On the Reduction of Enol Acetates and Enolates derived from α-Chiral Ketones with Lithium Tetrahydridoaluminate

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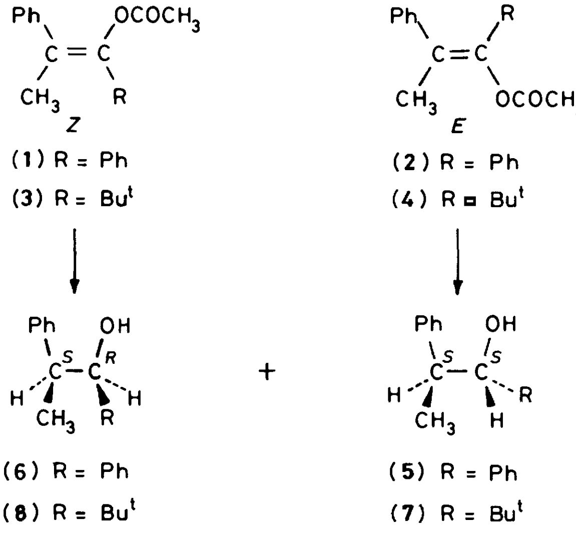
The *Z*- and *E*-isomers of 1-acetoxy-1,2-diphenylprop-1-ene (**1**) and (**2**), and of 3-acetoxy-4,4-dimethyl-2-phenylpent-2-ene (**3**) and (**4**), have been converted into their respective alcohols (1*RR*,2*SS*)- and (1*RS*,2*SR*)-1,2-diphenylpropan-1-ol (**5**) and (**6**), and (1*RR*,2*SS*)- and (1*RS*,2*SR*)-2,2-dimethyl-4-phenylpentan-3-ol (**7**) and (**8**), by treatment with lithium tetrahydridoaluminate in different solvents (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, triethylamine, and 1,4-dioxane). Deuteriolysis of the reaction mixture yields, almost quantitatively, the β-deuteriated products and, in every case, the reaction is completely stereoselective in the (*RR*,*SS*)-alcohol. From these results and the observation of the stereochemistry and conversion during the reaction, a mechanism is proposed. This includes a metallated ketone as a chiral intermediate in the reduction process.

The *Z*- and *E*-enol acetates derived from 1,2-diphenylprop-1-one, (**1**) and (**2**), and from 2,2-dimethyl-4-phenylpentan-3-one, (**3**) and (**4**), have been reduced by lithium tetrahydridoaluminate (LAH) to the related diastereoisomeric alcohols, (1*RR*,2*SS*)- and (1*RS*,2*SR*)-1,2-diphenylpropan-1-ol, (**5**) and (**6**), and 2,2-dimethyl-4-phenylpentan-3-ol, (**7**) and (**8**), respectively (Scheme 1). The course of the reduction is highly stereoselective. From this result and from the fact that the ratio of the diastereoisomeric alcohols is independent on the configuration of the starting enol acetate, valuable mechanistic information can be obtained. The mechanistic proposal is also based on the results of the reduction of the lithium enolates related to the enol acetates (**1**) and (**2**), and on the deuteriolysis of the reaction mixtures leading to the alcohols.



Scheme 1.

Results and Discussion

The results of the LAH reduction of the enol acetates (**1**), (**2**), (**3**), and (**4**) (or of known composition mixtures of them) are presented in the Table.

