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PREPARATION OF CHIRAL 4-SUBSTITUTED γ-LACTAMS AND THE CORRESPONDING γ-AMINOBUTYRIC ACIDS. (REVIEW)*

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Data on the synthesis of chiral γ-lactams substituted at position 4 and the corresponding β-substituted γ-aminobutyric acids for the period from 1991 to 2006 are reviewed.

Keywords: diastereomers, lactams, asymmetric synthesis, chirality, enzymatic synthesis.

Cyclic amides (lactams) are an often encountered structural element of medical products. The present review examines the preparation of γ-lactams (pyrrolidones) substituted at position 4. This group includes piracetam (oxiracetam, phenotropil, cebaracetam), rolipram, and others. The γ-amino acids corresponding to the above-mentioned lactams (analogs of the natural neuromediator γ-aminobutyric acid) also often exhibit biological characteristics, e.g., the β-aryl-substituted derivatives phenibut and baclofen. The 4-substituted lactams examined in this article and also the corresponding β-substituted γ-aminobutyric acids contain a chiral center*[2]. It is known that in most cases only the *R*-isomers of these compounds are biologically active, whereas the *S*-isomers are practically inactive. The production of optically pure isomers of these compounds therefore becomes an urgent issue. In this review methods of resolving racemic lactams into the optical isomers, various examples of asymmetric synthesis, and also enzymatic methods are examined.

1. RESOLUTION OF RACEMIC LACTAMS INTO OPTICAL ISOMERS

One of the classical methods for the resolution of racemates into optical isomers is crystallization of the racemic mixture with a chiral substance capable of forming a well crystallized compound with the substrate being separated. While reacting with racemic 3-(*p*-chlorophenyl)glutamic acid (**1**), *S*-(-)-α-phenylethylamine forms with the *R*-isomer a poorly soluble salt, which is precipitated while the *S*-isomer remains in solution. The *R*-isomer of the acid isolated in this way is then converted into *R*-4-amino-3-(*p*-chlorophenyl)butyric acid (baclofen) (**2**) [1].

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* Dedicated to Prof. Ivars Kalvinsh to mark his 60th birthday

*[2] For the stereoselective synthesis of γ-aminobutyric acids, see also the review: M. Ordóñez and C. Cativela, *Tetrahedron; Asymmetry*, **18**, 3 (2007) (Editor's note).

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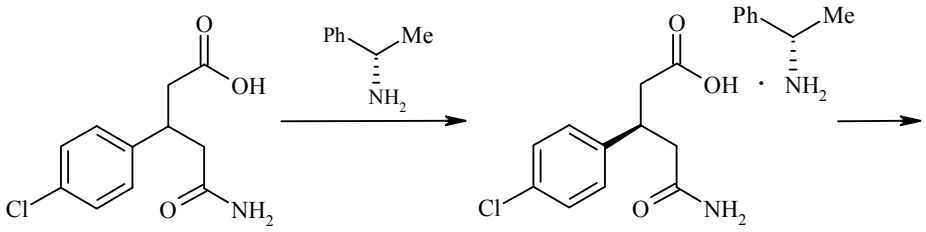
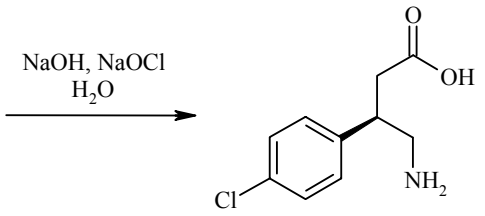
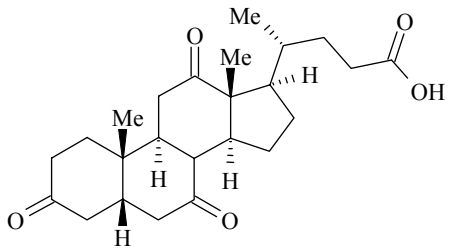




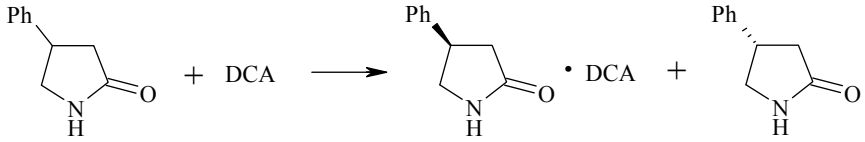
R-**2**

There are data in the literature on the resolution of racemic lactams into the optically active isomers by crystallization with dehydrocholic acid (DCA).



Dehydrocholic acid

If DCA is added to a solution of racemic lactam (**3**) in a mixture of ethyl acetate and ether a complex of DCA and the lactam is precipitated, and the lactam in the complex is enriched in one of the optical isomers [2]:



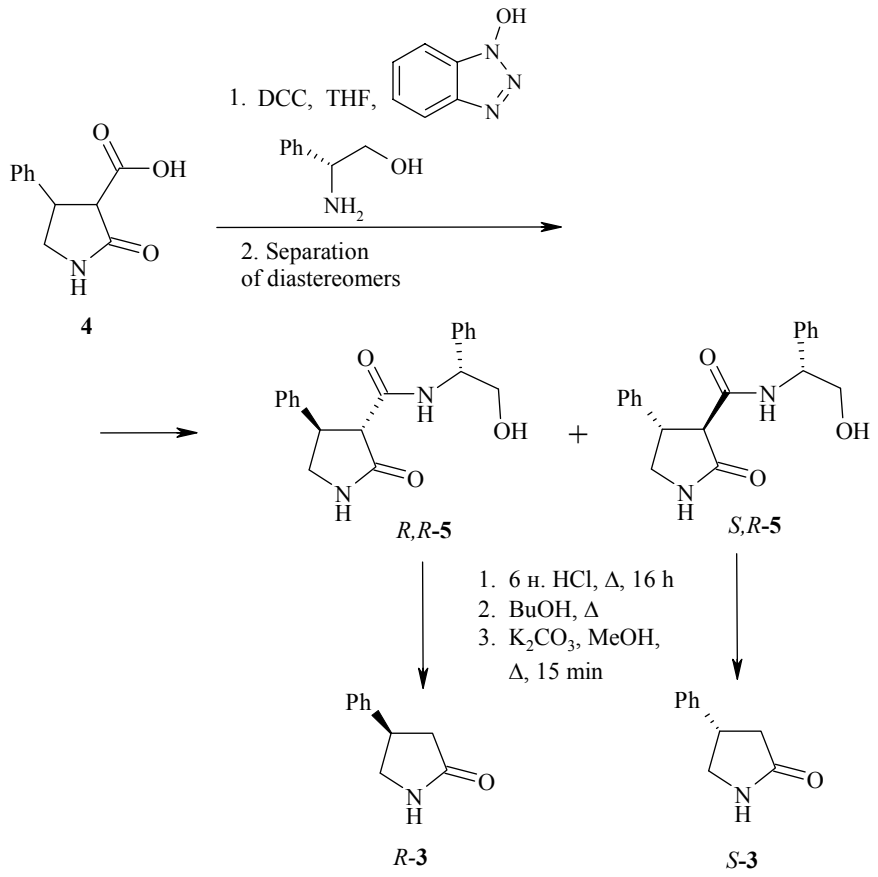
R,S-**3**

complex of R-3 with DCA
(in the precipitate)

S-**3**
(in solution)

The solution is accordingly enriched in the other optical isomer. The enriched lactam is obtained by treating the complex with sodium carbonate; depending on the structure of the lactam, the optical enrichment in one crystallization cycle can amount to 64% *ee*. The optical purity is increased if the crystallization of the enriched lactam with DCA is repeated. Disadvantages of the method include the need to use a large excess of the lactam in relation to the DCA (~5:1) and also the low degree of enrichment in each crystallization cycle. As a result lactams with high optical purity can only be obtained with multiple recrystallization and with a low overall yield.

A more effective method for the resolution of the isomers is condensation with some chiral substance followed by separation of the obtained mixture of isomers and removal of the chiral auxiliary group. For example, the chiral lactam can be obtained by the condensation of racemic 4-phenyl-2-pyrrolidinone-2-carboxylic acid (**4**) with *R*-(−)-phenylglycinol. The obtained mixture of diastereomers is separated by chromatography, after which the pure diastereomers **5** are submitted to hydrolysis and decarboxylation, and the optical isomers of 4-phenylpyrrolidinone **3** are obtained [3].



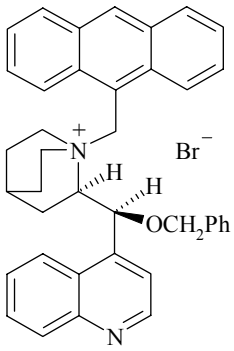
2. ASYMMETRIC SYNTHESIS

Methods for the synthesis of lactams with a specific optical configuration are more often encountered in the literature. Chiral catalysts are widely used in the contemporary synthesis of optically active substances; the method involving the introduction of a chiral auxiliary group into the substrate molecule is also employed.

2.1. The Use of Chiral Catalysts

Chiral lactams can be obtained by various multistage processes using chiral catalysts at specific stages.

The modified cinchonine (**6**) or cinchonidine (**7**) catalysts are used in the addition of nitromethane to chalcone **8**. Successive oxidation of the obtained product with *m*-chloroperbenzoic acid (*m*-CPBA) and reduction with $NiCl_2$–$NaBH_4$ lead to chiral 4-(4-chlorophenyl)-2-pyrrolidinone **10** [4]:



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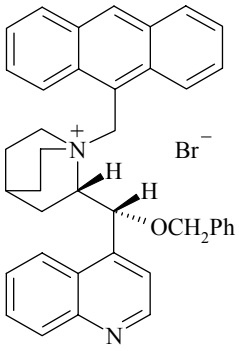
Cinchonine catalyst



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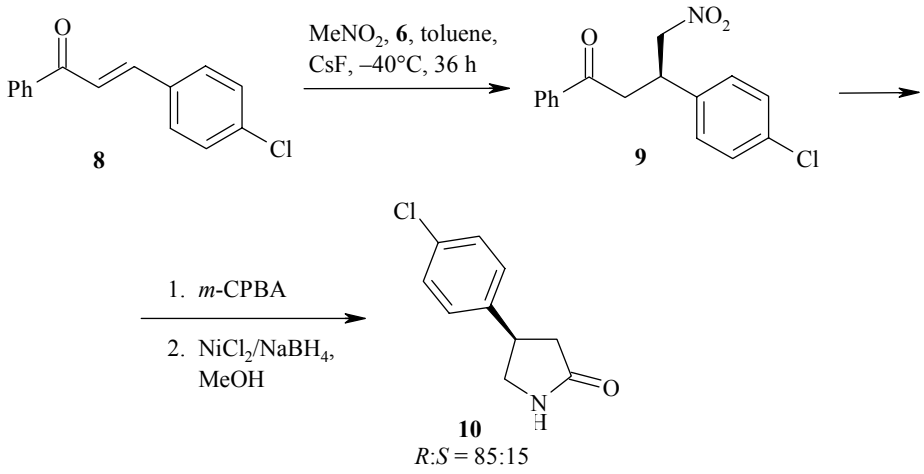
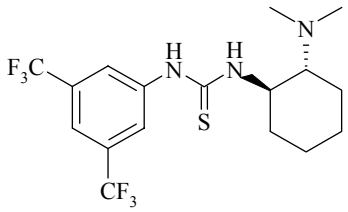
Cinchonidine catalyst



