Title: PROCESS FOR THE PREPARATION OF β-AMINOCARBOXYLIC ACIDS

Abstract: The present invention relates to a method of producing β-aminocarboxylic acids or their derivatives by conversion of compounds of formula (I) with ketene acetals in the presence of a base.

\[ \text{H} \quad \text{N} \quad \text{R}^1 \]
\[ \text{R}^2 \quad \text{SO}_2 \quad \text{R}^3 \]
Process for the Preparation of β-Aminocarboxylic Acids

The present invention is directed to a process for the production of β-aminocarboxylic acids (β-amino carboxylic acids) and β-aminocarboxylic acid derivatives. In particular this invention is concerned with the reaction of a compound of general formula (I)

\[ \text{R}^1 \text{NH} \rightarrow \text{H} \]
\[ \text{R}^2 \text{SO}_2 \text{R}^2 \]

with a ketene acetal under basic conditions.

In recent years racemic and enantiomerically enriched β-aminocarboxylic acids and their derivatives have gained much attention within the chemical community for being versatile tools for preparatively working organic chemists. Enantiomerically enriched β-aminocarboxylic acids occur in natural substances such as alkaloids and antibiotics, and their isolation is increasingly attracting interest, not least on account of their increasing importance as essential intermediate products in the preparation of medicaments (see, inter alia: E. Juaristi, H. Lopez-Ruiz, Curr. Med. Chem. 1999, 6, 983-1004). Both the free form of enantiomerically enriched β-aminocarboxylic acids and their derivatives show interesting pharmacological effects and can also be employed in the synthesis of modified peptides.

Several routes are known which lead to the synthetic creation of β-aminocarboxylic acids (Mei et al., Tetrahedron 2002, 58, 79991-8035). For example, adding an ester enolate equivalent to an amine - the so-called Rodionov-reaction - furnishes β-aminocarboxylic acid derivatives (Radionov et al., Zhurnal Obshchei Khimii 1958,
28, 2242). However, this reaction gives only poor results when contemplated from a technical point of view.

Recently, Kobayashi and Jacobsen have reported an asymmetric version of this reaction with impressive ee-values (JACS 2002, 124, 12964-65). In this reaction TMS-enolethers are added to aniline derived imines or Boc-protected imines using Lewis acid catalysts. Unfortunately, the need to remove the aniline oxidatively with ceric ammonium nitrate (CAN) and the expense in preparing the TMS-enolether impose a limit on the practical applicability of this approach.

In particular, the diastereoselective addition of lithium phenylethylamide (A. F. Abdel-Magid, J. H. Cohen, C. A. Maryanoff, Curr. Med. Chem. 1999, 6, 955-970) have been established as methods for the preparation of β-aminocarboxylic acids. The latter method is regarded as having been intensively researched and is preferentially adopted, despite numerous disadvantages that arise in the process. On the one hand, stoichiometric quantities of a chiral reagent are required, which represents a great disadvantage in comparison with catalytic asymmetrical methods. Furthermore, expensive and, moreover, hazardous auxiliary substances such as, for example, n-butyllithium are required for activating the stoichiometric reagent by deprotonation. For sufficient stereoselectivity, in addition, the implementation of the reaction at low temperatures of about -70 °C is important, which signifies a high demand on the material of the reactor, additional costs and a high consumption of energy.

Other forms of obtaining enantiomerically enriched β-aminocarboxylic acids by enzymatic resolution techniques are presented in WO03080854, EP1361279 and EP1367129 and cited literature.
In sum, the methods known in the art for forming the β-aminocarboxylic acids and derivatives are preferentially used on lab scale rather than in a technical process.

Now the object underlying the present invention is to make available a new, simple and economically practicable process for preparing, in particular enantiomerically enriched β-aminocarboxylic acids and their derivatives.