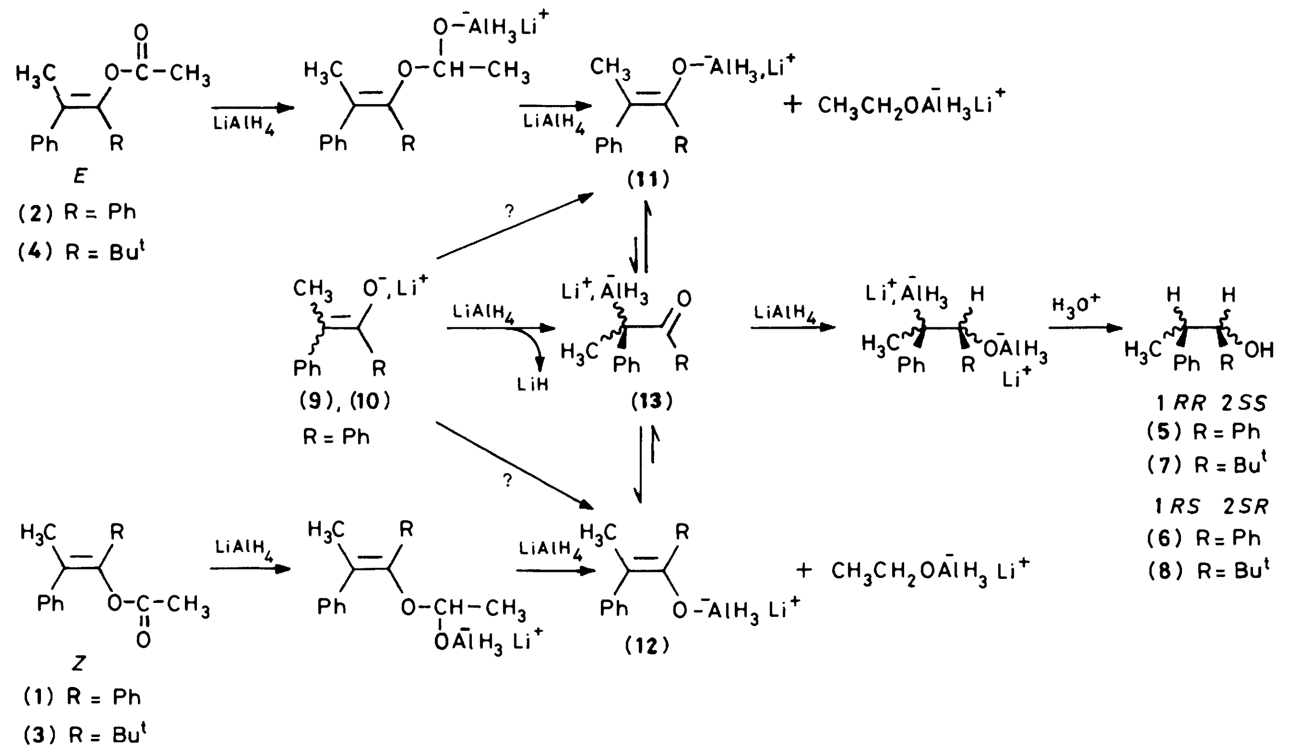
The isomeric acetates (**1**) and (**2**) were separated by flash chromatography on silica gel followed by fractional crystallization from the enriched eluates. It was characterized by spectroscopic techniques (i.r., ^1H and ^{13}C n.m.r., and u.v.). The isomeric acetates (**3**) and (**4**) could not be separated by standard procedures, although the analysis of the reaction mixture allowed us to establish its *E*:*Z* composition as 41:59 and to assign the n.m.r. parameters for both isomers. Owing to the difficulty of obtaining good conversions into alcohols, a high ratio of reagent to enol acetate (20:1) was used.

Standardization of the procedure and analysis of aliquots at various reaction times demonstrated the reproducibility of results. The influence of solvent (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, triethylamine, and 1,4-dioxane) on the conversion into alcohols was tested but no alteration in the stereochemical course was detected.

Some observations can be drawn from the Table. (*a*) *E*- and *Z*-diastereoisomeric acetates afford the same stereochemical result and give identical yields at a definite time (entries 1—6); (*b*) reduction of achiral *Z*- and *E*-enol acetates is highly stereoselective; (*c*) reaction stereoselectivity is not modified along the reaction time; (*d*) the process is self-accelerated ($\Delta\%/\Delta t$ in the Table). This effect is not dependent on the solvent and is not due to concentration changes in the reaction mixture; (*e*) reaction rate is higher in solvents other than ether and the yields are almost quantitative in tetrahydrofuran and 1,4-dioxane at 96 h.