The *R*-isomer is produced with the cinchonine catalyst (**6**), while the *S*-isomer is formed with the cinchonidine catalyst (**7**).

Catalysts **11** and **12** are used in the asymmetric Michael addition of malonic esters to nitroolefins.



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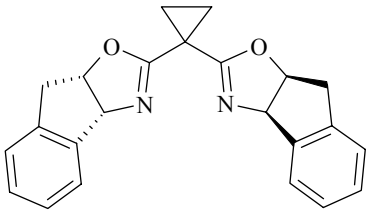

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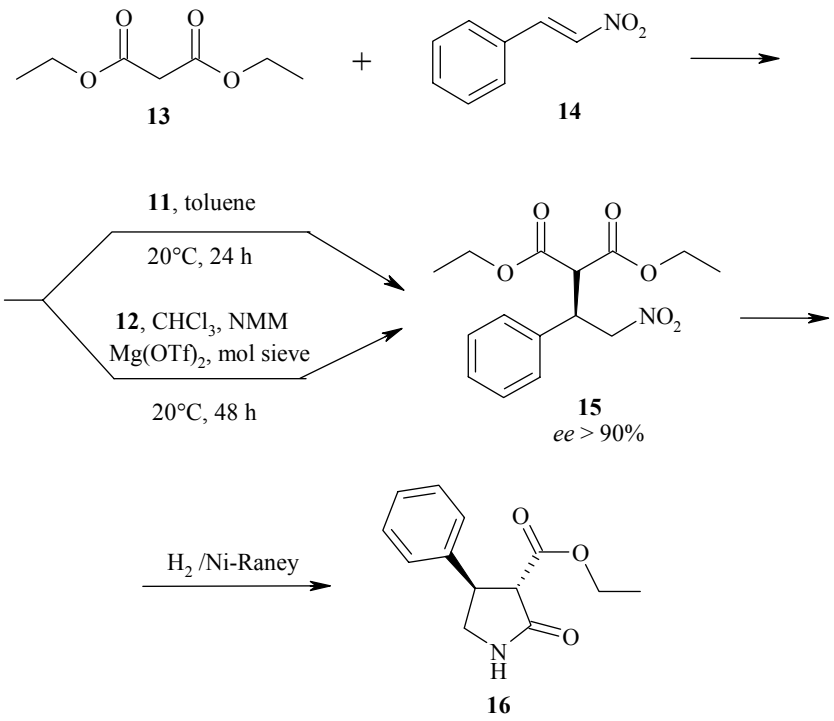
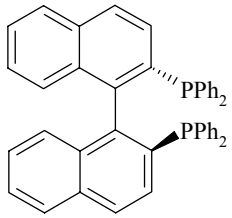
Catalyst **11** contains a chiral 1,2-diaminocyclohexane fragment, which in the course of the reaction forms a complex with the substrate molecules and also acts as base [5-7]. Catalyst **12** forms a complex with the magnesium ion and the malonate molecule, leading to asymmetric addition of the latter to the nitroolefin molecule. The magnesium ions needed for this reaction are introduced in the form of magnesium triflate; N-methylmorpholine (NMM) is used as base [8, 9]. The condensation of diethyl malonate (**13**) with ω-nitrostyrene (**14**) in the presence of these catalysts leads to the Michael addition product **15** with high enantiomeric selectivity [5, 8].



The chiral lactam **16** was obtained by reducing the product **15** with hydrogen in the presence of Raney nickel.

Chiral 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (**17**) (BINAP) is widely used in asymmetric synthesis, including the synthesis of chiral lactams.