This object is achieved by a process for the preparation of β-aminocarboxylic acid derivatives by reacting a compound of general formula (I)

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{R}^1 \\
\text{R}^2 & \quad \text{SO}_2 \text{R}^2
\end{align*}
\]  

wherein

R\(^1\) denotes a N-protecting group,

R\(^3\) is a group (C\(_1\)-C\(_8\))-alkyl, wherein the linking C-atom is a tertiary one, (C\(_5\)-C\(_{18}\))-aryl, (C\(_7\)-C\(_{19}\))-aralkyl, wherein the linking C-atom is a tertiary one, (C\(_3\)-C\(_8\))-heteroaryl, (C\(_4\)-C\(_{19}\))-heteroaralkyl, wherein the linking C-atom is a tertiary one, ((C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_6\)-C\(_{18}\))-aryl, ((C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_3\)-C\(_8\))-heteroaryl, (C\(_3\)-C\(_8\))-cycloalkyl, wherein the linking C-atom is a tertiary one, ((C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_3\)-C\(_8\))-cycloalkyl, wherein the linking C-atom is a tertiary one, (C\(_3\)-C\(_8\))-cycloalkyl-(C\(_1\)-C\(_8\))-alkyl, wherein the linking C-atom is a tertiary one, adamantyl,

R\(^2\) is (C\(_1\)-C\(_8\))-alkyl, (C\(_5\)-C\(_{18}\))-aryl, (C\(_7\)-C\(_{19}\))-aralkyl, ((C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_6\)-C\(_{18}\))-aryl, (C\(_3\)-C\(_8\))-cycloalkyl, ((C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_3\)-C\(_8\))-cycloalkyl, (C\(_3\)-C\(_8\))-cycloalkyl-(C\(_1\)-C\(_8\))-alkyl,

with a ketene acetal in the presence of a base in a very surprising and nonetheless advantageous manner.
Moreover, a process for the preparation of β-aminocarboxylic acids by reacting a compound of general formula (I)

\[
\begin{array}{c}
H \\
N \quad R^1 \\
\hat{\text{R}}^2 \quad \text{SO}_2 R^2
\end{array}
\]

(I)

wherein

R\(^1\) denotes a N-protecting group,

R\(^3\) is (C\(_1\)-C\(_9\))-alkyl, wherein the linking C-atom is a tertiary one, (C\(_6\)-C\(_{18}\))-aryl, (C\(_7\)-C\(_{19}\))-aralkyl, wherein the linking C-atom is a tertiary one, (C\(_3\)-C\(_8\))-heteroaryl, (C\(_4\)-C\(_{19}\))-heteroaralkyl, wherein the linking C-atom is a tertiary one, (C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_6\)-C\(_{18}\))-aryl, (C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_3\)-C\(_8\))-heteroaryl, (C\(_3\)-C\(_8\))-cycloalkyl, wherein the linking C-atom is a tertiary one, (C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_3\)-C\(_8\))-cycloalkyl, wherein the linking C-atom is a tertiary one, (C\(_3\)-C\(_8\))-cycloalkyl-(C\(_1\)-C\(_8\))-alkyl, wherein the linking C-atom is a tertiary one, adamantyl,

R\(^2\) is (C\(_1\)-C\(_8\))-alkyl, (C\(_6\)-C\(_{18}\))-aryl, (C\(_7\)-C\(_{19}\))-aralkyl, (C\(_1\)-C\(_8\))-alkyl)\(_{1-3}\)-(C\(_6\)-C\(_{18}\))-aryl, (C\(_3\)-C\(_8\))-cycloalkyl, (C\(_1\)-C\(_8\))-cycloalkyl-(C\(_1\)-C\(_8\))-alkyl,

with a ketene acetal in the presence of a base and subsequently deprotecting the product thus obtained at the N- and/or C-terminal end, optionally in an enantioselective manner, may furnish in a simple and easy to handle process, optionally highly enantiomerically enriched, β-aminocarboxylic acids or their derivatives.

Both processes are advantageously performed on large scale using no reagents being harmful to men or extreme reaction conditions difficult to realise in big vessels.

Preferably compounds of formula (I) are transformed in which R\(^1\) is formy, Boc, Z, R\(^2\) is (C\(_1\)-C\(_8\))-alkyl, ((C\(_1\)-C\(_8\))-
alkyl)_{1-3}-(C_6-C_{18})-aryl, R^3 is (C_1-C_8)-alkyl, wherein the linking C-atom is a tertiary one, (C_6-C_{18})-aryl, (C_3-C_{18})-heteroaryl, ((C_1-C_8)-alkyl)_{1-3}-(C_6-C_{18})-aryl, ((C_1-C_8)-alkyl)_{1-3}-(C_3-C_{18})-heteroaryl.