In addition, the lithium enolates (**9**) and (**10**), obtained from the enol acetates (**1**) and (**2**) by treatment with methyl-lithium in 1,2-dimethoxyethane, were reduced with LAH in diethyl ether at 25 °C. After 48 h the conversion into alcohols was only *ca.* 7% and after 96 h it was found to be 23%. The stereochemical results were identical to those obtained in the direct reduction of the enol acetates (**1**) and (**2**). It may be concluded that the enolates are less reactive than the related acetates but that the stereochemical behaviour of both should be equivalent.

Deuteriolysis of the reaction crude resulted in deuteriation at the β-position (>98% deuteriated products) evidencing the formation of a bond between aluminium and the ethylenic β-carbon atom of the enol acetates during the reduction process. Since deuteriolysis of the C–Al bond is a configuration-retaining process,[1] an account of the observed stereochemical results can be based on the assumption of a chiral substrate common to both the acetates and the enolates considered, which will be attacked by the nucleophile preferentially on one prochiral face. The formation of this common intermediate, both from *Z*- and



Scheme 2. Mechanism of the reduction of enol acetates and enolates derived from α-chiral ketones with lithium tetrahydridoaluminate

E-diastereoisomeric acetates and enolates, must be a kinetically slow, although not limiting, process to explain the different reactivity between the two types of substrates.

The mechanism shown in Scheme 2 accounts for all the above considerations. According to this, the racemic metallated ketone (**13**) is considered as the precursor of the diastereoisomeric alcohols (**5**), (**6**) and (**7**), (**8**). The former originates either from the lithium enolates (**9**) and (**10**) by transmetallation with LAH, or from the alkoxyaluminates (**11**) and (**12**) formed from the enol acetates in the way shown by [1,3]-rearrangement of the aluminium residue.

Rates of transmetallation of the enolates (**9**) and (**10**) and of isomerization of the alkoxyaluminates (**11**) and (**12**) to the metallated ketone (**13**) must be of the same order as that for the reduction of the ketone (**13**) to explain the different conversions of enolates *vs.* acetates and to account for the process of self-acceleration. Thus, the formation of the metallated ketone (**13**) will be dependent on its intrinsic reactivity, whilst its concentration will be dependent on the formation of the alkoxyaluminates (**11**) and (**12**) for the acetates, and of (**9**) and (**10**) for the enolates. Therefore, the concentration of the metallated ketone (**13**) will increase with time, justifying the slow but self-accelerated progress of the reaction.

The difference in reactivity between the enolates (**9**) and (**10**) and the enol acetates (**1**) and (**2**) is consistent with the above hypothesis. The transmetallation process of the former should be slower than the reductive fission of the acetates. This, whether it occurs with direct formation of the ketone (**13**) or through the aluminates (**11**) and (**12**), will produce an initial concentration of metallated ketone (**13**) higher than that formed from the enolates (**9**) and (**10**). Finally, the stereochemistry of the ketone (**13**) can be explained on the basis of a mechanism involving the intermolecular transfer of the reacting hydride through a Felkin-type transition state.[2] According to this, reactive conformations will place the aluminate residue opposite the direction of the attacking nucleophile (see Figure) to relieve repulsive interaction of coulombic and steric origins. Attack of hydride will take place as shown following a direction slightly deviating from orthogonality to avoid repulsion by the oxygen atom. It is clearly seen that the *pro*-(*RR*,*SS*) transition state implies less steric interaction than the *pro*-(*RS*,*SR*) one: (R–CH$_3$) *vs.* (R–Ph) and (AlH$_4^-$–CH$_3$) *vs.* (AlH$_4^-$–Ph). This difference accounts for the observed stereochemical results.