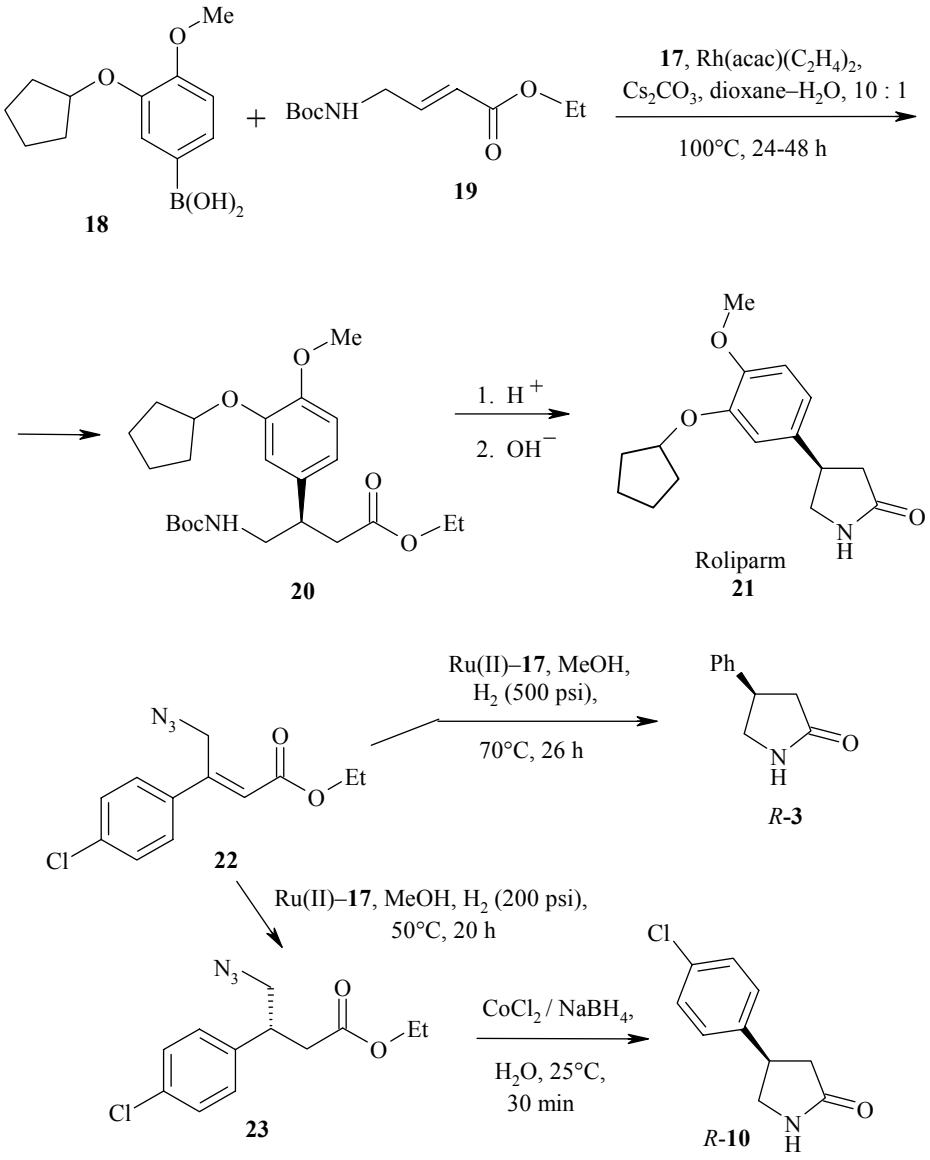


S-(-)-BINAP

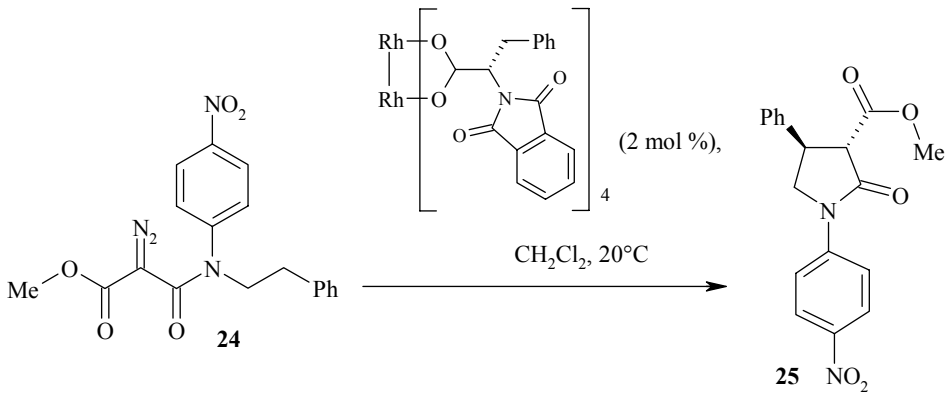
17

The addition of 3-cyclopentyloxy-4-methoxyphenylboric acid (**18**) to ethyl 4-(N-Boc-amino)crotonate (**19**) in the presence of a rhodium catalyst and *S*-BINAP gave the chiral compound **20**, which then gave the chiral lactam **21** known in medicine as rolipram [10]:

Various chiral lactams were obtained by catalytic hydrogenation of ethyl 4-azido-3-(4-chlorophenyl)crotonate (**22**) under various conditions in the presence of ruthenium and *S*-BINAP [11]:



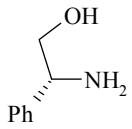
A complex of rhodium with *S*-3-phenyl-2-phthalimidopropionic acid catalyzes the transformation of compound **24** to the chiral lactam **25** [12]:



2.2. Introduction of Chiral Auxiliary Groups

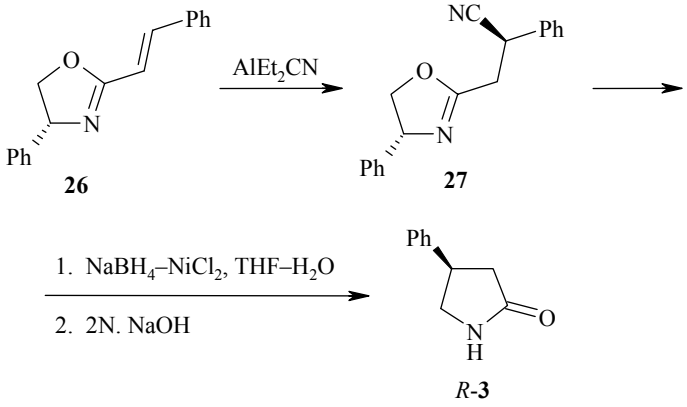
One of the methods used for the synthesis of optically active substances is the introduction of a chiral group into the substrate molecule. If the chiral center of the auxiliary group in the molecule of the obtained product is not far from the atom or bond that subsequently interact with the other reagent, one of the diastereomers is formed preferentially as a result of this reaction.