In a further preferred embodiment the residues for R^1 is formyl, for R^2 is tolyl, for R^3 is phenyl, 4-MeO-phenyl, 4-OH-phenyl, 4-NO_2-phenyl.

Preferred is a process, in which the ketene acetal is a compound of the general formula (II)

\[
\begin{array}{c}
R^7 \\
\text{H} \\
R^6O \\
\text{OR}^5
\end{array}
\]  

wherein

R^6 and R^5 are independently of each other (C_1-C_8)-alkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, (C_3-C_8)-cycloalkyl, ((C_1-C_8)-alkyl)_{1-3}-(C_3-C_{8})-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, and may be linked via a (C_3-C_5)-alkylene bridge,

R^7 denotes H, (C_1-C_8)-alkyl; (C_1-C_8)-alkyloxy, (C_2-C_8)-alkoxyalkyl.

Preferably, ketene acetals of formula (II) are used in which R^7 is H. On reaction with compounds of formula (I) they lead to α-unsubstituted β-aminocarboxylic acid derivatives. However, if an α-substituted β-aminocarboxylic acid is to be generated the respective radical R^7 may adopt above mentioned structures.

It is further preferred to use compounds of formula (II) wherein R^5 and R^6 are (C_1-C_8)-alkyl, more preferably methyl, ethyl, n-propyl or n-butyl and most preferably n-propyl or n-butyl.

Ketene acetals are commercially available reagents or can be obtained by methods known in the art. Normally, ketene acetals are produced from equivalent orthoesters or α-halogenated acetals via simple elimination or by O-
alkylation of enolations of esters (Beyer-Walter, Lehrbuch
Verlag, s. 261; Organikum, 16. Auflage, 1986, S. 236).

The process of the invention is conducted in the presence
of a base. The base can be any organic or inorganic base
known to the artisan suitable for this reaction. Preferred
are common bases derived from amines or carbonates.
Advantageously, the base is chosen from the group
consisting of triethyl amine, DBU, Hünig-base, dicyclohexyl
amine, alkaline and earth alkaline carbonates and hydrogen
carbonates.

The solvent used for the reaction according to the
invention can be chosen by the man skilled in the art.
Circumstances having an impact on the choice of the solvent
may be the optimum performance of the reaction in question
in view of impurity-generation, space-time-yield and
practicability. Preferably, the reaction is performed in an
aprotic polar organic solvent. The solvent may more
preferably be chosen from the group consisting of toluene,
methylene dichloride, chloroform, acetonitrile.

The temperature applied during the reaction should be high
enough to allow complete reaction within a minimum time,
but should be low enough to keep the impurity profile
acceptable. The skilled worker can arrange for an optimal
temperature to perform the reaction in question. Preferably,
the reaction is performed at a temperature range from -20°C
- 110°C, more preferably from -10°C - 90°C and most
preferably from 0°C - 50°C.

As stated earlier the β-aminocarboxylic acid derivatives
can further be transformed to the free form of β-
aminocarboxylic acids via routes known to the skilled
worker.

In a very preferred mode this deprotection is performed via
an enantioselective method, e.g. in the presence of special
enzymes. Deacylation can be conducted in the presence of a hydrolase (WO03/080854). More preferred is a process wherein the enantioselective deprotection of the ester moiety is performed in the presence of a lipase (EP1361279; EP1367129).

In a further preferred embodiment the reaction between compounds of formula (I) and (II) is performed in the presence of a Lewis-acid catalyst. It has been observed that the reaction rates are enhanced by adding such a catalytic system. Preferred catalysts are typical Lewis-acids used for such purposes like Ti, B, Cu(I), Al, Si-based Lewis-acids. Most advantageously the present reaction is conducted in the presence of an optically active Lewis-acid known in the art (Catalytic Asymmetric Synthesis, Ed.: I. Ojima, Wiley-VCH, 1993, p. 413 et seq.), e.g. like complexes of CuOTf with bisoxazoline derivatives. It is thus possible to generate enantiomerically enriched products.

The production of compounds of general formula (I) is up to the skilled man’s knowledge. Combining an aldehyde, the acyl amide and sodium phenylsulfinate furnishes (I) in excellent yield (Sisko et al. Org. Synth. 2000, 77, 198-205).

