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PROCESS FOR REDUCTION OF CARBONYL COMPOUNDS

TECHNICAL FIELD

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The present invention relates to a process for reducing carbonyl compounds.

BACKGROUND ART

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Reduction of carbonyl compounds constitutes a very important technology in various fields, for example in the production of drug intermediates. As the so far known practical methods of reducing carbonyl compounds, there may be mentioned the Meerwein-Ponndorf-Varley reduction (MPV reduction) and the reduction using diisobutylaluminum hydride (DIBAH).

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The MPV reduction is a method of reducing carbonyl compounds using an aluminum trialkoxide, such as $\text{Al}(\text{O}-i\text{Pr})_3$, as a reducing agent or reduction catalyst. This method is in frequent use as an economical method of reducing various ketones and aldehydes, since the aluminum trialkoxide used there and the alcohol such as isopropyl alcohol are inexpensive [Organic Reactions, volume 2, page 178 (1944)].

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However, the MPV reduction, which uses an aluminum trialkoxide, has problems. The progress of the reaction tends to be very slow at low reaction temperatures mainly because of the low reactivity of said reagent. For increasing the reaction rate and the yield, a high reaction temperature not lower than 50°C , for example, is required. Said reduction is thus unsuited for the reduction of unstable carbonyl compounds or, in the case of carbonyl compounds showing low reactivity, the reduction reaction can hardly proceed even when the reaction temperature is raised.

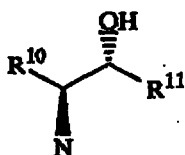
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The reduction of carbonyl compounds using DIBAH is a very useful method from the industrial viewpoint because of excellent reactivity and economics, among others. This method is in use, for example, for the reduction of

1 α -aminochloroketone derivatives derived from leucine. When
said α -aminochloroketone derivatives are reduced at -78°C
using DIBAH, the erythro form can be obtained preferentially
with an about 75% diastereomer excess [Tetrahedron Letters,
5 36, 5453 (1995)].

The term "erythro form" as used herein means an isomer in
which the neighboring amino and hydroxyl groups show the
following relative configuration:



However, this reduction method requires a very low
15 temperature in order that the reactivity may be controlled.
Furthermore, when the method is applied to the reduction of
said α -aminochloroketone derivatives, it is impossible to
attain such a high stereoselectivity as 90% or more as
expressed in terms of diastereomer excess.

20 Referring to the reduction reaction of carbonyl compounds
with diisobutylaluminum hydride, the literature suggests the
possibility that the diisobutylaluminum alkoxides formed as
reaction intermediates be partly involved in the reduction
reaction [Journal of Organic Chemistry, 38, 4232 (1973)].

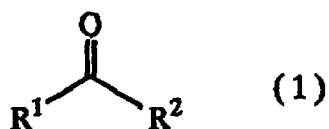
25 However, no reports have ever suggested that dialkylaluminum
monoalkoxides such as diisobutylaluminum isopropoxide might
be effective in the reduction or stereoselective reduction of
carbonyl compounds. Likewise, no reports have ever suggested
that reducing agents prepared from a dialkylaluminum hydride,
30 such as diisobutylaluminum hydride, and an alcohol, such as
isopropyl alcohol, might be effective in the reduction or
stereoselective reduction of carbonyl compounds.

In view of the foregoing, it is an object of the present
invention to provide a method of reducing carbonyl compounds
35 to the corresponding hydroxyl compounds in an easy and simple

1 manner and under milder conditions. Another object is to
provide a method of reducing certain carbonyl compounds that
can hardly be reduced with ordinary aluminum trialkoxides and,
in particular, a method for stereoselectively reducing
5 α -aminoketone derivatives.

