pérez-Ossorio (P‡),[10] and Felkin (F‡).[11] In Figure 2 a generic conformer is represented. It also shows the attack of the nucleophile on its less hindered side (medium, M, and small, S, groups *versus* medium and large, L, groups).

The prediction of the stereoselectivity involves the selection of competitive transition states. To do this two different theoretical approaches have been followed. Karabatsos and Felkin choose only two transition states, one leading to the *RR*,*SS*-carbinol and the other

TABLE 2

Observed stereoselectivity (% *RS*) in the reactions of BrMgPh [a] with (4) and (5) and of BrMgMe [b] with (5) in different solvents [$E_T(30)$] at 30°

RMgX	Substrate	NEt_3 (33.3)	Pr^i_2O (34.0)	Et_2O (34.6)	1,4-Dioxan (36.2)	THF (37.4)	$H_4C_2(OMe)_2$ (38.6)	Diglyme (38.9)
BrMgPh	(4)	26	31	36	49	61	73	66
BrMgPh	(5)	87	83	78	71	71	73	68
BrMgMe	(5)		30	29	21	24	24	20

[a] Solution 0.25M. [b] Solution 0.15M.

to the *RS,SR*-carbinol, according to estimates of the energy related to the interactions between close groups. The explicit application of the Curtin–Hammett principle by Karabatsos or the implicit use of it by Felkin allows determination of the sense in which induction takes place.

Taking into account the difficulty of an *a priori* selection of only two competitive transition states, in particular when structural complexity is present, Fernández González and Pérez-Ossorio [10] proposed a kinetic scheme involving all the Karabatsos-type conformers by allowing internal rotation of the L, M, and S groups.

Upon consideration of the two possibilities of attack

$$N_x/N_y = \frac{\sum_i e^{-G_i X^{\ddagger}/RT}}{\sum_i e^{-G_i Y^{\ddagger}/RT}} \qquad (3)$$

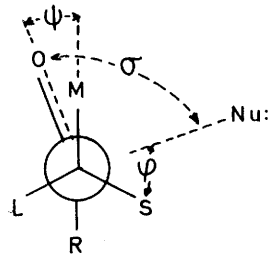
for each conformer, equation (3) was proposed. In this so-called ' generalized Curtin–Hamett principle ', N_x/N_y is the molar ratio of diastereoisomeric carbinols X and Y, and $G_i^{X\ddagger}$ and $G_i^{Y\ddagger}$ are the differential contents in free energy of the transition states leading to X and Y from each conformer *i*.

Application of this method to a large number of reactions has been previously reported.[12] The analysis of the six reactions reported in the present paper is summarized in Table 3 together with the results for the same reactions obtained by application of Karabatsos and Felkin models. As far as theoretical predictions are concerned the results collected in Table 3 are expressed, as the qualitative excess of one of the diastereoisomeric carbinols whenever Karabatsos and Felkin models are followed in the analysis. In such cases, transition states responsible for the extent of the induction are also indicated; they are chosen by application of the selection rules inherent in each model.

As stated above, in applying the Pérez-Ossorio method all competitive transition states were considered *ab initio*. Nevertheless, evaluation of their differential energy contents led to an *a posteriori* selection which in non-marginal cases agrees well with the selection offered by the Karabatsos model.

As seen in Table 3, the same theoretical results are obtained independently of the method used for the reactions of (1) and (2). Agreement with the experimental value is also good.* The reaction of (3) involves a 1,3-induction, where the observed diastereoisomeric excess amounts to 17% of the *SR,RS*-isomer. This result can only be predicted by the Pérez-Ossorio method. The others allow only qualitative predictions and, in fact, have not been applied to related examples.

