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Enzymatic synthesis of optically active mono-alkylated malonic monoesters

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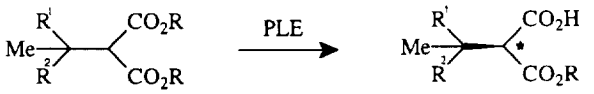
Abstract: Pig-liver esterase hydrolysis of tertiary-alkyl malonic diesters **1** leads to malonic monoesters **2** in high yields and with enantiomeric excesses up to 96% *ee*. The configuration of the new stereogenic carbon atom was determined by crystal structure analysis of the (*S*)-1-phenylethylamide of **2b**. The monoesters **2** are stable against racemisation between pH 2 to pH 12 as shown for **2b**. © 1997 Elsevier Science Ltd

Enzymes are useful reagents for asymmetric synthesis.[1] Pig-liver esterase (PLE) finds widespread use in stereoselective hydrolysis of diesters forming enantiomerically enriched monoesters. In particular 2,2-dialkylated malonic diesters have been stereoselectively hydrolysed by PLE, resulting in optically active monoacids with high enantiomeric excesses.[1b,2] These building blocks can be further converted to a variety of 1,3-difunctionalised optically active compounds.[3] PLE-catalysed hydrolysis of monoalkylated malonic diesters on the other hand, has been described to lead to racemic monoesters or those with *ee*s below 10%.[4,5]

These studies, however, omitted the enzymatic hydrolysis of tertiary-alkyl substituted malonic diesters **1**, whose PLE-catalysed conversion to monoesters **2** is reported here (Scheme 1).[6] The diesters **1** are easily prepared by Knoevenagel-condensation[7] and subsequent 1,4-addition of an alkyl cuprate.[8] The enantiomeric excesses of **2** were determined by capillary gas chromatography of their (*S*)-1-phenylethylamides.[9,10] Contrary to the results in lit.[4,5] in most cases good yields and high *ee*s were obtained (Table 1). Thus the enantiomerically enriched tertiary alkyl malonic monoesters, that are not accessible by diastereoselective alkylation of malonates substituted with a chiral auxiliary,[11] can be prepared.



1 **2**

Scheme 1.

The configuration at the new stereogenic center at C2 was determined to be *S* for the major enantiomer of **2b** by crystal structure analysis of the (*S*)-1-phenylethylamide of the minor enantiomer of **2b**.[13] The (*S*)-configuration for the major enantiomer is also predicted by applying the model of the PLE-pocket proposed by Jones.[14] It appears very reasonable, that the major enantiomers of the other monoesters **2** also have the (*S*)-configuration.

The configurational stability of the enantiomerically enriched monoacids **2** was investigated in the case of **2b**. Suspensions or solutions of **2b** in water were stirred at room temperature varying the pH

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Table 1. PLE-catalysed hydrolysis of tertiary-alkyl malonic diesters **1** to monoesters **2**[12]

	R^1	R^2	R	conversion of **1** [%]	yield of **2** [%][a]	*ee* of **2** [%][b]
a	Me	Me	Me	100	87[12a]	89
b	Me	Me	Et	100	86[12a]	92
c	Me	Et	Et	90	75[12b]	82
d	Me	Ph	Et	90	70[12c]	94
e	Me	Ph	Me	80	68[12d]	90
f	Et	Et	Et	15	10[12e]	45
g	Me	H	Et	100	88[12f]	0
h	$-(CH_2)_6-$		Et	50	45[12e]	96

[a] Determined by isolation; [b] Determined by capillary gas chromatography (50 m HP-1, 150 - 300 °C, 2 °C/min) after conversion into the (*S*)-1-phenylethylamide.

value from 2 to 12. No racemisation of **2b** was detected by capillary glc of the (*S*)-1-phenylethylamide. The configurational stability of the tertiary-alkyl substituted stereogenic carbon atom compared to malonic monoesters with primary or secondary alkyl groups[4,5] appears to be due to the impeded enolate formation caused by sterical strain induced by the tertiary-alkyl group.

PLE-catalysed hydrolysis of isopropyl malonic diethylester **1g** resulted in formation of racemic monoacid **2g**. This underlines the effect of tertiary alkyl substituents on the configurational stability of malonic monoesters, and is in accordance with the observations by Björkling[5] and Gutman.[15]

The monoacid **2f** is formed in low yield only and with a moderate enantiomeric excess. The conversion of **1f**, where the tertiary alkyl group is slightly more bulky, is much slower compared to the other diesters **1** and the enantiomeric excess is only moderate. On the other hand R^2 being phenyl **1d,e** or R^1 and R^2 being part of a six-membered ring **1h** leads to high *ee*s. The monoesters **2** can serve as intermediates for the preparation of enantiomerically enriched 1,3-difunctionalised products such as 3-hydroxyacids or α-aminoacids.

Experimental

2 mmol **1** and 0.5 mL PLE (Boehringer Mannheim) was added to 12.5 mL of phosphate buffer (pH 7). While stirring 1 N NaOH was added to the mixture via an automatical titrator keeping the pH between 7.0 and 7.3. Substrate conversion was followed by measuring the amount of 1 N NaOH added. After complete conversion or 24 h maximal reaction time the reaction mixture was filtered, acidified with concentrated hydrochloric acid to pH 2 and extracted with diethyl ether. The combined organic phases were dried over sodium sulfate. After removal of the solvent 20–60 mg monoacid **2** was reacted with (*S*)-1-phenylethylamine as described in the literature.[9] Pure monoester **2** was prepared by extracting the unreacted diester **1** prior to acidification of the reaction mixture.

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13. X-Ray crystal structure analysis of the (*S*)-1-phenylethylamide of (*R*)-**2b**: $C_{17}H_{25}NO_3$, M_r=291.38 g mol^{-1}, crystal size: 0.6×0.2×0.1 mm, *a*=9.985 (1), *b*=17.650 (3), *c*=20.354 (2) Å, *V*=3587.1 (8) Å^3, $\rho_{calc.}$=1.079 g cm^{-1} , μ=5.9 cm^{-1}, empirical correction of absorbtion, *Z*=8, orthorhombic, space group $P2_12_12_1$ (Nr. 19), Enraf–Nonius CAD4-diffractometer, λ=1.54178 Å, *T*=223(2) K, 4099 measured reflexes (−h,+k,−l), $[(\sin\Theta)/\lambda]_{max.}$=0.62 Å^{-1}, 4099 independent and 2488 observed reflexes [$I \geq 2\sigma(I)$], 456 refined parameters, 2 independent and structurally similar molecules in the asymmetric unit, phenyl group in one molecule and ester group in the other disordered, *R*=0.050, wR^2=0.120, Flack-parameter=−0.8(4), programs used: SHELXS-86, SHELXL-93, SCHAKAL-92. Other details of the crystal structure analysis can be ordered at the "Fachinformationszentrum Karlsruhe", D-76344 Eggenstein–Leopoldshafen, deposition number CSD-405477.
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