SUMMARY OF THE INVENTION

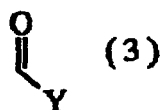
The gist of the present invention, which is directed to
the reduction of carbonyl compounds, consists in that a
10 carbonyl compound of the general formula (1)



15 (wherein R^1 and R^2 each independently represents a substituted
or unsubstituted alkyl group containing 1 to 30 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
30 carbon atoms, a substituted or unsubstituted aryl group
20 containing 6 to 30 carbon atoms, a cyano group, a hydrogen
atom, a group of the general formula (2)

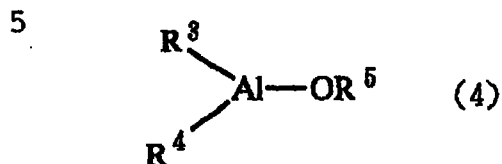


25 (in which X represents a halogen atom and n represents an
integer of 0 to 2), or a group of the general formula (3)

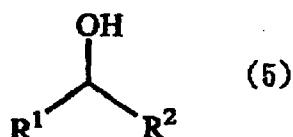


30 (in which Y represents an alkoxy group, an aralkyloxy group,
a substituted or unsubstituted amino group or an alkylthio
group), provided that one of R^1 and R^2 is a substituted or
unsubstituted alkyl group containing 1 to 30 carbon atoms, a
35 substituted or unsubstituted aralkyl group containing 7 to 30

1 carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 30 carbon atoms) is reacted with an
organoaluminum compound of the general formula (4)



(wherein R³ and R⁴ each independently represents a substituted
10 or unsubstituted alkyl group containing 1 to 10 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
20 carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 20 carbon atoms and R⁵ represents a
substituted or unsubstituted primary alkyl group containing 1
15 to 20 carbon atoms, a substituted or unsubstituted secondary
alkyl group containing 1 to 20 carbon atoms, a substituted or
unsubstituted primary aralkyl group containing 7 to 30 carbon
atoms or a substituted or unsubstituted secondary aralkyl
group containing 7 to 30 carbon atoms) to provide the
20 corresponding alcohol compound of the general formula (5)



(wherein R¹ and R² are as defined above).

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows an NMR spectrum of the product obtained in
30 Example 5, namely t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
chloropropyl]carbamate.

Fig. 2 shows an IR spectrum of the product obtained in
Example 5, namely t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
chloropropyl]carbamate.

35 Fig. 3 shows an NMR spectrum of the product obtained in

1 Example 8, namely methyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate.

Fig. 4 shows an IR spectrum of the product obtained in Example 8, namely methyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate.

Fig. 5 shows an NMR sepctrum of the product obtained in Example 9, namely benzyl [1(R)-phenylthiomethyl-2(S)-hydroxy-3-chloropropyl]carbamate.

Fig. 6 shows an IR spectrum of the product obtained in Example 9, namely benzyl [1(R)-phenylthiomethyl-2(S)-hydroxy-3-chloropropyl]carbamate.

Fig. 7 shows an NMR sepctrum of the product obtained in Example 14, namely methyl 2(R,S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-phenylbutyrate.

Fig. 8 shows an IR spectrum of the product obtained in Example 14, namely methyl 2(R,S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-phenylbutyrate.

Fig. 9 shows an NMR sepctrum of the product obtained in Example 15, namely ethyl [1(S)-benzyl-2(R,S)-hydroxy-3,3-dichloropropyl]carbamate.

Fig. 10 shows an IR spectrum of the product obtained in Example 15, namely ethyl [1(S)-benzyl-2(R,S)-hydroxy-3,3-dichloropropyl]carbamate.

DETAILED DESCRIPTION OF THE INVENTION

Referring to the carbonyl compounds of the above general formula (1), R^1 and R^2 each independently represents a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 30 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 30 carbon atoms, a cyano group, a hydrogen atom, a group of the above general formula (2) or a group of the above general formula (3), provided that one of R^1 and R^2 is a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a

1 substituted or unsubstituted aralkyl group containing 7 to 30
carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 30 carbon atoms.