The reduction of (4) with phenylmagnesium bromide in ethyl ether affords 40% of the *SR,RS*-diastereoisomeric carbinol. The qualitative prediction reached by the Felkin's model is just the opposite. Both the Karabatsos and Pérez-Ossorio models, applied to this case, consider that the participation of transition state (X) (*RR*), according to an estimate of the steric energy, is responsible for the observed diastereoisomeric excess. It is worth mentioning that for values of $\phi < 60°$ (Karabatsos and Pérez-Ossorio), (VIII) and (X) (Table 3) are the only possible competitive transition states and that their relative energies depend basically on the values of the interactions $(=O-Ph)_{1,2e} + (Me-Me)_{1,2g}$ in (*X*) *versus* $(=O-Me)_{1,2e} + (Ph-Me)_{1,2g}$ in (VIII). According to Karabatsos,[14] for the initial state, $(=O-Ph)_{1,2e}$ is 1.67 kJ mol^{-1} larger than $(=O-Me)_{1,2e}$. On the other hand, $(Me-Me)_{1,2g}$ has been evaluated as 3.55 kJ mol^{-1} and the minimal value for $(Ph-Me)_{1,2g}$ given in the literature is 6.27 kJ mol^{-1}.[12f] Obviously the steric control of approach favours transition state (X) leading to the *RR*-carbinol.



	$ET^{\ddagger}$	$K^{\ddagger}$	$P^{\ddagger}$	$F^{\ddagger}$
ψ (°)		0	15	30
σ (°)		90	90	90
φ (°)		30	45	60

FIGURE 2 Theoretical models for predicting stereoselectivity

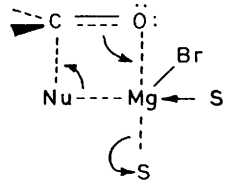


FIGURE 3 Four-centre transition for reaction of Grignard reagent with carbonyl compound

The reaction of (5) with methyl- and phenyl-magnesium bromide in ethyl ether yields, respectively, an excess of the *RR*- and *SR*-carbinols. Both results can be anticipated by all the mentioned models.

It can be concluded that an *a priori* selection of the competitive transition states involves a serious limit-

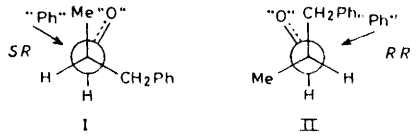
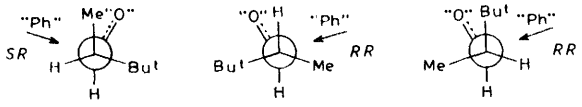
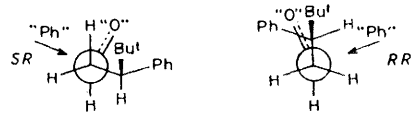
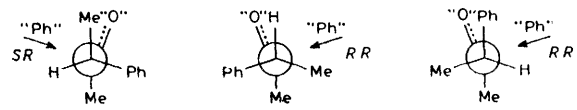
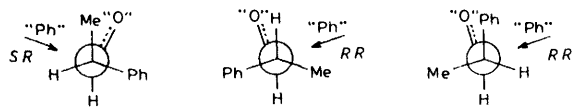
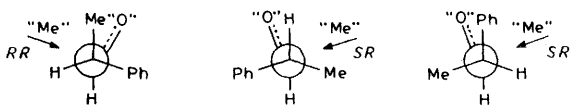
* The agreement between the theoretical and experimental results for reaction (2) may be improved by assuming a deviation in the angle of attack (>90°) which would favour transition state (III) rather than (IV) (see ref. 13). We acknowledge suggestions by a referee on this point.

ation as a result of the inaccuracy of the steric interactions evaluated for any model. On the other hand, the constant value of $\sigma = 90°$, a premise that has been questioned,[13] may lead to error in the theoretical value of induction and even in its sense. Therefore, the problem is not easy to solve in a generalized manner.