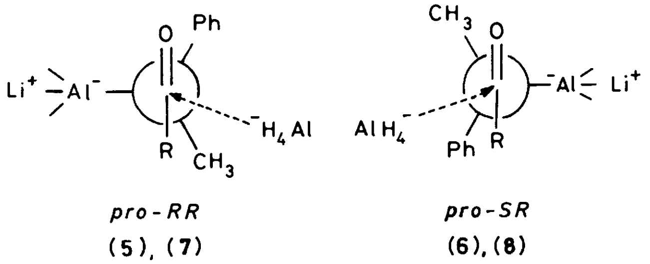


Figure. Felkin-type competitive transition states in the reduction of chiral α-metallated ketones with lithium tetrahydridoaluminate

In summary, metallated ketones of the type shown are only marginally reactive due to their low electrophilic character and to the high degree of steric crowding. Reduction of these metallated ketones affords β-metallated alcohol derivatives which may have synthetic utility.

Experimental

Methods and Apparatus.—G.l.c. was carried out on a Perkin-Elmer Sigma 3 gas chromatograph equipped with a Sigma 10 Data Station. Method A: 10% UCC on Chromosorb G-AW-DMCS; column length 3 m; internal diam. 1/8 in; method B: 10% Carbowax on Chromosorb G-AW-DMCS; column length 3 m; internal diam. 1/8 in; method C: Capillary column OV-101;

Table. Reduction experiments of (*Z*)- and (*E*)-isomers of 1-acetoxy-1,2-diphenylprop-1-ene (**1**) and (**2**), and 3-acetoxy-4,4-dimethyl-2-phenylpent-2-ene (**3**) and (**4**), with $LiAlH_4$ [a]

Entry	Substrate [b]	Solvent [c]	Temp./°C	React. time/h	% (1*RR*,2*SS*) (**5**) or (**7**)	Conversion (% alcohols)	Δ% alcohols/Δ*t* (h^{-1})
1	(**1**)	Et_2O	25	48	*d*	13	0.27
2	(**1**)	Et_2O	25	72	89	19	0.25
3	(**1**)	Et_2O	25	96	89	44	1.04
4	(**2**)	Et_2O	25	48	*d*	12	0.25
5	(**2**)	Et_2O	25	72	89	22	0.42
6	(**2**)		25	96	90	50	0.96
7	(**1**) + (**2**)	Et_2O	25	96	88	50	
8	(**2**) [e]	Et_2O	25	16	90	26	
9	(**1**) + (**2**)	Et_3N	25	48	78	34	0.71
10	(**1**) + (**2**)	Et_3N	25	96	80	70	0.75
11	(**1**) + (**2**)	1,4-D	25	48	88	42	0.88
12	(**1**) + (**2**)	1,4-D	25	96	89	96	1.13
13	(**1**) + (**2**)	THF	25	48	93	33	0.69
14	(**1**) + (**2**)	THF	25	96	93	93	1.25
15	(**1**) + (**2**)	DME	25	48	92	28	0.58
16	(**1**) + (**2**)	DME	25	96	92	84	1.17
17	(**1**) + (**2**)	1,4-D	100	3			
18	(**1**) + (**2**)	1,4-D	100	18	*d*	11	0.73
19	(**1**) + (**2**)	1,4-D	100	48	89	74	2.10
20	(**1**) + (**2**)	1,4-D	100	66	88	92	1.00
21	(**3**) + (**4**)	Et_2O	25	96	99	23	