In a general procedure compounds of formula (I) are combined with those of formula (II) in an appropriate solvent in the presence of a base. The sequence of adding the respective reagents may be chosen by the skilled worker to optimise the results of instant transformation.

An example of how to proceed may be depicted from following scheme.

![Chemical diagram]

1. Base
2. Reagent
Table 1: Results of present transformation

<table>
<thead>
<tr>
<th>R</th>
<th>Base</th>
<th>Yield [%]</th>
<th>Condition</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-</td>
<td>Et₃N</td>
<td>80</td>
<td>a</td>
<td>6a</td>
</tr>
<tr>
<td>Ph-</td>
<td>DBU</td>
<td>48</td>
<td>b</td>
<td>6b</td>
</tr>
<tr>
<td>Ph-</td>
<td>Cs₂CO₃</td>
<td>90</td>
<td>a</td>
<td>6c</td>
</tr>
<tr>
<td>4-NO₂-Ph-</td>
<td>Et₃N</td>
<td>77</td>
<td>a</td>
<td>6d</td>
</tr>
<tr>
<td>4-MeO-Ph</td>
<td>Et₃N</td>
<td>67</td>
<td>a</td>
<td>6e</td>
</tr>
<tr>
<td>4-OH-Ph</td>
<td>Et₃N</td>
<td>62</td>
<td>a</td>
<td>6f</td>
</tr>
<tr>
<td>2-Thiophene</td>
<td>Cs₂CO₃</td>
<td>55</td>
<td>a</td>
<td>6g</td>
</tr>
<tr>
<td>tert.-butyl</td>
<td>Et₃N</td>
<td>35%</td>
<td>a</td>
<td>9</td>
</tr>
</tbody>
</table>

a: 6 equiv. of base, 24 h, reflux, CH₂Cl₂
b: 2 equiv. of base, 24 h, RT, CH₂Cl₂

Derivatives of β-aminocarboxylic acids according to the invention mean, in particular, esters or respective compounds bearing an N-protecting group.

Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl or octyl, together with all their bond isomers, can be considered as (C₁-C₈)-alkyl radicals.

The (C₁-C₈)-alkoxy radical corresponds to the (C₁-C₈)-alkyl radical, with the proviso that this is bonded to the molecule via an oxygen atom. As (C₂-C₈)-alkoxyalkyl, radicals in which the alkyl chain is interrupted by at least one oxygen function are meant, wherein two oxygen atoms cannot be joined to one another. The number of carbon atoms gives the total number of carbon atoms contained in the radical. A (C₃-C₈)-alkylene bridge is a carbon chain with three to
five C atoms, this chain being bonded to the molecule in question via two different C atoms.
The radicals just described can be mono- or polysubstituted with NH₂, NO₂, OH, SH-groups or halogens and/or radicals containing N, O, P, S or Si atoms. These are particularly alkyl radicals of the type mentioned above having one or more of these heteroatoms in their chain or being bonded to the molecule via one of these heteroatoms.

(C₃-C₈)-Cycloalkyl means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals etc. These can be substituted with one or more halogens and/or radicals containing N, O, P, S or Si atoms and/or can have N, O, P or S atoms in the ring, such as e.g. 1-, 2-, 3-, 4-piperidyl, 1-, 2-, 3-pyrrolidinyl, 2-, 3-tetrahydrofuryl, 2-, 3-, 4-morpholiny.

A (C₃-C₈)-cycloalkyl-(C₁-C₈)-alkyl radical refers to a cycloalkyl radical as set out above, which is bonded to the molecule via an alkyl radical as stated above.

(C₁-C₈)-Acyloxy within the framework of the invention means an alkyl radical as defined above with a maximum of 8 C atoms, which is bonded to the molecule via a COO- function.

(C₁-C₈)-Acyl within the framework of the invention means an alkyl radical as defined above with a maximum of 8 C atoms, which is bonded to the molecule via a CO- function.