These ideas are incorporated in a four-centre mechanism [15] with simultaneous removal of a molecule of solvent (*S* in Figure 3) upon reaching the activated complex. The extent of co-ordination of the carbonyl oxygen atom to the electrophilic magnesium in the four-membered pseudo-ring could induce important geo-

TABLE 3

Steric control of the asymemetric induction. Stereoselectivity prediction in the reactions of PhMgBr with (1)—(5), and MeMgBr with (5) in Et_2O at 30°

Substrate	Competitive transition states	Theoretical prediction	Experimental values (% *SR*)
(1)	 I II	K‡ I*SR* ≥ II*RR* P‡ *SR* = 51% F‡ I*SR* ≥ II*RR*	51 ± 3
(2)	 III IV V	K‡ III*SR* > V*RR* P‡ *SR* = 77% F‡ III*SR* > IV*RR*	98 ± 3
(3) *	 VI VII	P‡ *SR* = 64%	67 ± 3
(4)	 VIII IX X	K‡ VIII*SR* < X*RR* P‡ *SR* = 38% F‡ VIII*SR* > X*RR*	40 ± 3
(5)	 XI XII XIII	K‡ XI*SR* > XIII*RR* P‡ *SR* = 62% F‡ XI*SR* > XII*RR*	78 ± 3
(5)	 (XIV) (XV) (XVI)	K‡ XIV*RR* > XVI*SR* P‡ *SR* = 38% F‡ XIV*RR* > XV*SR*	29 ± 3

* Significant TS‡ evaluated from quantitative analysis following the Pérez-Ossorio method.

Although the method of Pérez-Ossorio appears to be very suitable for the analysis of the results reported in the present paper, this is not the case for other structurally related cases [12i] involving reactions of certain alkyl aryl ketones. For all these reasons, the treatment in these cases has been extended by assuming large deviations in the dihedral angles. The term ' tetrahedral ' has been used by the authors to distinguish between the latter situation and the above described ' trigonal ' or reactant-like transition state.

metrical deviations in the transition states in relation to the models considered. The more basic the solvent the larger these deviations would be.

Further difficulties would arise if the two diastereotopic faces of the carbonyl group were not isotropic in electron density. In this case, steric control of asymmetric induction is an important, but not exclusive, contribution to the stereochemical result.

Polar Control of Approach.—Evidence for the polar control of approach in reduction reactions of cyclic

ketones with complex metallic hydrides has been reported by Felkin *et al.*[16] Similar evidence has been obtained from the theoretical analysis of the electric field of the carbonyl group in cyclohexanone reported recently by Royer.[17] Likewise, Klein,[18a] Anh,[18b] and Ashby[18c] have proposed new theories of stereochemical control in reduction reactions of ketones by metallic hydrides based on orbital symmetry and on the unequal electronic distribution around the carbonyl group.

We present here new evidence for polar control of asymmetric induction by showing the stereoselectivity dependence upon the nature of the solvent in the addition reaction of phenylmagnesium bromide to (4). This dependence could have its origin in a solvent-induced variation of the polarization of the bonds at the chiral centre. Therefore, a linear dependence on the $E_T(30)$ parameter of the solvent in the system phenylmagnesium bromide–(4) (entry 1, Table 2) may be reasonable on the basis that only two transition states, one leading to the *RR,SS*-carbinol and the other to the *RS,SR*-carbinol, are operative. From a previous choice based on steric grounds, of transition states (VIII) (*SR*) and (X) (*RR*) (see Table 3), it appears that the former is favoured as it increases the $E_T(30)$ parameter of the solvent. In (VIII) the arrangement of phenyl group (with a $-I$ effect) favours charge transfer from the nucleophile in the anticlinal-antiperiplanar direction[16] allowed by the optimum angle of attack. Such an electric anisotropic effect on the diastereotopic faces of the carbonyl group is not operative in the lower energy transition state (XIII) (*RR*) due to the parallelism of the C–Ph and C=O bonds.

If the assumption of Felkin that only (VIII) and (IX) (Table 3) are operative were true and that compensation of the variation induced by the solvent on the polarization of the bond between the phenyl substituent and the chiral centre in both transition states took place, then almost constant stereoselectivity would result.

The effect on the stereoselectivity due to solvent change in the case of condensation of (5) with phenyl- and methyl-magnesium bromide (Table 2) is considerably smaller than in the case of (4). In both reactions of (5) an increase in the polarity of the solvent decreases the percentage of the *RS,SR*-carbinol.

In any case, conformational ambiguity in the substrate is higher for aldehyde (5) than for ketone (4). The participation of transition state (XV) should involve internal compensation of the polar factor which makes its influence on induction much smaller. This is in accord with observed data.