[a] A molar ratio $LiAlH_4$: acetate of 20:1 (final solution 5×10^{-3} M in acetate) was used in all the experiments, unless otherwise stated. The composition of the reaction mixtures was calculated, after hydrolysis, by g.l.c. (error ±1%) using biphenyl as an internal standard. Besides biphenyl, only the ketone and alcohols were detected. [b] Ratio (**1**):(**2**) = 53:47; ratio (**3**):(**4**) = 74:23 (enriched mixture eluted from flash chromatography). [c] 1,4-D = 1,4-dioxane; THF = tetrahydrofuran; DME = 1,2-dimethoxyethane. [d] Could not be calculated due to the low yield and the high stereoselectivity. [e] Ratio $LiAlH_4$:(**2**) = 40:1 (final concentration in acetate 10^{-3}M).

length 25 m; oven temperature 170 °C. U.v. spectra were measured using a Beckman DB-GB spectrophotometer. I.r. spectra were recorded with a Perkin-Elmer 731 spectrophotometer. ^{1}H N.m.r. spectra were recorded in a Varian T-60A or Varian FT-80A instrument and ^{13}C n.m.r. spectra were recorded in a Varian FT-80A spectrometer.

Synthesis of (Z)- *and* (E)-1-*Acetoxy*-1,2-*diphenylprop*-1-*ene*, (**1**) *and* (**2**).—1,2-*Diphenylpropan*-1-*ol*.[3] This was obtained from 2-phenylpropanal (0.15 mol) and phenylmagnesium bromide (0.19) mol as previously described,[4] in anhydrous diethyl ether. A colourless liquid (29.6 g, 93%) was obtained which was analysed by g.l.c. (method A, oven temperature 170 °C) which showed the presence of two products of R_t 18 min (75%) and 19 min (24%). The i.r. and ^{1}H n.m.r. spectra of the diastereoisomeric mixture were coincident with those previously described.[3]

1,2-*Diphenylpropan*-1-*one*.[5] This was obtained from 1,2-diphenylpropan-1-ol (0.12 mol) by oxidation with Sarrett's reagent [CrO_3 (0.72 mol), pyridine (1.44 mol) in CH_2Cl_2 (750 ml)].

1-*Acetoxy*-1,2-*diphenylprop*-1-*ene*. A 250 ml reaction flask equipped with a septum, nitrogen inlet, and magnetic stirrer, was alternately evacuated and flushed with nitrogen three times. Di-isopropylamine (9.4 ml, 0.066 mol) and anhydrous THF (200 ml) were then added *via* syringe. The reaction flask was cooled in an acetone–liquid air bath and then methyl-lithium (0.066 mol) was added with a double needle device. The mixture was allowed to reach room temperature, after which 1,2-diphenylpropan-1-one (11.7 g, 0.056 mol) in THF (10 ml) was added with vigorous stirring. After 2 h the flask was cooled with an ice–water bath and acetyl chloride (16 ml, 0.22 mol) was added. Stirring was maintained for a further 10 min and then the crude reaction was poured into light petroleum–saturated aqueous $NaHCO_3$ solution. Sodium hydrogen carbonate was added with vigorous stirring until neutralization was achieved. The organic layer was washed with aqueous sodium hydrogen carbonate and water, and dried. After removal of the solvent, a liquid (15.2 g) was obtained. G.l.c. analysis (method A, oven temperature 160 °C) revealed the presence of four products: *N*,*N*-di-isopropylacetamide, 1,2-diphenylpropan-1-one, and two more compounds (α, R_t 32 min, 39%, and β, R_t 33 min, 17%). Flash chromatography on silica gel with light petroleum–ethyl acetate (98:2) as the eluant afforded an α-enriched fraction (1.8 g), a β-enriched fraction (0.9), and a third fraction containing approximately equal quantities of α and β (53:47; 2.5 g).

Component β was isolated by fractional crystallization from pentane as a transparent crystalline solid, m.p. 84 °C, to which was unequivocally assigned the (*E*)-1-acetoxy-1,2-diphenylprop-1-ene (**2**) structure by spectroscopic analysis, $\lambda_{max.}$(EtOH) 253 nm; $\nu_{max.}$(KBr) 1 745 and 1 650 cm^{-1}; δ_H (60 MHz; CCl_4) 1.73 (3 H, s), 2.07 (3 H, s), and 7.4—7.1 (10 H, m); δ_C (20 MHz; $CDCl_3$) 19.94, 20.35, 125.96, 126.81, 127.30, 127.90, 128.63, 135.53, 140.15, 141.91, and 169.20.