A (C₆-C₁₈)-aryl radical is understood to mean an aromatic radical with 6 to 18 C atoms. These include in particular compounds such as phenyl, naphthyl, anthryl, phenanthryl or biphenyl radicals, or systems of the type described above annelated to the molecule in question, such as e.g. indenyl systems, which can optionally be substituted with Hal, (C₁-C₈)-alkyl, (C₁-C₈)-alkoxy, OH, NO₂, NR¹R², (C₁-C₈)-acyl or (C₁-C₈)-acyloxy, (C₁-C₈)-haloalkyl.
A (C_7-C_{19})-aralkyl radical is a (C_6-C_{18})-aryl radical bonded to the molecule via a (C_1-C_8)-alkyl radical.

A (C_3-C_{18})-heteroaryl radical within the framework of the invention refers to a five-, six- or seven-membered aromatic ring system of 3 to 18 C atoms, which contains heteroatoms such as e.g. nitrogen, oxygen or sulfur in the ring. In particular, radicals such as 1-, 2-, 3-furyl, such as 1-, 2-, 3-pyrrolyl, 1-, 2-, 3-thienyl, 2-, 3-, 4-pyridyl, 2-, 3-, 4-, 5-, 6-, 7-indolyl, 3-, 4-, 5-pyrazolyl, 2-, 4-, 5-imidazolyl, acridinyl, quinoliny1, phenanthridinyl and 2-, 4-, 5-, 6-pyrimidinyl are considered as such heteroaromatics.

A (C_4-C_{19})-heteroaralkyl means a heteroaromatic system corresponding to the (C_7-C_{19})-aralkyl radical.

Fluorine, chlorine, bromine and iodine are suitable as halogens (Hal). Preferred are chlorine and bromine.

The term enantiomerically enriched within the framework of the invention means the proportion of an enantiomer in a mixture with its optical antipode in a range of >50 % and <100 %. The ee value is calculated as follows:

$$\frac{([\text{Enantiomer}1]-[\text{Enantiomer}2])}{([\text{Enantiomer}1]+[\text{Enantiomer}2])} = \text{ee value}$$

N-Protecting groups can be (C_1-C_8)-acyl or (C_1-C_8)-acyloxy or (C_7-C_{19})-aralkyloxy carbonyl groups that are conventionally used in amino acid chemistry for the protection of nitrogen atoms. The following can be particularly mentioned in this capacity: formyl, acetyl, Moc, Boc, Boc, Alloc, Z, Fmoc, Triflat.

The literature references cited in this document are deemed to be contained in the disclosure.

The chemical structures shown relate to all possible stereoisomers which may be obtained by modifying the configuration of the individual chiral centres, axes or
planes, i.e. any possible diastereomers, as well as any optical isomers (enantiomers) included therein.
EXPERIMENTAL:

3-Phenyl-1-piperidin-1-yl-propenone 3:

Benzaldehyde (0.0047mol, 0.48ml) and piperidine (0.0047mol, 0.47ml) were dissolved in dichloromethane (10ml). Diethyl ketene acetal (0.0094 mol, 1.24ml) was added in one portion and the resulting solution was refluxed for 18 hours. After the evaporation of volatile compounds under vacuum, the resulting residue was purified by column chromatography (hexane : AcOEt 1:1) to afford 3 (0.17g, 17%) as slightly yellow solid.

General procedure for the synthesis of 6a-g:

To a solution of 4 (0.0150mol) in dichloromethane (70ml) was added triethylamine (0.0900mol, 12.5ml) followed by diethyl ketene acetal (0.0300mol, 3.9ml). The resulting suspension was refluxed for 24 hours. After cooling to room temperature the solution was extracted with water (2-times 20ml). The organic layer was dried over MgSO₄, concentrated under vacuum and the residue was purified by SiO₂ column chromatography (hexane:AcOEt 1:1) to afford 6.

3-Formylamino-3-phenyl-propionic acid ethyl ester 6a:

According to general procedure, yellowish oil, 80%.

6b - 6g were prepared accordingly (see table 1).

3-Amino-4,4-dimethyl-pentanoic acid 9:

4 (0.0150mol) was added to dichloromethane (70ml). Triethylamine (0.0900mol, 12.5ml) followed by diethyl ketene acetal (0.0300mol, 3.9ml) was added and resulting suspension was refluxed for 24 hours. After cooling to room temperature the solution was extracted with water (2-times 20ml). The organic layer was dried over MgSO₄ and
concentrated under vacuum. To the residue was added concentrated HCl (10ml) and the resulting emulsion was stirred 5 hours at 50°C. After cooling to room temperature the suspension was extracted with AcOEt (3-times 20ml) and the aqueous phase was applied to a strongly acidic ion exchange resin to afford crude 9 (0.76g, 35%) as an off-white solid.