Finally, in the reactions of (1)—(3) with phenylmagnesium bromide no significant variation of stereoselectivity upon changing solvent (Et_2O, THF) has been observed. The absence of a polar group, together with internal compensation of the inductive effects of groups attached to the induction centre may explain these results.

It is concluded that this two-fold analysis, both steric and polar, represents a general improvement in the understanding of asymmetric induction.

EXPERIMENTAL

I.r. spectra were measured on a Perkin-Elmer 257 spectrophotometer. N.m.r. spectra were recorded on a Varian T-60 spectrometer; carbon tetrachloride was used as solvent and tetramethylsilane as internal reference. G.l.c. was carried out on a Hewlett-Packard 5750 instrument provided with a flame ionization detector and on a Perkin-Elmer Sigma-3 instrument with a Sigma-10 data collector. Mass spectra were recorded on a Varian MAT-711 spectrometer.

(a) *Syntheses.**—*3-Phenyl-2-methylpropanal* (1). *Method A.* 3-Phenyl-2-methylpropanoic acid (and methyl ester). The procedure described by Greger[19] for metallation and alkylation of higher acids was used. Propionic acid (5 g, 0.067 mol) and benzyl chloride (8.51 g, 0.067 mol) yielded a mixture (6.3 g) of starting material and the related benzylated acid. This mixture was esterified with diazomethane in the usual manner. Fractional distillation of the reaction mixture yielded two fractions, b.p. 90—100 and 247—252 °C). The lower boiling one (1.25 g) was characterized by g.l.c. (5% polyphenyl ether on a Chromosorb G-AW column; length 2 m; internal diam. ¼ in) as methyl propionate by comparison with an authentic sample. The higher boiling fraction (5.6 g, 47%) was identified as methyl 3-phenyl-2-methylpropanoate, $\nu_{max.}$ 1 735 cm^{-1}; δ 1.1 (d, 3 H), 2.3—3.6 (m, 3 H), 3.6 (s, 3 H), and 7.2 (s, 5 H).

3-Phenyl-2-methylpropanol. Reduction of methyl 3-phenyl-2-methylpropanoate (5.6 g, 0.035 mol) in THF (24 ml) was achieved with lithium aluminium hydride (1.2 g, 0.034 mol) in THF (75 ml) after 2 h refluz. A chromatografically pure product (4.48 g, 95%) was obtained and characterized as 3-phenyl-2-methylpropanol, $\nu_{max.}$ 3.400 cm^{-1}; δ 0.9 (d, 3 H), 2.5 (m, 3 H), 3.5 (d, 2 H), 4.2 (s, OH), and 7.2 (s, 5 H).

Oxidation of 3-phenyl-2-methylpropanol. The procedure described by Ratcliffe[20] was employed. From 2-methyl-3-phenylpropanol (0.6 g, 0.004 mol) and CrO_3 (1.24 g, 0.024 mol), 2-methyl-3-methylpropanal (0.470 mg, 82%) was obtained. The purity was tested by g.l.c., $\nu_{max.}$ (neat) 2 800 and 1 715 cm^{-1}, δ 1.15 (d, 3 H), 2.50—3.25 (m, 3 H), 7.22 (s, 5 H), and 11.3 (s, 1 H); *m/e* 148 (39%, M^+), 133 (12), 117 (7), 105 (20), 92 (100), and 78 (16).

Method B. Preparation of 2-ethyl-4,4,6-trimethyl-5,6-dihydro-4*H*-1,3-oxazine. Meyers' method was followed.[21] From propiononitrile (60.5 g, 1.1 mol) and 2-methylpentane-2,4-diol (118 g, 1 mol), the oxazine (83.4 g, 53.8%) was obtained, $\nu_{max.}$ (neat) 3 350 and 1 660 cm^{-1}; δ 1.00 (s, 3 H), 1.05 (s, 6 H), 1.15 (d, 3 H), 1.30 (m, 1 H), 1.65 (dd, 1 H), 2.05 (q, 2 H), and 3.90 (m, 1 H).