There are published data on the use of phenylglycinol as a chiral auxiliary group.



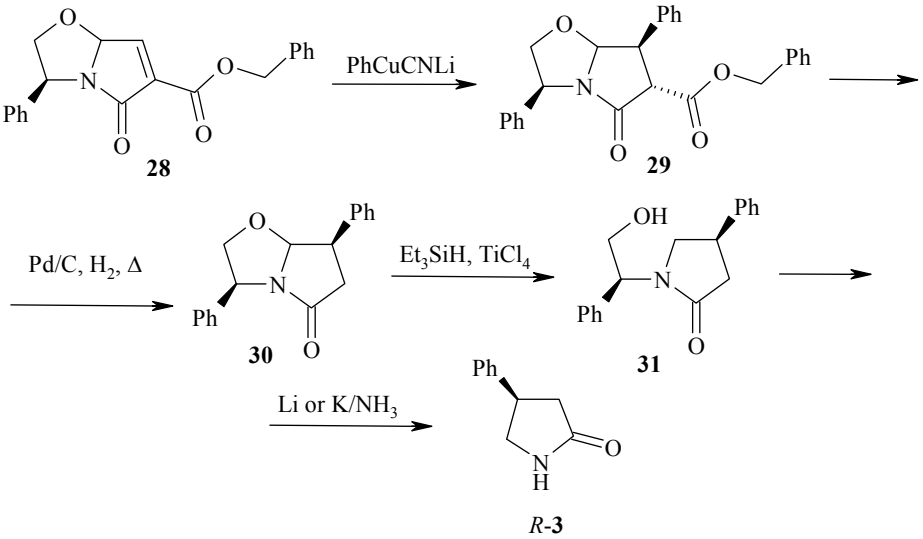
R-Phenylglycinol

The oxazoline **26**, which is the product from the condensation of phenylglycinol and cinnamic acid, reacts with diethylaluminum cyanide and forms compound **27** with ~50% diastereoselectivity. Further transformations give the chiral lactam **3**; the optical purity of the product corresponds to the optical purity of the diastereomer **27**, i.e., ~50% [13]:



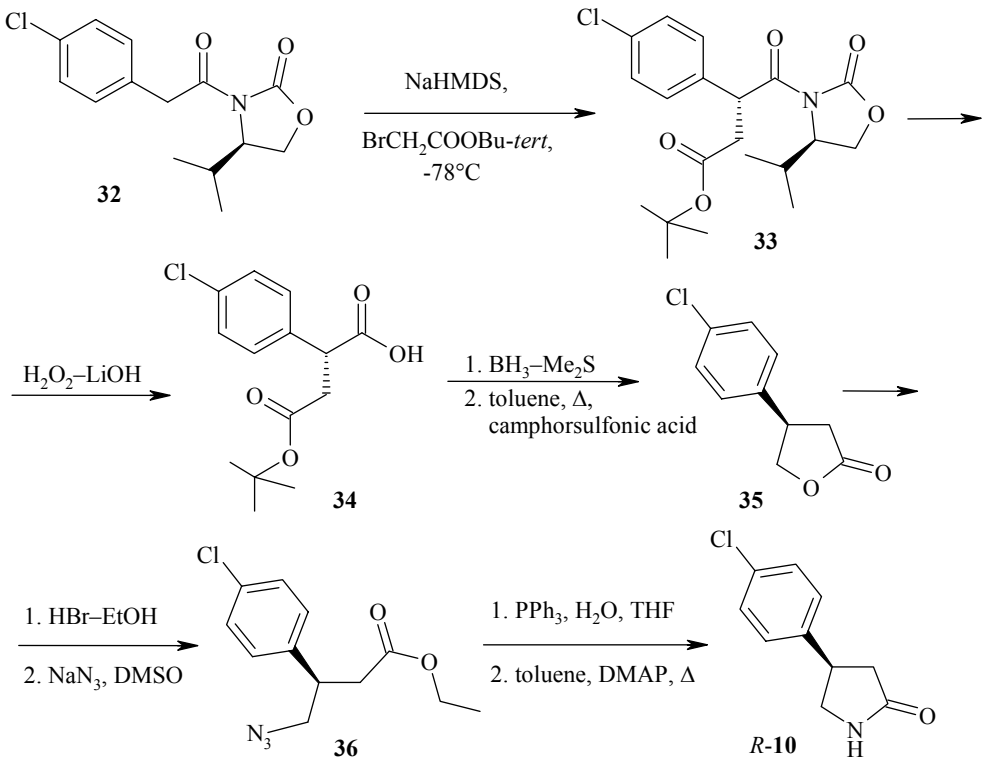
26 **27** *R*-**3**

Compound **28**, which contains the *S*-phenylglycinol fragment, reacts with PhCuCNLi to form the phenyl-substituted lactam **29** with diastereoselectivity *RS*:*SS* = 98:2. Removal of the phenylglycinol fragment leads to the lactam **3** [14]:

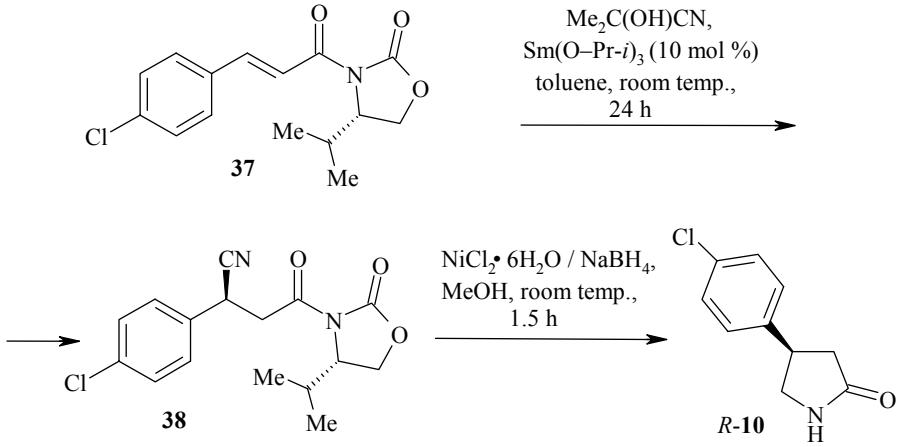


28 **29** **30** **31** *R*-**3**

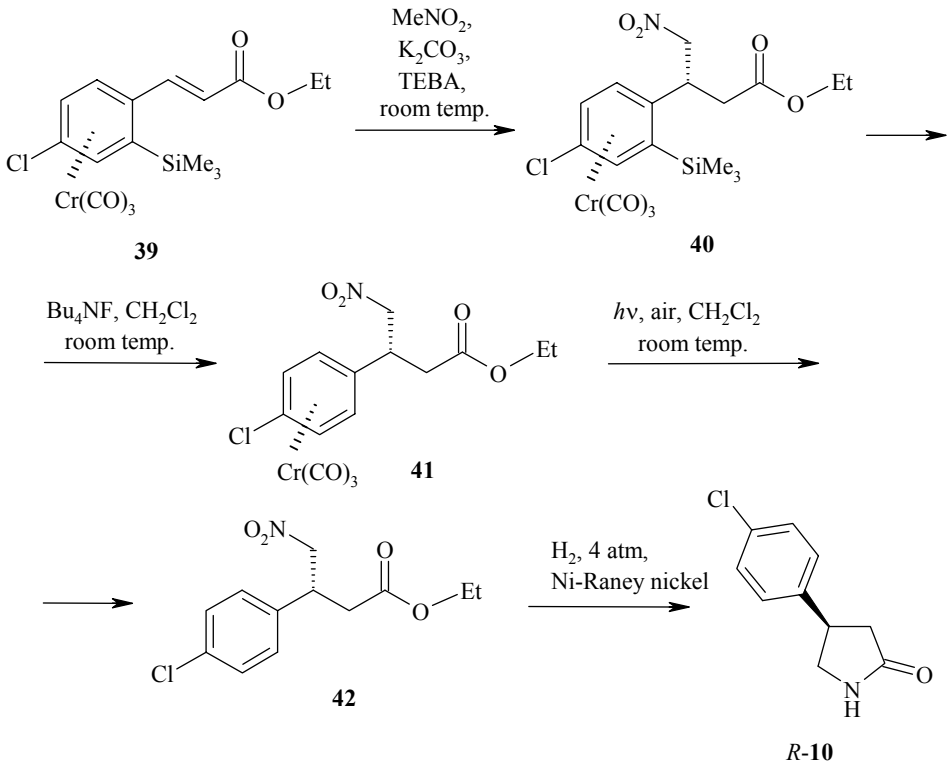
A derivative of 4-chlorophenylacetic acid with the *R*-valinol fragment (**32**) is alkylated enantioselectively by *tert*-butyl bromoacetate (ratio of stereomers >95:5). By a chain of further transformations it is possible to obtain the chiral lactam **10** [15].



In a similar way a derivative of *p*-chlorocinnamic acid and *S*-valinol (**37**) react stereoselectively with acetone cyanohydrin in the presence of Sm(O-Pr-*i*)$_3$. Reduction of the obtained cyanide **38** with $NiCl_2$–$NaBH_4$ gives the lactam *R*-**10** with 99% *ee* optical purity [16].



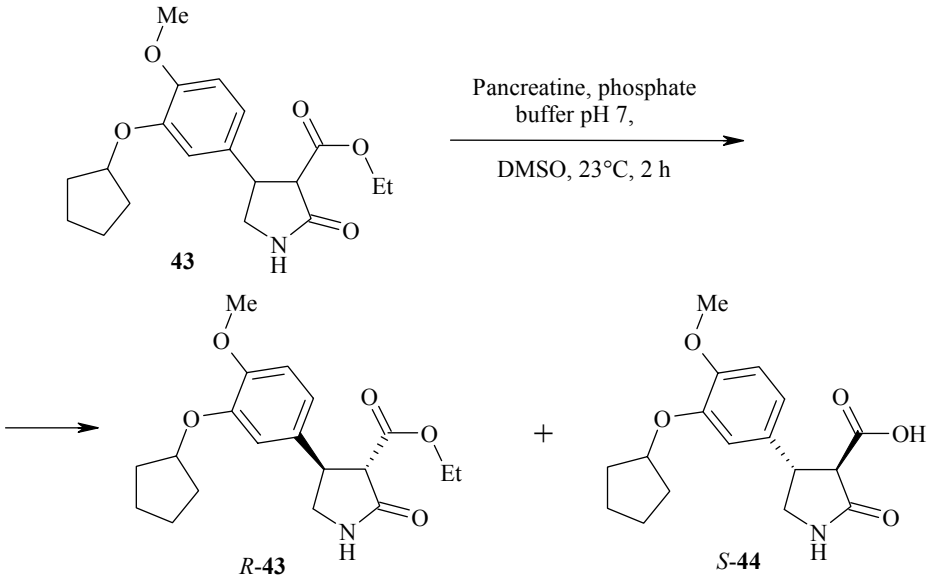
The unique chiral complex of ethyl 2-trimethylsilyl-4-chlorocinnamate with tricarbonylchromium (**39**) adds nitromethane asymmetrically. Subsequent desilylation, oxidation, and reduction of the obtained Michael adduct **40** lead to the formation of the lactam *R*-**10** (96% *ee*) [17].