Procedure for NOVOZYM 525 L-catalysed enzymatic resolution of 6a:

6a (0.0136mol, 3g) was added to a phosphate buffer (100ml, pH=7.00 at 20°C) and NOVOZYM 525 L was added (3.0g). The pH of the vigorously stirred emulsion (at about 27°C) was maintained at 7.0 using an autotiter (718 STAT Titrino). After 56 hours, the next portion (0.5g) of NOVOZYM 525 L was added. After 78 hours the pH was adjusted to 8.5 and the reaction mixture was extracted with tert-butyl methyl ether (3-times 70ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuum to afford unreacted 6a (conversion 55%, 1.12g, 83%, 95%ee) as a yellowish oil. The pH of the aqueous phase was adjusted to 2.0 and the mixture was carefully extracted with methyl ethyl keton (5-times 50ml). The combined organic layers were dried over MgSO₄ and concentrated under vacuum. To the residue were added 12 ml of 36% HCl and the resulting solution was stirred for 2.5 hours at 75°C. After cooling to room temperature the solution was extracted with dichloromethane (3-times 10ml). The aqueous phase was concentrated to dryness to afford 16 (0.37g, 30%, 80%ee) as an off-white solid.
Claims:

1. Process for the preparation of β-aminocarboxylic acid derivatives by reacting a compound of general formula (I)

\[
\text{HN}^{-} \quad \text{SO}_{2} \quad \text{R}^{2}
\]

wherein
- \(R^{1}\) denotes a N-protecting group,
- \(R^{3}\) is \((C_{1}-C_{8})\)-alkyl, wherein the linking C-atom is a tertiary one, \((C_{6}-C_{18})\)-aryl, \((C_{7}-C_{19})\)-aralkyl, wherein the linking C-atom is a tertiary one, \((C_{3}-C_{18})\)-heteroaryl, \((C_{4}-C_{19})\)-heteroaralkyl, wherein the linking C-atom is a tertiary one, \((C_{1}-C_{8})\)-alkyl\(_{1-3}\)-(C_{6}-C_{18})-aryl, \((C_{1}-C_{8})\)-alkyl\(_{1-3}\)-(C_{3}-C_{18})-heteroaryl, \((C_{3}-C_{8})\)-cycloalkyl, wherein the linking C-atom is a tertiary one, \((C_{1}-C_{8})\)-alkyl\(_{1-3}\)-(C_{3}-C_{8})-cycloalkyl, wherein the linking C-atom is a tertiary one, \((C_{3}-C_{8})\)-cycloalkyl\(_{1-3}\)-(C_{1}-C_{8})-alkyl, wherein the linking C-atom is a tertiary one, adamantyl,

- \(R^{2}\) is \((C_{1}-C_{8})\)-alkyl, \((C_{6}-C_{18})\)-aryl, \((C_{7}-C_{19})\)-aralkyl, \((C_{1}-C_{8})\)-alkyl\(_{1-3}\)-(C_{6}-C_{18})-aryl, \((C_{3}-C_{8})\)-cycloalkyl, \((C_{1}-C_{8})\)-alkyl\(_{1-3}\)-(C_{3}-C_{8})-cycloalkyl, \((C_{3}-C_{8})\)-cycloalkyl\(_{1-3}\)-(C_{1}-C_{8})-alkyl,

with a ketene acetal in the presence of a base.

2. Process for the preparation of β-aminocarboxylic acids by reacting a compound of general formula (I)
wherein

\[ R^4 \text{ denotes a } N\text{-protecting group,} \]