Metallation and benzylation of the oxazine. The procedure described previously was employed.[22] From the oxazine (11.3 g, 0.073 mol) and benzyl chloride (15 g, 0.11 mol), 2-(1-benzylethyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-1,3-oxazine (11.24 g, 62.8%) was obtained. The purity was tested by g.l.c., $\nu_{max.}$ (neat) 3 300, 1 660—1 600, and 1 490 cm^{-1}; δ 0.75—1.40 (m, 13 H), 1.55 (dd, 1 H), 2.50 (m, 3 H), 3.75 (m, 1 H), and 6.90 (s, 5 H).

Reduction of the benzyl derivative. Meyers' procedure was followed.[21] From the benzyl derivative (9.7 g, 0.040 mol) and sodium borohydride (1.51, g, 0.040 mol), the tetra-

* 2-Phenylpropanal (5) was purchased from Merck.

hydro-compound (9.2 g, 93.1%) was obtained. The crude product was used directly in the next step. The reaction was followed by i.r. (complete disappearance of C=N band). The purity was tested by g.l.c.

Hydrolysis of the tetrahydro-compound. This was carried out with oxalic acid by Meyers' procedure.[21] The crude product was purified with Girard T reagent and 3-phenyl-2-methylpropanal (4.31 g, 78.2%) was obtained. The purity was tested by g.l.c. as for method A; characterization was by i.r., n.m.r., and mass spectra.

2,3,3-*Trimethylbutanal*. The procedure described by Greger [19] was followed.

2,3,3-Trimethylbutanoic acid (and methyl ester). Starting from 2,3-dimethylbutanoic acid (5 g, 0.043 mol) and an excess of methyl iodide, the crude product was directly esterified with diazomethane to yield a chromatographically pure product (5.76 g, 93.0%). This was characterized as methyl 2,3,3-trimethylbutanoate by spectroscopy, $\nu_{max.}$ (neat) 1 740 cm^{-1}, δ 0.9 (s, 9 H), 1.1 (d, 3 H), 2.2 (q, 1 H), and 3.6 (s, 3 H).

2,3,3-Trimethylbutanol. This was prepared by reduction of methyl 2,3,3-trimethylbutanoate (5.7 g, 0.040 mol) with lithium aluminium hydride (0.75 g, 0.020 mol) in THF (Method A). After purification a pure product (4.2 g, 90.5%) was isolated (g.l.c. in analogous conditions to these reported above). It was characterized as 2,3,3-trimethylbutanol, $\nu_{max.}$ (neat) 3 400 cm^{-1}; δ 0.85 (s, 9 H), 0.95 (d, 3 H), 1.2 (m, 1 H), 3.5 (dd, 1 H), 3.65 (dd, 1 H), and 4.05 (s, 1 H).

Oxidation of 2,3,3-trimethylbutanol. Method A was followed. 2,3,3-Trimethylbutanol (1.2 g, 10 mmol) yielded only one product (1.04 g, 86%); the purity was tested chromatographically as before. It was characterized as 2,3,3-trimethylbutanal, $\nu_{max.}$ 1 720 cm^{-1}; δ 0.9 (s, 9 H), 1.0 (d, 3 H), 2.55 (m, 1 H), and 9.5 (d, 1 H).

3-*Phenyl*-4,4-*dimethylpentanal*. The method described in ref. 12*d* was applied to this compound, $\nu_{max.}$ (neat) 1 725 cm^{-1}; δ 0.95 (s, 9 H), 2.77 (m, 3 H), 7.07 (s, 5 H), and 9.53 (t, 1 H); *m/e* 190 (6%, M^+), 162 (9), 134 (44), 105 (83), 91 (83), 84 (54), 77 (25), 74 (18), 57 (100), and 49 (61).

3-*Phenylbutanone*. This was obtained by oxidation of 3-phenylbutan-2-ol.