5 As the substituent, there may be mentioned a halogen
atom, an alkoxy carbonyl group, an alkoxy group, a protected
amino group, a cyano group, a nitro group, a sulfinyl group,
a sulfonyl group, an alkylthio group and the like. Each group
represented by R^1 or R^2 may have two or more such
substituents.

10 The above-mentioned substituted or unsubstituted alkyl
group containing 1 to 30 carbon atoms is not limited to any
particular species but includes, for example, methyl, ethyl,
butyl, isopropyl, cyclohexyl and the like. Preferred are
those groups which contain 1 to 20 carbon atoms.

15 The above-mentioned substituted or unsubstituted aralkyl
group containing 7 to 30 carbon atoms is not limited to any
particular species but includes, for example, benzyl,
phenylpropyl, phenylethyl, p-methoxybenzyl,
1-(N-t-butoxycarbonylamino)-2-phenylethyl,
20 1-(N-benzyloxycarbonylamino)-2-phenylethyl and the like.
Preferred are those groups which contain 7 to 20 carbon atoms.

The above-mentioned substituted or unsubstituted aryl
group containing 6 to 30 carbon atoms is not limited to any
particular species but includes, for example, phenyl,
25 p-chlorophenyl, p-nitrophenyl, naphthyl and the like.
Preferred are those groups which contain 6 to 20 carbon atoms.

Referring to the group represented by the above general
formula (2), X represents a halogen atom and n represents an
integer of 0 to 2.

30 Said halogen atom is not limited to any particular
species but includes a chlorine atom, a bromine atom, an
iodine atom or a fluorine atom and preferably is a chlorine
atom.

The above-mentioned group of general formula (2) is not
35 limited to any particular species but includes, among others,

1 chloromethyl, dichloromethyl, trichloromethyl, bromomethyl,
dibromomethyl, tribromomethyl, fluoromethyl, difluoromethyl,
trifluoromethyl, iodomethyl, diiodomethyl, triiodomethyl and
the like. Preferred among them are chloromethyl,
5 dichloromethyl and trichloromethyl.

Referring to the above-mentioned group of general formula
(3), Y represents an alkoxy group, an aralkyloxy group, a
substituted or unsubstituted amino group or an alkylthio
group.

10 Said alkoxy group is not limited to any particular
species but includes, for example, methoxy, ethoxy, t-butoxy
and the like. Preferred are those containing 1 to 10 carbon
atoms.

The above-mentioned aralkyloxy group is not limited to
15 any particular species but includes benzyloxy and the like,
among others. Preferred are those groups which contain 6 to
20 carbon atoms.

The above-mentioned substituted or unsubstituted amino
group is not limited to any particular species but includes,
20 for example, amino, dimethylamino and the like.

The above-mentioned alkylthio group is not limited to any
particular species but includes methylthio, phenylthio and
the like, among others.

The above-mentioned group of general formula (3) is not
25 limited to any particular species but includes, among others,
methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl,
t-butoxycarbonyl and the like. Preferred are methoxycarbonyl
and ethoxycarbonyl, however.

As the above-mentioned carbonyl compound of general
30 formula (1), there may be mentioned, for example, aldehydes
such as benzaldehyde, isobutyraldehyde, etc.; and ketones
such as acetophenone, propiophenone, cyclohexanone, ethyl
acetoacetate, methyl benzoylformate, phenacyl chloride,
 α -dichloroacetophenone, α -trichloroacetophenone, ethyl
35 4-chloroacetoacetate, benzoyl cyanide, t-butyl 1(S)-benzyl-2-

1 oxo-3,3-dichloropropylcarbamate, t-butyl 1(S)-benzyl-2-oxo-
3,3,3-trichloropropylcarbamate, methyl 3(S)-(N-benzyloxy-
carbonylamino)-2-oxo-4-phenylacetate, etc.