Component α was also isolated by fractional crystallization from hexane as a crystalline solid, m.p. 67 °C, which was identified as the (*Z*)-1-acetoxy-1,2-diphenylprop-1-ene (**1**) from its spectroscopic data, $\lambda_{max.}$(EtOH) 260 nm; $\nu_{max.}$(KBr) 1 740 and 1 650 cm^{-1}; δ_H (60 MHz; CCl_4) 2.04 (3 H, s), 2.14 (3 H, s), and 6.9—7.3 (10 H, m); δ_C (20 MHz; $CDCl_3$) 18.88, 20.23, 126.57, 126.69, 127.25, 127.39, 127.85, 128.67, 128.73, 135.60, 140.41, 143.21, and 168.01.

Synthesis of (Z)- *and* (E)-3-*Acetoxy*-4,4-*dimethyl*-2-*phenylpent*-2-*ene* (**3**) *and* (**4**).—2,2-*Dimethyl*-4-*phenylpentan*-3-*ol*.[6] This was prepared from 2-phenylpropanal (0.15 mol) and t-butylmagnesium chloride (0.48 mol) as previously described.[4] A colourless liquid (20.4 g) was obtained which was analysed by g.l.c. (method A, oven temperature 130 °C) and showed the presence of two products of R_t 22 min (56%) and 19 min (3%). The i.r. and ^1H n.m.r. spectra of the diastereoisomeric mixture were coincident with those previously described.[6]

2,2-*Dimethyl*-4-*phenylpentan*-3-*one*.[6] This was obtained by oxidation of the above crude reaction mixture (2.0 g) with Sarrett's reagent [CrO_3 (0.62 mol), pyridine (1.25 mol) in CH_2Cl_2 (650 ml)].

3-*Acetoxy*-4,4-*dimethyl*-2-*phenylpent*-2-*ene*. The procedure described above for compounds (**1**) and (**2**) was followed, using di-isopropylamine (6.2 ml, 0.044 mol), methyl-lithium (0.044 mol), and 2,2-dimethyl-4-phenylpentan-3-one (7.0 g, 0.037 mol). The reaction crude was analysed by g.l.c. (method A, oven temperature 130 °C) which showed the presence of three products: the starting ketone (14 min; 40%), α (26 min; 26%), and β (29 min; 34%). The last two products were separated from the ketone by flash chromatography on silica gel with light petroleum–ethyl acetate (98:2) as the eluant, but their individual isolation was not attained. The ^1H n.m.r. analysis of the eluted mixture ($\alpha:\beta = 26:74$) allowed the characterization of α and β as the (*E*)- and (*Z*)-isomers respectively: δ_H (60 MHz; $CDCl_3$) 0.88 (9 H, s, *Z*), 1.27 (9 H, s, *E*), 1.45 (3 H, s, *E*), 1.73 (3 H, s, *Z*), 2.05 (3 H, s, *E*), 2.10 (3 H, s, *Z*), and 7.2—7.0 (10 H, m, *E* and *Z*); δ_C (20 MHz; $CDCl_3$) 19.75 (*E*), 19.94 (*E*), 20.46 (*Z*), 22.53 (*Z*), 29.16 (*E*), 29.86 (*Z*), 35.75 (*E*), 37.18 (*Z*), 124.62 (*E*), 124.67 (*Z*), 126.06 (*E*), 126.48 (*Z*), 127.57 (*E*), 127.73 (*Z*), 128.67 (*E*) and (*Z*), 142.07 (*Z*), 143.14 (*E*), 149.64 (*Z*), 149.86 (*E*), 168.34 (*Z*), and 169.20 (*E*); $\nu_{max.}$(neat) 1 750 and 1 660 cm^{-1}.