3-Phenylbutan-2-ol. This was prepared from 2-phenylpropanal (71 g, 0.53 mol) and methylmagnesium iodide in Et_2O [from magnesium (14.6 g, 0.60 mol) and methyl iodide (85.17 g, 0.60 mol) twice distilled over P_2O_5]. After 6 h the mixture was hydrolysed with a saturated solution (400 ml) of NH_4Cl. The organic layer was dried ($MgSO_4$) and after removal of the solvent distilled through a 20 cm fractionating column. The fraction distilling at 106—109 °C and 11 Torr, was collected and shown to be chromatographically pure (5% polyphenyl ether on a Chromosorb G-AW-DMCS column; length 2 m; internal diam. ¼ in; 150 °C), $\nu_{max.}$ (neat) 2 400 cm^{-1}; δ 0.95 (d, 3 H), 0.98 (d, 3 H), 1.25 (d, 3 H), 1.35 (d, 3 H), 2.75 (m, 2 H), 3.10 (s, 2 H), 3.65 (m, 2 H), and 7.20 (s, 5 H). Duplication of some signals is due to the formation of both diastereoisomeric racemates (*RR,SS*)- and (*RS,SR*)-3-phenylbutan-2-ol.

Oxidation of 3-phenylbutan-2-ol. Method A described above was followed. 3-Phenylbutan-2-ol (5 g, 0.33 mol) yielded a chromatographically pure product (4.17 g, 85.3%), characterized as 3-phenylbutanone, $\nu_{max.}$ (neat) 1 710 cm^{-1}; δ 1.45 (d, 3 H), 1.95 (s, 3 H), 3.65 (q, 1 H), and 7.25 (s, 5 H) *m/e* 148 (10%, M^+), 133 (6), 105 (100), 79 (10), 77 (9), and 43 (14).

(b) *Preparation and Titration of Grignard Reagent Solutions*.—These were prepared from magnesium, previously heated and dried in *vacuo* (0.1 Torr) for 3 h, and bromobenzene twice distilled over P_2O_5 for the case of PhMgBr. Solvents, Et_2O and THF, were molecularly distilled over lithium aluminium hydride. The reaction were carried out under a continuous flow of dry nitrogen. Solutions of the magnesium compounds were decanted after 12 h and transferred to a burette which was connected to the apparatus from the start and from which air had been previously evacuated. In every case clear, slightly yellow solutions were obtained.

Ethereal solutions of the Grignard reagents were used to prepare solutions in the other solvents. For this purpose Et_2O was eliminated to dryness and the Grignard reagent was redissolved in the new solvent, injected through a septum. All solvents were purified in the usual manner.*

Magnesium was titrated complexometrically with EDTA, and bromine by the Volhard method. Titration confirmed that no non-stoicheiometric magnesium bromide was present.

(c) *Condensation Reactions*.—Condensation reactions of phenyl- and methyl-magnesium bromide with compounds (1)—(5) were carried out by the following procedure. A four-necked flask, provided with a magnetic stirrer and a nitrogen inlet and outlet, was directly connected to the burette containing the magnesium compound; air was evacuated (0.1 Torr) and a dry nitrogen current passed through. An excess of Grignard reagent (5 : 1) was added † and the solution was thermostatted at 30°. After 30 min, the carbonyl compound (200 mg), dissolved in the minimum amount of solvent, was introduced, through a septum; stirring was continued for 2 h at 30°. Finally the mixture was hydrolysed with a stoicheiometric volume of water, followed by adding a saturated (50 cm^3) solution of NaCl. The organic layer was decanted and the aqueous layer extracted with several portions of ether. The ethereal extracts were dried ($MgSO_4$), and after removal of the solvent *in vacuo*, the residue was analysed by chromatography. The total conversion was obtained in every case; biphenyl was produced as a by-product. The stereochemistry of the products was investigated by the methods described below.

(d) *Estimation of Mixtures of Diastereoisomeric* α- *and* β-*Carbinols*.—(1) α *and* β-1,3-*Diphenyl*-2-*methylpropan*-1-*ol* (6). Two methods were followed.

Method a. This was based on the differences in ^{1}H n.m.r. chemical shifts of the resonance signals of the CH_3 and H-C(1) protons in each diastereoisomer (Table 4). Signals, appropriately expanded, were repeatedly integrated. The values obtained are collected in Table 1.