5 Referring to the above-defined symbols R^3 and R^4 , the
substituted or unsubstituted alkyl group containing 1 to 10
carbon atoms is not limited to any particular species but
includes, for example, methyl, ethyl, n-butyl, isobutyl,
isopropyl, cyclohexyl, methoxymethyl and the like. Said group
preferably contains 1 to 6 carbon atoms and is more
10 preferably isobutyl.

Further referring to the symbols R^3 and R^4 , the aralkyl
group containing 7 to 20 carbon atoms is not limited to any
particular species but includes, for example, benzyl,
3-phenyl-1-propyl, α -phenylethyl, p-methoxybenzyl and the
15 like. Those containing 7 to 15 carbon atoms are preferred.

Again referring to the symbols R^3 and R^4 , the aryl group
containing 6 to 20 carbon atoms is not limited to any
particular species but includes, for example, phenyl,
p-hydroxyphenyl, p-chlorophenyl, p-nitrophenyl, naphthyl and
20 the like. Those containing 6 to 15 carbon atoms are
preferred.

Referring to the symbol R^5 defined above, the substituted
or unsubstituted primary alkyl group containing 1 to 20
carbon atoms or the substituted or unsubstituted secondary
25 alkyl group containing 1 to 20 carbon atoms is, for example,
methyl, ethyl, isopropyl, cyclohexyl, 2,4-dimethyl-3-pentyl
or the like. Preferred are those containing 1 to 10 carbon
atoms. More preferred are isopropyl, cyclohexyl and
2,4-dimethyl-3-pentyl.

30 Referring to the symbol R^5 , the substituted or
unsubstituted primary aralkyl group containing 7 to 30 carbon
atoms or the substituted or unsubstituted secondary aralkyl
group containing 7 to 30 carbon atoms is, for example,
benzhydryl, benzyl, phenylpropyl, α -phenylethyl,
35 p-methoxybenzyl and the like. Those containing 7 to 15 carbon



1 atoms are preferred and benzhydryl is more preferred.

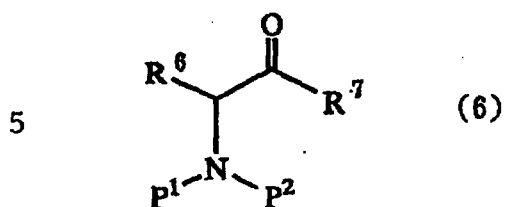
As the organoaluminum compound represented by the above general formula (4), there may be mentioned, among others, diisobutylaluminum isopropoxide, diisobutylaluminum
5 diphenylmethoxide, diisobutylaluminum ethoxide, diisobutylaluminum cyclohexyloxide, diisobutylaluminum 2,4-dimethyl-3-pentyloxide, diethylaluminum ethoxide and the like. Among them, diisobutylaluminum isopropoxide and diisobutylaluminum diphenylmethoxide are preferred.

10 The organoaluminum compound of the above general formula (4) can be prepared, for example, by (1) the reaction of a dialkylaluminum hydride with an alcohol, (2) the reaction of a trialkylaluminum with an alcohol (German Patent Specification No. 2507532), (3) the use, as such, of the
15 reaction mixture obtained upon reduction of a carbonyl compound, such as acetone, with DIBAH, (4) the reaction of a trialkylaluminum with a trialkoxyaluminum (German Patent Specification No. 2304617), or (5) the reaction of a trialkylaluminum with a trialkyl borate (German Patent
20 Specification No. 2151176).

