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PLE-catalyzed Resolution of α-substituted ß-Ketoesters Application to the Synthesis of (+)-Nitramine and (-)-Isonitramine

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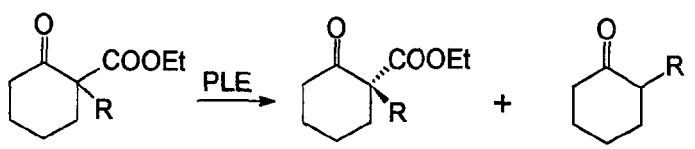
Abstract: Substituted ß-Ketoesters can be prepared in enantiomerically pure form by pig liver esterase catalyzed hydrolysis of their racemic precursors. With the asymmetric carbon atom possessing a quaternary centre, (+)-Nitramine and (-)-Isonitramine have been synthesized.

Natural products containing quaternary carbon centres are the target of many current synthetic accomplishments Therefore, considerable effort has been directed towards the synthesis of these centres. Although a number of methods are available to generate these centres in enantiomerically pure form[1,2], it is still necessary to provide versatile procedures

Enzymatic resolution, which is a very effective method to obtain EPC-building blocks, is of only limited utility for hydrolysis of substrates containing quaternary centres. Studying the PLE-models (pig liver esterase) provided by Jones[3], Ohno[4] and Tamm[5], we imagined that α-substitued ß-ketoesters **1** might be substrates for esterases like PLE. The main feature of this method is shown in Scheme 1. Enzymatic digestion of one enantiomer leads to a ß-ketoacid, which is decarboxylated to yield **4** during workup. The remaining ß-ketoester **2** can be recovered easily. They represent valuable building blocks containing an asymmetric quaternary carbon centre.

Scheme 1



1a-h **2a-h** **3a-h**

conditions: pH-stat conditions, pH 8, phosphate buffer, 20 °C, acidic workup

To investigate the substrate specificity of **1** towards PLE a series of suitable substrates with various alkyl groups was synthesized. The results of the treatment with the enzyme are presented in the Table.

Table

Substrate 1	Reaction time [h]	% ee [a] Configuration [b] 2	% Yield [c]	$[\alpha]_D^{20}$ [d]
a $-CH_3$	6	> 99 (S)	88	+66.1
b $-C_2H_5$	50	/	/	/
c $-C_3H_7$	83	70	< 10 (GC)	/
d $-C_4H_9$	49	> 99 (S)	40	+97.5
e $-C_5H_{11}$	22	> 98 (S)	58	+98.6
f $-(CH_2)_2CN$	47	> 99 (R)	70	+121.6
g $-(CH_2)_3CN$	95	> 99 (R)	60	+100.7
h Benzyl	no hydrolysis after 48 h			

a: The enantiomeric excess (ee) was determined by GLC using a cyclodextrin modified column

b. The configuration was assigned by correlation with compounds reported previously [1,8], the change of configuration in 2f,g is due to the changed preference of substituents;

c: Isolated yield, yield is based on 50 % hydrolysed **1**, all compounds exhibit satisfactory spectroscopic and elemental analysis;

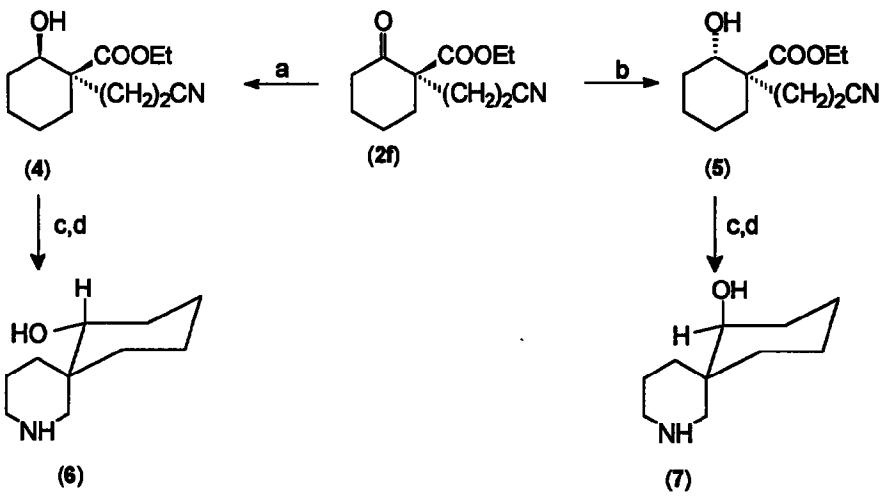
d All optical rotations were measured in $CHCl_3$.

