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(R)- AND (S)-2-ACETOXY-1,1,2-TRIPHENYLETHANOL - EFFECTIVE SYNTHETIC EQUIVALENTS OF A CHIRAL ACETATE ENOLATE

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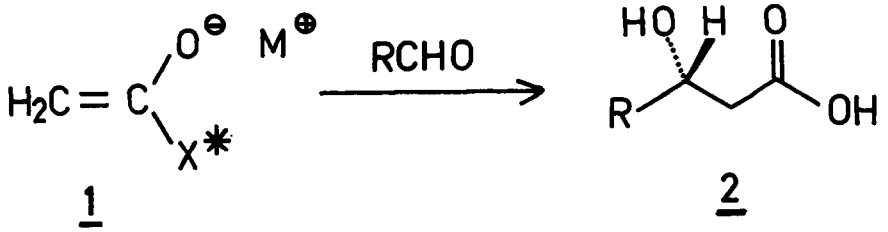
Abstract: The enolate 3, easily available by double deprotonation of (R)-2-acetoxy-1,1,2-triphenylethanol (5), adds in a highly stereoselective manner to aldehydes. Hydrolysis of the adducts 6/7 affords the acids 2.

Despite of the impressive progress made in stereoselective aldol reactions[1], the problem of the addition of an (α-unsubstituted) acetate enolate 1 to aldehydes in order to give enantiomerically pure ß-hydroxycarboxylic acids 2 could not be resolved, although many chiral auxiliary groups X* were employed[2,3]. In this communication, we describe stereoselective aldol reactions, using the dianion 3 of (R)-2-acetoxy-1,1,2-triphenylethanol (5) as an easily available, effective synthetic equivalent of the chiral acetate enolate 1.



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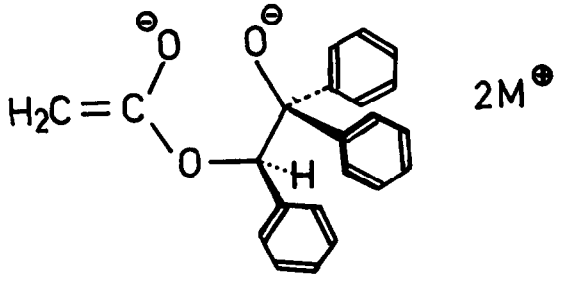

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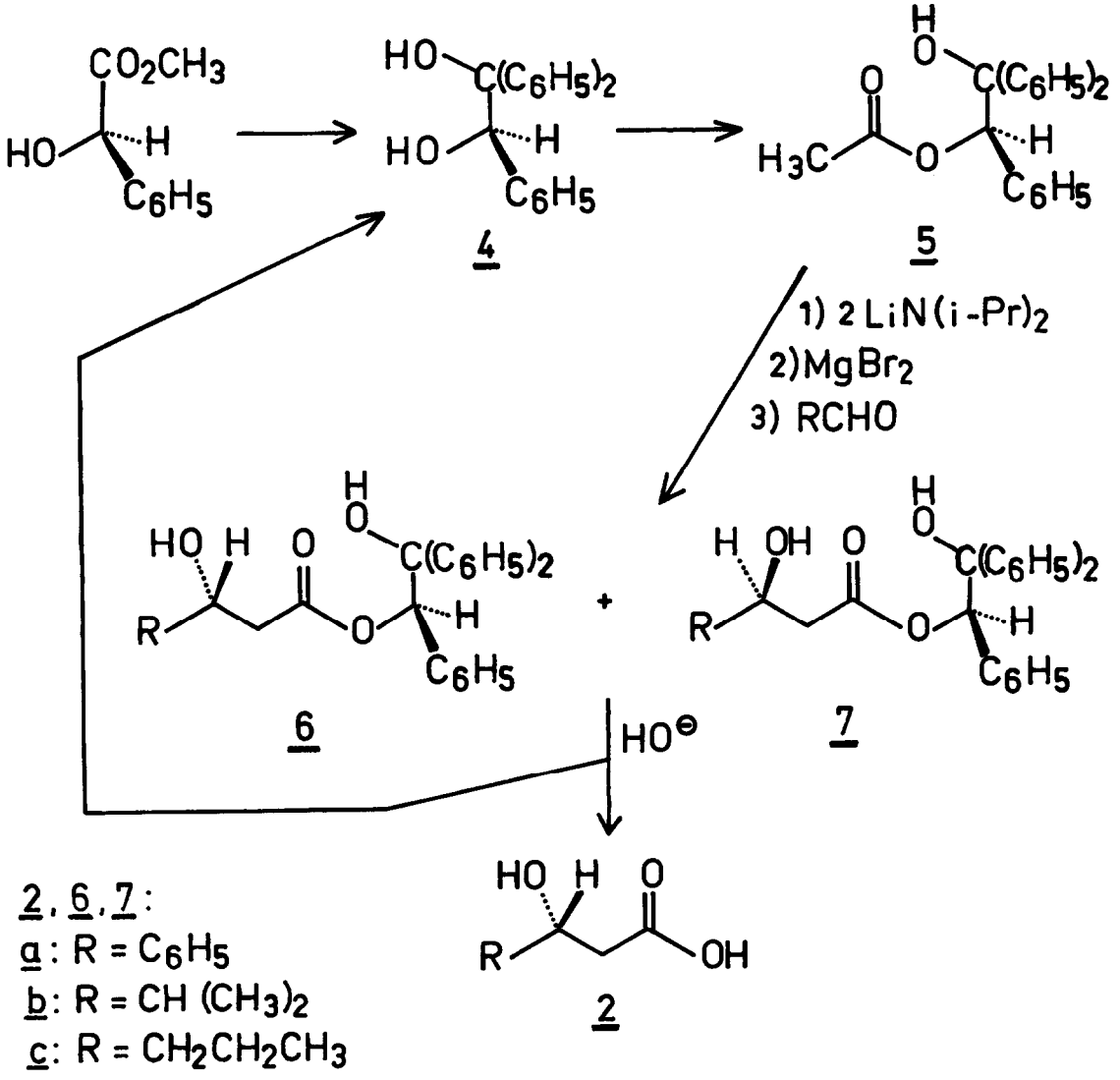
The (R)-diol 4, formed by addition of phenylmagnesium bromide to (R)-mandelic acid methyl ester[4], is converted (acetyl chloride, pyridine, CH_2Cl_2; 0°C) into (R)-2-acetoxy-1,1,2-triphenylethanol (5), $[\alpha]_D^{20} = 209°$ (c = 1.3, pyridine). Deprotonation to the enolate 3 (M = Li) with lithium diisopropylamide and reaction with benzaldehyde at -78°C afforded a 85:15 mixture of the diastereomers 6a and 7a. It turned out, however, that the selectivity is distinctly improved by transmetallation of the lithium enolate 3 (M = Li) with magnesium bromide and by cooling to -115°C during the addition of the aldehydes RCHO.
Since the ratio of the diastereomers 6 and 7, obtained in this way, could not be determined by ^{1}H-NMR spectroscopy, the crude adducts 6/7 were cleaved into the ß-hydroxycarboxylic acids 2 and the diol 4 by heating in aqueous methanol with potassium hydroxide. The absolute configuration and the enantiomeric