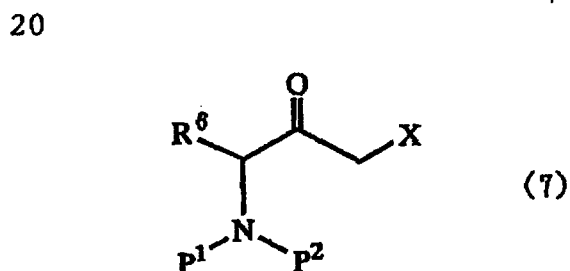
The process for reducing carbonyl compounds according to the present invention can be applied to the reduction of α -aminoketone derivatives of the general formula (6) shown below and the reduction of α -aminohaloketone derivatives of
25 the general formula (7) shown below. The process for reducing carbonyl compounds according to the present invention makes it possible to produce α -aminoalcohol derivatives of the general formula (8) shown below from the α -aminoketone derivatives of general formula (6) or produce α -aminohalohydrin
30 derivatives of the general formula (9) shown below from the α -aminohaloketone derivatives of general formula (7). These α -aminoalcohol derivatives and α -aminohalohydrin derivatives are compounds useful as intermediates for medicinal compounds.

The process for producing the α -aminoalcohol
35 derivatives mentioned above comprises reacting an

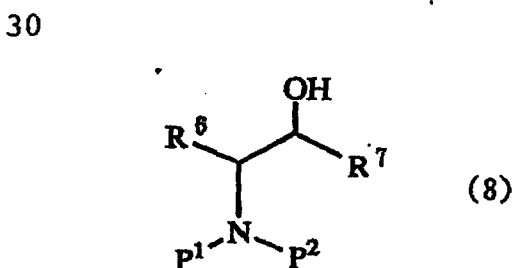
1 α -aminoketone derivative of the general formula (6)



(wherein R^6 represents a substituted or unsubstituted alkyl group containing 1 to 20 carbon atoms, a substituted or
10 unsubstituted aralkyl group containing 7 to 20 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or a hydrogen atom, R^7 represents a group of the above general formula (2) or a group of the above general formula (3) and P^1 and P^2 each independently represents a
15 hydrogen atom or an amino-protecting group or P^1 in combination with P^2 represent a phthaloyl group, with the exception of the case in which P^1 and P^2 are the same and each is a hydrogen atom), in particular an α -aminohaloketone derivative of the general formula (7)

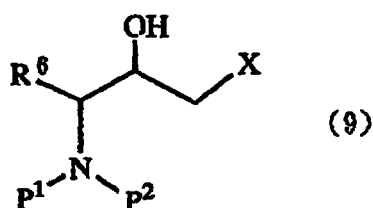


25 (wherein X represents a halogen atom and R^6 is as defined above) with an organoaluminum compound of the above general formula (4) to provide the corresponding α -aminoalcohol derivative of the general formula (8)



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1 (wherein R^6 , R^7 , P^1 and P^2 are as defined above), in particular the corresponding α -aminohalohydrin derivative of the general formula (9)



10 (wherein X , R^6 , P^1 and P^2 are as defined above).

Referring to the above-mentioned α -aminoketone derivative of general formula (6) and α -aminohaloketone derivative of general formula (7), R^6 is the side chain of a familiar α -amino acid or the side chain of an α -amino acid derivative obtained by processing such a familiar α -amino acid and represents a substituted or unsubstituted alkyl group containing 1 to 20 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or a hydrogen atom.

Said substituted or unsubstituted alkyl group containing 1 to 20 carbon atoms is not limited to any particular species but includes, for example, methyl, ethyl, isopropyl, isobutyl, t-butyl, hydroxymethyl, 1-hydroxyethyl, mercaptomethyl, methylthiomethyl, etc. Preferred are those containing 1 to 10 carbon atoms.

Said substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms is not limited to any particular species but includes, for example, benzyl, p-hydroxybenzyl, p-methoxybenzyl, phenylthiomethyl, α -phenethyl, etc. Preferred are those containing 7 to 15 carbon atoms.

Said substituted or unsubstituted aryl group containing 6 to 20 carbon atoms is not limited to any particular species but includes, for example, phenyl, p-hydroxyphenyl,

1 p-methoxyphenyl, etc. Preferred are those containing 6 to 15
carbon atoms.