The first substrate studied was **1a**. A crude PLE-extract[6] was used to carry out the enzymatic resolution. After a period of 6 h, the CD-GLC-analysis[7] revealed that the reaction mixture consisted of only one enantiomer of (±)-**1a**, the optical purity was >99 %ee. After recovery of the remaining ß-ketoester **2a**, the $[\alpha]_D$-value revealed[1,8], that the (R)-enantiomer of **1a** had been preferentially hydrolyzed. As a result, the configuration of C-2 in **2a** is (S). Prolonged reaction time caused the complete hydrolysis of **1a**. The same procedure was applied to **1b-h** It was striking, that **1b,c** showed only poor selectivity towards PLE. The enzymatic hydrolysis was very slow as demonstrated by the CD-GLC analysis. After 50 h, **1b** was completely hydrolyzed allowing no isolation of enantiomerically enriched **2b**, whereas **1c** showed little selectivity towards the enzyme, after 70 h **2c** could be detected with 70 %ee. Compounds **1d,e** turned out to be excellent substrates; after 48 h and 60 h, respectively, only one enantiomer could be detected The optical purity of **2d,e** was high showing ee-values of 99 % and 98 %, respectively. In contrast to the enzymatic hydrolysis of **1a**, prolonged reaction time did not result in any notable increase of hydrolyzed product of **1d,e**.

Nitrile derivatives **1f,g** had almost the same selectivity towards PLE as their alkylated counterparts **1d,e**. It can be concluded that nitrile groups do not interfere with the active site of the enzyme. The optical purity of **2f,g** is very high (> 99 %ee) and therefore, they represent valuable starting materials for the synthesis of the spirocyclic alkaloids nitramine or histrionicotoxin and their congeners[9].

The assignment of the (R)-configuration of the quaternary stereogenic centre in **2f,g** was based on the chemical correlation with (+)-nitramine (**6**) and (-)-isonitramine (**7**), respectively. The synthesis of these spirocyclic alkaloids according to Hellberg[10] was accomplished by employing **2f** as the starting material (Scheme 2). Reduction of **2f** with $Al(OiPr)_3$/isopropanol[11] gave predominantly **4** (d.e.>80%) in high chemical yield. The following steps were carried out as described for the synthesis of **6**. The spectral data and optical rotation of **6** and **7** were in good agreement to those reported; **6** $[\alpha]_D^{20}$ +22.8 (CH_2Cl_2, c=1.9), Lit. [12]: +23.0 (CH_2Cl_2, c=1.58); **7** $[\alpha]_D^{20}$ -4.9 ($CHCl_3$, c=1.6), Lit. [13]: -5 ($CHCl_3$, c=2.1).

Scheme 2



a: $NaBH_4$, CH_3OH, 2 h, 82%, b: $Al(OiPr)_3$, iPrOH, 3 h, 82%; c: H_2/PtO_2, EtOH, 60 °C, 65%; d: LAH, THF, 15 h, 74%.

In conclusion we have shown that ß-ketoesters **2** can be obtained in excellent enantiomeric purity by PLE catalyzed hydrolysis of the racemic precursor **1**. This strategy should be applicable to other types of ß-ketoesters. The progress of further investigations will be published in due course.

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7. Cyclodextrin modified columns were employed (Lipodex E, Macherey & Nagel, Germany). We like to thank Prof. W. König, Univ. Hamburg, Germany for his suggestions concernig the use of Lipodex E
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