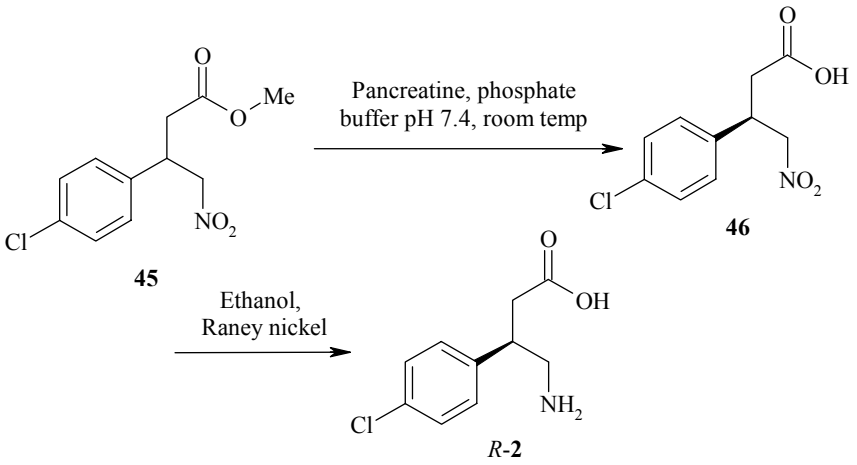
3. ENZYMATIC METHODS

In biological systems enzymes act as selective catalysts; here they are selective not only with respect to the substrate but also, in the presence of a chiral center, to its optical configuration. As a rule enzymes are capable of catalyzing the reaction of only one of the optical isomers, or the enzyme converts each of the isomers into different products. If the molecule of the substrate is symmetrical while the product contains a chiral center, one of the optical isomers is formed preferentially in the enzymatic reaction.

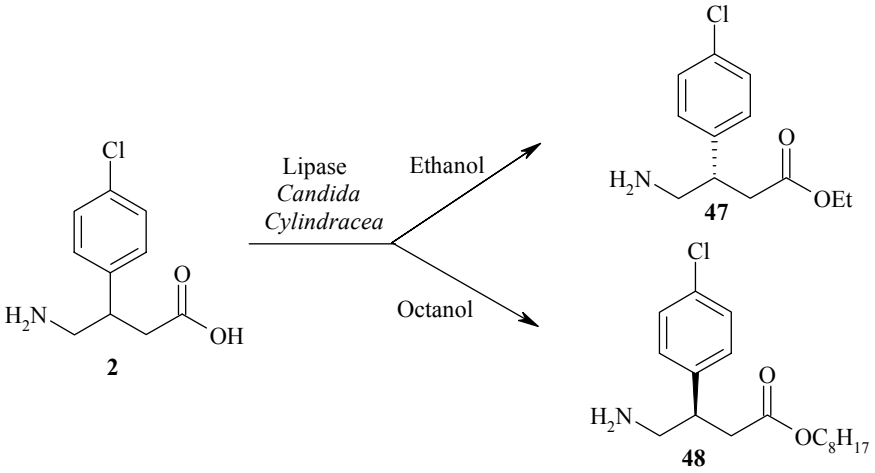
The enzyme pancreatine hydrolyzes the *S*-isomer of the ester stereoselectively, whereas the *R*-isomer remains unchanged. By simple procedures it is possible to separate the acid **44** from the unreacted ester [18]:



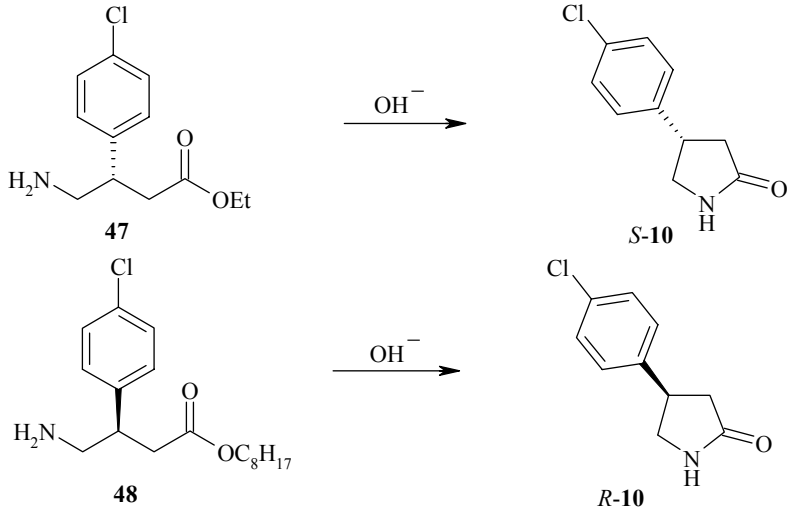
Pancreatine also hydrolyzes methyl *R*-3-(*p*-chlorophenyl)-4-nitrobutyrate (**45**), leaving the *S*-isomer untouched. Reduction of the obtained nitro ester **46** leads to chiral baclofen *R*-**2** [19].