Method b. This was by g.l.c. [5% Carbowax 20 M (5%) on Chromosorb G-AW-DMCS; length 3 m; internal diam. ⅛ in; column temperature 200°; gas flow 65 ml min^{-1}]. The retention times for the α-carbinol were 120 min and for the β-carbinol 129 min. The method of triangulation and measurement of areas was followed. Results are collected in Table 1.

(2) (α *and* β)-1-*Phenyl*-2,3,3-*trimethylbutan*-1-*ol* (7). This was carried out by ^{1}H n.m.r. by measurement of the relative intensities of the signals of the H–C(1) protons. Only

* The stereochemical results were unchanged when the Grignard reagent was prepared directly in the solvent used.

† At this point the solvent was changed for the condensations in Et_3N, dimethoxyethane, 1,4-dioxan, Pr^i_2O, and diglyme.

one signal was observed, δ 4.4 (d). The corresponding signal for the α-isomer, δ 4.98 (d),[23] was not detected. Results are reported in Table 1.

TABLE 4

Chemical shifts (δ) and assignment of signals for diastereoisomeric (α and β)-1,3-diphenyl-2-methylpropan-1-ol

Diastereoisomer	Chemical shift	Assignment
α	0.58	CH_3
	4.20	H–C(1)
	0.75	CH_3
β	4.32	H–C(1)

(3) (α *and* β)-1,3-*Diphenyl*-4,4-*dimethylpentan*-1-*ol* (8). This was carried out by g.l.c. [15% BDS on Celite 545 (60—100 mesh); length 0.90 m; internal diam. 1.4 in, column temperature 170 °C; gas flow 85 ml min^{-1}]. The retention times for the α-carbinol were 54 min and for the β-carbinol 49 min. The result (h_β/h_α) was interpolated on a calibration curve constructed from the measurements of apparent height ratios of five samples of known composition (% β/% α). Results of the various condensations are given in Table 1.

(4) (α *and* β)-2,3-*Diphenylbutan*-2-*ol* (9). Two methods were used.

Method a. ^1H N.m.r. To differentiate the signals of [H_3C–C(1)] addition of [$^2H_{27}$]Eu(fod)$_3$ was necessary. Results of the relative measurements of areas are collected in Table 1.

Method b. G.l.c. conditions: 15% Apiezon on Chromosorb G-AW-DMCS; length 2 m; internal diam. ¼ in; column temperature 160 °C. The retention times of the α-carbinol were 80 min and of the β-carbinol 88 min. The method of triangulation and measurement of areas was followed. Results are given in Table 1.

(5) α *and* β-1,2-*Diphenylpropan*-1-*ol* (10). G.l.c. conditions: 15% UCC on Chromosorb G-AW-DMCS; length 2 m; internal diam. ⅛ in; column temperature 150 °C; gas flow 65 ml min^{-1}. The retention times were for the β-carbinol 19 min and for the α-carbinol 22 min.

(6) α *and* β-3-*Phenylbutan*-2-*ol* (11). G.l.c. conditions: 5% PFE on Chromosorb G-AW-DMCS; length 2 m; internal diam. ⅛ in; column temperature 120 °C; gas flow 65 ml min^{-1}. The retention times were for the β-carbinol 25 min and for the α-carbinol 28 min.

(e) *Configuration Assignments.*—Assignment of relative configurations (*RR,SS* and *RS,SR*) for carbinols (6)—(11) gave the correspondence: α-carbinol = *RR,SS*; β-carbinol = *RS,SR*. For carbinols (10) and (11) the assignment was previously reported.[24] For carbinols (6)—(8), the ^1H n.m.r. data were compared with those previously reported for the same compounds.[25] Carbinol (7) is described here for the first time and the configurational assignment is based on ^1H n.m.r. data[23] which showed an *RS,SR*-configuration for the β-diastereoisomer.