Referring to the above-mentioned α -aminoketone
derivatives of general formula (6) and to the above-mentioned
5 α -aminohaloketone derivatives of general formula (7), P^1 and
 P^2 each independently represents a hydrogen atom or an amino-
protecting group or P^1 in combination with P^2 represent a
phthaloyl group, with the exception of the case in which P^1
and P^2 are the same and each is a hydrogen atom.

10 Said amino-protecting group is not limited to any
particular species provided that it is effective in
protecting the amino group from the reduction reaction in
question. It thus includes such protective groups as those
described in Theodora W. Green: Protective Groups in Organic
15 Synthesis, 2nd edition, John Wiley & Sons, 1990, pp. 309 to
384, for example, ethoxycarbonyl, methoxycarbonyl,
t-butoxycarbonyl, benzyloxycarbonyl, acetyl, trifluoroacetyl,
benzyl, dibenzyl, tosyl, benzoyl, phthaloyl, etc. The amino-
protecting group should preferably be selected taking the
20 stereoselectivity of the reduction reaction into
consideration. The reduction reaction can be caused to
proceed with high erythroselectivity by employing, for
example, such an alkoxycarbonyl group as methoxycarbonyl,
t-butoxycarbonyl or ethoxycarbonyl or such an aralkyloxy
25 carbonyl group as benzyloxycarbonyl.

Referring to the above-mentioned α -aminoketone
derivatives of general formula (6), R' represents a group of
the above general formula (2) or a group of the above general
formula (3).

30 Referring to the above-mentioned α -aminohaloketone
derivatives of general formula (7), X represents a halogen
atom.

Said halogen atom is not limited to any particular
species but may be a chlorine, bromine, iodine or fluorine
35 atom. It is preferably a chlorine atom, however.

1 The above-mentioned α -aminoketone derivatives of
general formula (6) includes, but is not limited to, optically
active t-butyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
5 methyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
ethyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
ethyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
10 benzyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
methyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
15 methyl (S)-(t-butoxycarbonylamino)-2-oxo-4-phenylbutyrate,
methyl (R)-(t-butoxycarbonylamino)-2-oxo-4-phenylbutyrate,
methyl (S)-(methoxycarbonylamino)-2-oxo-4-phenylbutyrate,
methyl (R)-(methoxycarbonylamino)-2-oxo-4-phenylbutyrate,
benzyl [1(S)-benzyl-2-oxo-3,3,3-trichloropropyl]carbamate,
20 benzyl [1(R)-benzyl-2-oxo-3,3,3-trichloropropyl]carbamate,
ethyl [1(S)-benzyl-3,3-dichloro-2-oxopropyl]carbamate,
ethyl [1(R)-benzyl-3,3-dichloro-2-oxopropyl]carbamate, etc.

 The above-mentioned α -aminohaloketone derivatives
includes, but is not limited to, optically active
25 t-butyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
methyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
ethyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
30 ethyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
benzyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
35 t-butyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,

1 t-butyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
methyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
ethyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
5 ethyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
etc. Preferred among these are t-butyl (S)-(1-benzyl-
3-chloro-2-oxopropyl)carbamate and benzyl (S)-(1-
phenylthiomethyl-3-chloro-2-oxopropyl)carbamate.

Referring now to the process for reducing carbonyl
10 compounds according to the present invention, the reduction of
the carbonyl compound of general formula (1) is effected by
adding the carbonyl compound of general formula (1) to the
reaction system or adding the reducing agent to the carbonyl
compound of general formula (1), followed by stirring. The
15 reduction reaction is preferably carried out at a temperature
of -10 to 60°C, more preferably -10 to 30°C.

The organoaluminum compound of general formula (4) is
added preferably in an amount of 1 to 5 molar equivalents,
more preferably 1.5 to 3 molar equivalents, relative to the
20 carbonyl compound of general formula (1).