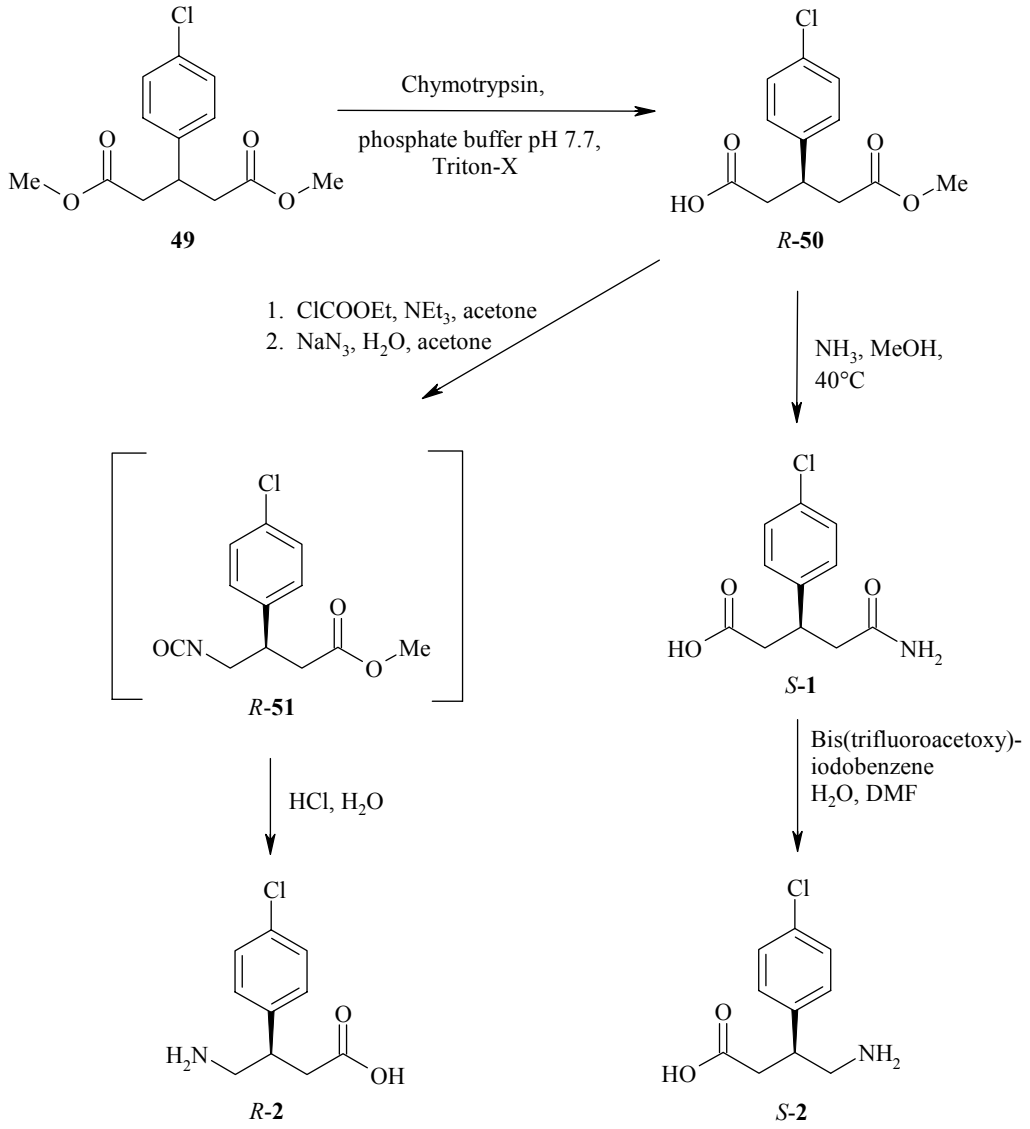
Lipase from the microorganism *Candida Cylindracea* esterifies baclofen **2** stereoselectively. In reaction with lower aliphatic alcohols (such as ethanol) in the presence of this enzyme the *S*-isomer is esterified preferentially (*ee* 66%), while the *R*-isomer mostly reacts with higher aliphatic alcohols (such as octanol) (*ee* 77%) [20].



The obtained esters readily undergo cyclization to the corresponding chiral lactams **10**:



The bacteria *Streptomyces halstedii olivaceus* selectively metabolize the *S*-isomer of baclofen **2**, leaving the *R*-isomer untouched (*ee* > 90%) [21]. The enzyme chymotrypsin selectively hydrolyzes one of the ester groups in dimethyl 3-(4-chlorophenyl)glutarate (**49**); the obtained *R*-monoester **50** (*ee* > 98%) is converted by chemical methods into the *R*- or *S*-isomer of the amino acid **2** [22].



49 *R*-**50** *R*-**51** *S*-**1** *R*-**2** *S*-**2**

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