Reduction of Enol Acetates with Lithium Tetrahydridoaluminate (*General Procedure*).—A 250 ml reaction flask, equipped with septum, nitrogen inlet, and magnetic stirrer, was connected to a dosifier burette containing a 0.1M solution of $LiAlH_4$ in diethyl ether, prepared and titrated according to the previously described procedure.[7] The system was evacuated and then nitrogen was let in (3 times) in order to exclude moisture. The necessary volume of hydride solution was then added for each experiment. At this point, if any solvent (THF, 1,4-dioxane, Et_3N, or DME) other than diethyl ether was required, the added solution was evaporated to total dryness and the new anhydrous solvent was introduced through the rubber septum. The mixture was stirred until dissolution was complete and then the necessary amount of the enol acetate and biphenyl (an internal standard for g.l.c.) in the solvent used was added *via* syringe. Stirring was maintained and several aliquots were taken at intervals. These were hydrolysed by pouring over a mixture of commercial diethyl ether (100 ml) and several drops of saturated aqueous ammonium chloride. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was removed to yield the crude reaction mixture for analysis.

Analysis of Reaction Mixtures.—This was performed by g.l.c. (method B, oven temperature 150 °C). Results are collected in the Table. The unequivocal configuration assignment to the diastereoisomeric alcohols (**5**), (**6**), and (**7**), (**8**) was made by comparison with synthetic samples obtained by the direct reduction of 1,2-diphenylpropan-1-one and 2,2-dimethyl-4-phenylpentan-3-one, respectively, with $LiAlH_4$ in diethyl ether.[3,6]

Reduction of Lithium Enolates with Lithium Tetrahydridoaluminate.—A 0.1M solution of the enol acetate in anhydrous 1,2-dimethoxyethane (DME) containing triphenylmethane (1% w/v) (indicator) was stirred at room temperature. A 1.0M solution of methyl-lithium in diethyl ether was then added dropwise with stirring until the solution assumed a persistent red colour. Stirring was maintained for several minutes and the DME was eliminated by connecting the apparatus to a vacuum line. Diethyl ether and a weighed amount of biphenyl were then added and the procedure continued as described above (see the general procedure for the reduction of enol acetates).

Control Experiments.—To a solution of $LiAlH_4$ hydrolysed with commercial diethyl ether containing several drops of saturated aqueous ammonium chloride were added weighed amounts of enol acetate and biphenyl. The organic layer was separated, washed twice with water, and dried ($MgSO_4$). After the solvent had been removed, the samples were analysed by g.l.c. (method B, oven temperature 150 °C). Biphenyl and the enol acetate were the only products found, in their original ratio.

Deuteriolysis Experiments.—A mixture of the enol acetates (**1**) and (**2**) (53:47; 0.6 mmol) was reduced with a 0.2M solution of $LiAlH_4$ in diethyl ether (12 mmol), following the procedure described above. After 96 h deuterium oxide (1.2 ml, 0.064 mol) was added. The reaction crude was washed repeatedly with aqueous sodium hydrogen carbonate (8 times) and water (3 times), and the organic layer was dried ($MgSO_4$) and concentrated. The resulting crude reaction mixture was analysed by ^1H n.m.r. spectroscopy (80 MHz; $CDCl_3$) and was shown to be a mixture of [2-^2H]-1,2-diphenylpropan-1-one (25%), (1*RR*,2*SS*)-[2-^2H]-1,2-diphenylpropan-1-ol (64%), and (1*RS*,2*SR*)-[2-^2H]-1,2-diphenylpropan-1-ol (11%), as from the 2-CH_3 signal multiplicity, thus demonstrating that deuteriation was higher than 98%. The g.l.c. analysis of the crude mixture (method C) confirmed this composition.

Acknowledgements

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