\[ R^3 \text{ is } (C_1-C_8)-\text{alkyl, } (C_2-C_9)-\text{alkoxyalkyl, } (C_6-C_{18})-\text{aryl,} \]
\[ (C_7-C_{19})-\text{aralkyl, } (C_3-C_{18})-\text{heteroaryl, } (C_4-C_{19})-\text{heteroaralkyl, } ((C_1-C_9)-\text{alkyl})_{1-3}-(C_6-C_{18})-\text{aryl,} \]
\[ ((C_1-C_9)-\text{alkyl})_{1-3}-(C_3-C_{18})-\text{heteroaryl, } (C_2-C_8)-\text{cycloalkyl, } ((C_1-C_9)-\text{alkyl})_{1-3}-(C_3-C_{18})-\text{cycloalkyl,} \]
\[ (C_3-C_8)-\text{cycloalkyl}-((C_1-C_8)-\text{alkyl,} \]
\[ R^3 \text{ is } (C_1-C_8)-\text{alkyl, } (C_6-C_{18})-\text{aryl, } (C_7-C_{19})-\text{aralkyl,} \]
\[ ((C_1-C_9)-\text{alkyl})_{1-3}-(C_6-C_{18})-\text{aryl, } (C_3-C_8)-\text{cycloalkyl,} \]
\[ ((C_1-C_9)-\text{alkyl})_{1-3}-(C_3-C_8)-\text{cycloalkyl, } (C_3-C_8)-\text{cycloalkyl}-(C_1-C_8)-\text{alkyl, adamantyl} \]

with a ketene acetal in the presence of a base and subsequently deprotecting the product thus obtained at the N- and/or C-terminal end, optionally in an enantioselective manner.

3. Process according to claim 1 or 2, wherein the ketene acetal is a compound of the general formula (II)

\[
\begin{align*}
R^7 & \quad H \\
R^8O & \quad OR^5
\end{align*}
\]

wherein

\[ R^8 \text{ and } R^5 \text{ are independently of each other } (C_1-C_9)-\text{alkyl, } (C_6-C_{18})-\text{aryl, } (C_7-C_{19})-\text{aralkyl, } (C_3-C_8)-\text{cycloalkyl, } ((C_1-C_9)-\text{alkyl})_{1-3}-(C_3-C_8)-\text{cycloalkyl,} \]
\[ (C_3-C_8)-\text{cycloalkyl}-(C_1-C_8)-\text{alkyl, and may be linked via a } (C_3-C_8)-\text{alkylene bridge,} \]
\[ R^7 \text{ denotes } H, (C_1-C_9)-\text{alkyl, } (C_1-C_9)-\text{alkyloxy, } (C_2-C_8)-\text{alkoxyalkyl.} \]

4. Process according to claim 1 or 2, wherein the base is chosen from the group consisting of triethyl amine, DBU, Hüning-base, dicyclohexyl amine, alkaline and earth alkaline carbonates and hydrogen carbonates.
5. Process according to one or more of the preceding claims, wherein the reaction is performed in an aprotic polar organic solvent.

6. Process according to one or more of the preceding claims, wherein the reaction is performed at a temperature range from 0°C-50°C.

7. Process according to one or more of claims 2 to 6, wherein the enantioselective deprotection is performed in the presence of a lipase.

8. Process according to one or more of the preceding claims, wherein the reaction between (I) and (II) is performed in the presence of a Lewis-acid catalyst, optionally an optically active Lewis-acid catalyst.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No.**

**PCT/EP2005/001140**

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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C07C231/12 C07C233/47 C07C229/08 C07C227/20 C07D333/24

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentary searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevance to claim No.</th>
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<tr>
<td>A</td>
<td>MECOZZI, TIZIANA ET AL: &quot;Reaction of .alpha.-amidoalkyl phenyl sulfoxides with Reformatskii reagents. A new entry to .beta.-amino esters.&quot; TETRAHEDRON LETTERS, 41(15), 2709-2712 CODEN: TELEAY; ISSN: 0040-4039, 2000, XP002326118 page 2710; table 1</td>
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<td>A</td>
<td>SCHUNK, STEFAN ET AL: &quot;Solid-phase synthesis of .beta.-amino ketones and six-ring carbamates via immobilized .alpha.-alkoxycarbonylamino sulfoxides&quot; ORGANIC LETTERS, 3(20), 3177-3180 CODEN: ORLEF7; ISSN: 1523-7060, 2001, XP002326119 page 3178, scheme 3 (c)</td>
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**X** Patent documents are listed in continuation of box C.

**X** Patient family members are listed in annex.

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**Date of the actual completion of the international search**

28 April 2005

**Date of resiling of the international search report**

10/05/2005

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**Name and mailing address of the ISA**

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**Authorized officer**

Fitz, W
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