Enantiospecific Syntheses of Trifunctional (*R*)-3-Hydroxy Esters by Baker's Yeast Reduction

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Asymmetric syntheses of the enantiomerically pure trifunctional (*R*)-3-hydroxy esters (**7**)—(**10**) can be achieved by baker's yeast reduction of the hydrolysed β-keto carboxylates (**2**)—(**5**) instead of by reduction of the corresponding esters.

Reduction of carbonyl compounds with baker's yeast is a convenient method for preparing chiral secondary alcohols.[1] Ethyl (*S*)-(+)-3-hydroxybutyrate (**6**) thus obtained from ethyl 3-oxobutyrate (**1**) was recently used for the preparation of various bifunctional building blocks.[2] The reductions of several other β-keto acid derivatives have been reported.[3] The optical yields, however, are somewhat low, or have not been reported, and it appears that attempts have not been made to

Table 1

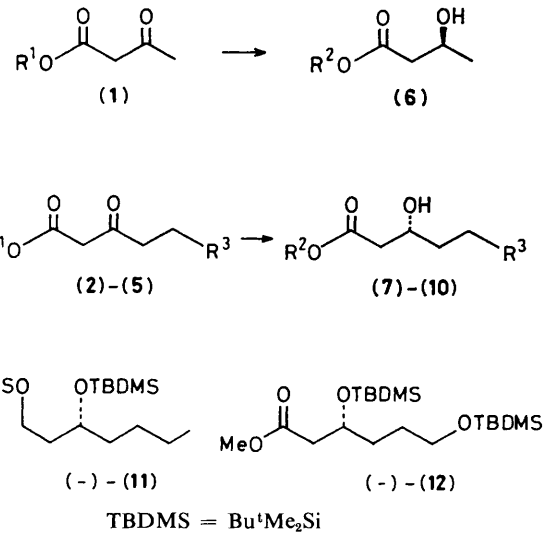
Substrate	Product	Optical purity,[a] % e.e., and, in parentheses, chemical yield[b] (%) R^1=K, R^2=Me[c]	$R^1=R^2$=Me	$R^1=R^2$=Et	$R^1=R^2$=Bu^t	Configuration	$[\alpha]_D$[d](°)
(2) R^3= CH=CH_2	(7)	>99 (38)[e]	92 (30)	80 (54)	81 (66)	*R*[g]	−22.1
(3) R^3= CMe=CH_2	(8)	>99 (55)	67 (18)	18 (15)	0 (22)	*R*[g]	−20.1
(4) R^3= CH=CMe_2	(9)	>99 (59)	92 (73)[f]	50 (12)	0 (40)	*R*[g]	−15.9
(5) R^3=CH_2OCH_2Ph	(10)	>99 (51)		87 (61, R^2=Me)[f] no reaction		*R*	−8.5
(1)	(6)		87 (23)	96 (32)	77 (45)	*S*	

[a] The optical purities were determined by 360 MHz ^{1}H n.m.r. chiral shift studies using tris[3-(trifluoromethylhydroxymethylene)-(−)-camphorato]europium(III). [b] The chemical yields in parentheses refer to chromatographically isolated products. [c] Isolated as the methyl ester after esterification with diazomethane; ^{1}H n.m.r. chiral shift studies indicated the total absence of the other enantiomer. [d] The specific rotations of optically pure methyl esters measured in $CHCl_3$ (*c* 1) at 23—26 °C. [e] See ref. 4. [f] The substrate was partially or completely hydrolysed during the reaction, so that the product acid was treated with diazomethane before purification. [g] All the absolute configurations of the enantiomers formed in excess of (7)—(9) derived from reduction of the esters (2)—(4) are the same as those of (7)—(9) derived from reduction of the hydrolysed carboxylates (2)—(4).

improve the stereoselectivity of the reductions by use of a substituent OR^1 other than ethoxy.

We now report that the stereoselectivity of the enzymic reduction of the β-keto esters (1)—(5) is strongly affected by a change in the carbonyl substituent OR^1 and that the hydrolysed carboxylates (2)—(5) can be stereospecifically reduced to the optically pure 3-hydroxy carboxylic acids (7)—(10) (R^2 = H), which are useful for the preparation of chiral trifunctional building blocks.[4]

The carbonyl substituents (OR^1) were varied as shown in Table 1. Interestingly, the ester substrates (2)—(4) gave better optical yields as R^1 became smaller, whereas in the case of acetoacetate (1) the ethyl ester gave the best result. When the ester (5) was hydrolysed with 1M KOH (2.2 equiv.) and then added to a fermenting yeast–glucose suspension,†‡ the reduction proceeded smoothly to give the optically pure methyl ester (10) in moderate yield after esterification with diazomethane. The unhydrolysed ethyl ester (5) was not reduced and remained unchanged under the usual fermenting conditions. Other hydrolysed carboxylates (2)—(4) (R^1 = K)† also gave optically pure alcohols (7)—(9). The absolute configuration of (7) was established by the total syntheses of compactin (ML-236B)§[4] and mevinolin (monacolin K).[5] The configurations of (8)—(10) were established by chemical



TBDMS = Bu^tMe_2Si

transformations to derivatives of (7), *i.e.*, (−)-(11), (−)-(12), and (−)-(12), respectively. The configurations of the products (7)—(10) are opposite to that of (6).

The authors are grateful to Professor K. Nakanishi for valuable discussions.

Received, 7th February 1983; Com. 171

† The pH of the fermenting mixtures remained *ca.* 7 throughout the reaction.

‡ The following procedure is representative: ethyl 3-oxohept-6-enoate (2; R^1=Et, R^3 = CH=CH_2) (0.029 mol) was hydrolysed in aqueous 1 M KOH (65 ml) in ethanol (90 ml) at 25 °C (20 h). After the ethanol had been removed *in vacuo*, the residue was diluted with 500 ml of water. A suspension of baker's yeast (Oriental Yeast Co., 160 g), D-glucose (180 g), KH_2PO_4 (380 mg), and $MgSO_4$ (190 mg) in water (500 ml) was stirred at 25 °C for 30 min. To this actively fermenting mixture was added the aqueous solution of the hydrolysed β-keto ester and the mixture was stirred at 25 °C. After 2 days, 240 g of Celite was added, and the mixture was stirred for 30 min, and filtered through a Celite pad. The filtrate was acidified to pH 2 with conc. HCl and then extracted with ether (3 × 600 ml). The organic extract was washed with satd. NaCl (500 ml) and dried over anhydrous $MgSO_4$ briefly, before evaporation *in vacuo*. The residue was esterified with diazomethane and then purified by silica gel column chromatography to give a 32% yield of methyl (*R*)-(−)-3-hydroxyhept-6-enoate (7; R^2 = Me, R^3 = CH=CH_2). The chemical yields of (7) varied between 26 and 38%.

§ Although the absolute configuration of compactin (ML-236B) has not been published, it was established by the Sankyo group (ref. 4, personal communication from Dr. A. Terahara, Sankyo Co.).

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