excess (e.e.) of the acids 2 have been determined by a comparison of the specific rotations and by ^{1}H-NMR spectroscopic investigation of the methyl esters in the presence of chiral shift reagents[5]. From the result can be deduced the diastereoselectivity in the addition step; the ratio of the diastereomers 6 : 7 is shown in table 1. Obviously, the enolate 3 (M = MgBr) shows remarkably higher stereoselectivity in the reaction with aldehydes than the previously investigated acetate enolates 1[2]. The chiral auxiliary agent, the diol 4, is regenerated by the hydrolysis mentioned above without racemization. Both enantiomers of 2-acetoxy-1,1,2-triphenylethanol (5) are readily available, since (R)- as well as (S)-mandelic acid are cheap commercial products. The carboxylic acids 2 are obtained in 76-85% total chemical yield, referred to 5.

Table 1: Adducts 6/7 and carboxylic acids 2

	Aldehyde	Ratio 6:7	Configuration of 2
a	C_6H_5CHO	97 : 3	R
b	$(CH_3)_2CHCHO$	95 : 5	R
c	$CH_3CH_2CH_2CHO$	92 : 8	S[a)]

a) Change of sign of configuration, since n-propyl - other than the groups R in 2a,b - has a lower order than CH_2COOH.

Typical procedure for the addition of 5 to aldehydes: A solution of 15.0mmol lithium diisopropylamide in tetrahydrofuran (THF), prepared in the usual way from diisopropylamine and n-butyllithium, is added to a stirred suspension of 1.99 g (6.0 mmol) 5 in 20 ml THF at -78°C. The mixture is allowed to warm up to 0°C to give a clear solution.

In a 250 ml three-necked flask, fitted with a low temperature thermometer, a dry ice cooled, pressure equalized dropping funnel with a septum, and a three way stopcock for admission of dry nitrogen, a mixture of 12.0 mmol magnesium bromide in 40 ml THF is prepared from 1,2-dibromoethane and magnesium turnings. Then 80ml dimethyl ether are condensed in the flask at -78°C.

The solution of the lithium enolate is added to this mixture via the dropping funnel at -78°C. After 1 h stirring the suspension is cooled to -115°C (ethanol/liquid nitrogen), treated with 1 ml benzaldehyde, and kept for 40

min at the same temperature. Addition of saturated NH_4Cl solution and warming up to room temperature, followed by extraction with chloroform give 2.55 g (97%) crude 6a/7a as a colorless solid. - ^{1}H-NMR ($CDCl_3$) δ 2.54 (2H, m, CH_2), 2.67 (2H, broad s, OH), 4.84 (1H, m, $C_6H_5C\underline{H}OH$), 6.64 (1H, s, $C_6H_5C\underline{H}OCOCH_2$), 6.8-7.6 (20H, m, aromatic H).
See ref. 3 for the hydrolysis to 2.

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References and Notes

1) D.A.Evans, J.V.Nelson, T.R.Taber, Top. Stereochem. 13, 1 (1982) and references cited therein.

2) The chiral auxiliary groups X*, which operate very well as propionic acid derivatives, are almost completely unselective, when they are used in α-unsubstituted acetate enolates 1 (typical e.e. values: 0 - 25%); see ref. 1, especially p. 95f. - With enolates of α-sulfinyl esters (chiral α-substituent) the products 2 can be obtained in high enantiomeric excess - albeit with loss of the chiral auxiliary agent: C.Mioskowski, G.Solladié, Tetrahedron 36, 227 (1980).

3) Although an improvement (typical e.e. values: 60 - 70%) was possible with (R)-N-acetyl-α-phenylglycinol, the selectivity was felt to be unsatisfactory: M.Braun, R.Devant, Angew. Chem. 95, 802 (1983); Angew. Chem., Int. Ed. Engl. 22, 789 (1983).

4) A.McKenzie, H.Wren, J.Chem.Soc. 97, 473 (1910); R.Roger, W.B.McKay, J. Chem.Soc. 1931, 2229.

5) Eu(hfc)$_3$ and/or Eu(tfc)$_3$ (Aldrich/EGA/Janssen).

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