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REFERENCES

[1] Part 16, C. Alvarez-Ibarra, M. S. Arias-Pérez and F. Fernández-Gonzalez. *An. Quim.*, 1979, **75**, 707.
[2] A. Horeau, *Tetrahedron Lett.*, 1962, 506.
[3] V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.
[4] D. H. R. Barton, *J. Chem. Soc.*, 1953, 1027.
[5] E. C. Ashby, *Bull. Soc. Chim. Fr.*, 1972, 2134.
[6] P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, 1969, **34**, 3566.
[7] E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, 1972, **37**, 1918.
[8] R. Pérez-Ossorio, A. Pérez-Rubalcaba, M. L. Quiroga, and M. Lasperas, *Tetrahedron Lett.*, 1980, 1565.
[9] G. J. Karabatsos, *J. Am. Chem Soc* , 1967, **89**, 1367.
[10] F. Fernández-González and R. Pérez-Ossorio, *An. Quim.*, **1972**, 68, 1411.
[11] M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 1968, 2199.
[12] (*a*) F. Fernández-González and R. Pérez-Ossorio, *An. Quim.*, 1973, **69**, 101; (*b*) C. Alvarez-Ibarra, F. Fernández-González, A. Garcíá-Martínez, R. Pérez-Ossorio, and M. L. Quiroga, *Tetrahedron Lett.*, 1973, 2715; F. Fernández-González, R. Pérez-Ossorio, and M. L. Quiroga, *An. Quim.*, 1974, **70**, (*c*) 536; (*d*) 917; (*e*) F. Fernández-González, R. Pérez-Ossorio, and J. Plumet, *ibid.*, 1975, **71**, 208; (*f*) C. Alvarez-Ibarra, F. Fernández-González, and R. Pérez-Ossorio, *ibid.*, p. 412; (*g*) C. Alvarez-Ibarra, A. I. Blanch, F. Fernández-González, A. García-Martínez, R. Pérez-Ossorio, J. Plumet, and M. L. Quiroga, *Rev. Real Acad. Cienc. Exactas, Fis. y Nat.*, 1975, 233; (*h*) A. García Martínez, R. Pérez-Ossorio, and J. Plumet, *An. Quim.*, 1976, **72**, 873; (*i*) M. Lasperas, A. Pérez-Rubalcaba, and M. L. Quiroga, *Tetrahedron*, 1980, **36**, 3403.
[13] H. B. Burgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563.
[14] G. J. Karabatsos and N. Hsi. *J. Am. Chem. Soc.*, 1965, **87**, 2864.
[15] E. C. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, 1974, **7**, 272.
[16] M. Cherest, H. Felkin, P. Tacheau, J. Jacques, and D. Varech, *J. Chem. Soc., Chem. Commun.*, 1977, 372.
[17] J. Royer, *Tetrahedron Lett.*, 1978, 1343.
[18] (*a*) J. Klein, *Tetrahedron Lett.*, 4973, 4307; (*b*) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61; (*c*) E. C. Ashby and J. R. Boone, *J. Org. Chem.*, 1976, **41**, 2890.
[19] P. L. Greger, *J. Am. Chem. Soc.*, 1970, **92**, 1938.
[20] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1973, **35**, 4000.
[21] A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Plitzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. Portnoy, *J. Org. Chem.*, 1973, **38**, 36.
[22] C. Alvarez-Ibarra, M. S. Arias Pérez, M. T. García-Romo, M. T. Molina Orden, A. Pérez-Rubalcaba, and M. L. Quiroga, *Tetrahedron*, 1979, **35**, 1767.
[23] C. Alvarez-Ibarra, O. Arjona-Loraque, A. Pérez-Rubalcaba, and J. Plumet, *Rev. Real. Acad. Cienc. Exactas Fis y Nat.*, 1979, **73**.
[24] D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, 1952, **74**, 5828.
[25] (*a*) C. Alvarez-Ibarra, F. Fernández-González, M. L. Quiroga, and J. Santoro, *An. Quim.*, 1978, **74**, 449; (*b*) C. Alvarez-Ibarra, F. Fernández-González, and M. Rico Sarompas, *ibid.*, 1975, **71**, **314**; (*c*) A. García-Martínez and R. Pérez-Ossorio, *ibid.*, 1969, **67**, 79.