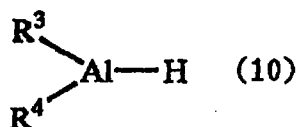
The solvent to be used in the practice of the present
invention is not limited to any particular species but
includes, among others, alcohol compounds of the formula R^5OH
in which R^5 is the same as R^5 in the general formula (4) shown
25 above, as well as toluene, hexane, cyclohexane, heptane,
tetrahydrofuran, t-butyl methyl ether, 1,2-dimethoxyethane,
methylene chloride, N,N-dimethylformamide and the like.
Preferred among the solvents other than the alcohols
mentioned above are toluene, tetrahydrofuran and hexane.

30 Although the procedure for after-treatment is not limited
to any particular one, the product alcohol compound of
general formula (5) can be recovered after completion of the
reaction by an ordinary after-treatment and isolation
procedure, for example, by hydrolyzing the reaction mixture
35 with an aqueous acid solution, extracting the same,

1 concentrating the extract and then subjecting the concentrate
to isolation treatment using a column, crystallization,
distillation and/or the like.

5 The compound of the above-mentioned general formula (4)
can also be prepared by the reaction mentioned below and the
thus-prepared reaction mixture can be used as such for the
reduction of carbonyl compounds of general formula (1), (6)
or (7).

10 Thus, the preparation product obtained by reacting an
organoaluminum compound of the general formula (10)



15 (wherein R³ and R⁴ each independently represents a substituted
or unsubstituted alkyl group containing 1 to 10 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
20 carbon atoms or a substituted or unsubstituted aryl group
20 containing 6 to 20 carbon atoms) with an alcohol compound of
the general formula (11)

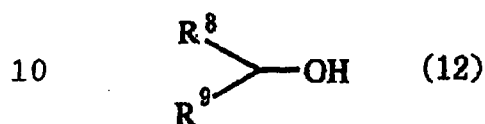


25 (wherein R⁵ is a substituted or unsubstituted primary alkyl
group containing 1 to 20 carbon atoms, a substituted or
unsubstituted secondary alkyl group containing 1 to 20 carbon
atoms, a substituted or unsubstituted primary aralkyl group
containing 7 to 30 carbon atoms or a substituted or
30 unsubstituted secondary aralkyl group containing 7 to 30
carbon atoms) can be used for the reduction of the carbonyl
compounds mentioned above.

The organoaluminum compound of the above general formula
(10) is, for example, diethylaluminum hydride,
35 diisobutylaluminum hydride and the like. Preferred among them

1 is diisobutylaluminum hydride.

The alcohol compound of the above general formula (11) is not limited to any particular species provided that it is high in hydrogen ion-donating ability. As examples, there
5 may be mentioned isopropanol, benzhydrol, 2,4-dimethyl-3-pentanol, cyclohexanol, 2-methoxycyclohexanol and the like. Preferred are alcohol compounds of the general formula (12)



(wherein R⁸ and R⁹ each independently represents a substituted or unsubstituted alkyl group containing 1 to 10 carbon atoms,
15 a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms or a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or R⁸ in combination with R⁹ represent a cycloalkyl group). More preferred are isopropanol and benzhydrol.

20 Said substituted or unsubstituted alkyl group containing 1 to 10 carbon atoms is, for example, methyl, ethyl, isopropyl or the like. Methyl is preferred, however.

Said substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms is, for example, benzyl,
25 phenylpropyl, α -phenylethyl, p-methoxybenzyl or the like.

Said substituted or unsubstituted aryl group containing 6 to 20 carbon atoms is, for example, phenyl, p-hydroxyphenyl, p-chlorophenyl, p-nitrophenyl, naphthyl or the like.

30 Said cycloalkyl group is, for example, cyclohexyl, cyclopentyl or the like.

The process for reducing carbonyl compounds according to the present invention can be carried out, for example, in the following manner.

35 First, the reducing agent is prepared by reacting the organoaluminum compound of general formula (10) with the

1 alcohol compound of general formula (11).

Said organoaluminum compound of general formula (10) is used in an amount below 3 molar equivalents, preferably in an amount of 1 to 5 molar equivalents, more preferably 1.5 to 3
5 molar equivalents, relative to the carbonyl compound of general formula (1).

Said alcohol of general formula (11) is added in an amount below 3 molar equivalents, preferably in an amount of 1 to 2 molar equivalents, relative to the organoaluminum
10 compound of general formula (10).

The preparation of the reducing agent by reacting said organoaluminum compound of general formula (10) with said alcohol compound of general formula (11) can be carried out, for example, by adding the alcohol compound of general
15 formula (11) to a solution of the organoaluminum compound of general formula (10) in toluene, tetrahydrofuran, hexane or the like and then stirring the mixture. The addition conditions are not critical but the addition is preferably carried out at -10 to 60°C, more preferably 0 to 40°C. The
20 stirring conditions are not critical but the stirring is preferably carried out at 0 to 30°C for 1 to 10 hours. It is also possible to add the organoaluminum compound of general formula (10) to the alcohol compound of general formula (11).

Then, the carbonyl compound of general formula (1) is
25 added to the reaction system, or the reducing agent is added to the carbonyl compound of general formula (1), and the mixture is stirred to effect the reduction of the carbonyl compound of general formula (1). The reduction temperature is preferably within the range of -10 to 60°C, more preferably
30 -10 to 30°C.

In accordance with the present invention, the carbonyl compound is reduced using an alkylaluminum alkoxide differing from the one derivable from the reactant carbonyl compound. In this case, by adequately selecting the alkoxide group of
35 said alkylaluminum alkoxide in view of the alkoxide group

1 formed as an intermediate from the carbonyl compound, it becomes possible to increase the rate of intermediate formation, carry out the reaction at low temperatures and control the configuration of the reduction product alcohol.

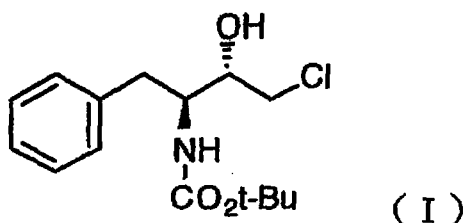
5 It is possible to reduce the carbonyl compound of formula (1), (6) or (7) under mild conditions and, furthermore, it is possible to stereoselectively reduce certain carbonyl compounds, for example α -keto ester derivatives, which can hardly be reduced with ordinary aluminum trialkoxides.

10 By adequately selecting the above-mentioned amino-protecting group, for example, it is possible to produce the erythro form of the α -aminoalcohol derivative of general formula (8) or of the α -aminohalohydrin derivative of general formula (9) with very high stereoselectivity. Thus, for
15 example, in the case of reduction of optically active t-butyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate, which is a phenylalanine derivative, the corresponding optically active aminohalohydrin can be obtained with a diastereomer excess (d.e.) of not lower than 94%. When benzhydrol, for instance,
20 is used as the alcohol compound, the corresponding optically active aminohalohydrin can be obtained with a surprisingly high diastereomer excess of 98%. In the case of reduction of methyl (S)-(t-butoxy carbonylamino)-2-oxo-4-phenylbutyrate, too, the corresponding optically active α -hydroxyester can
25 be obtained with a high erythroselectivity. The starting α -aminoketone derivative of general formula (7) can generally be produced by reacting the corresponding α -amino acid derivative (e.g. α -amino acid ester) with the magnesium enolate of α -chloroacetic acid, for instance (Japanese
30 Patent Application Hei-07-273547). An HIV protease inhibitor can readily be derived from the optically active aminohalohydrin mentioned above (Japanese Kokai Publication Hei-08-99959).

35 BEST MODE FOR CARRYING OUT THE INVENTION

1 The following examples are further illustrative of the
present invention but are by no means limitative of the scope
of the present invention.

5 Example 1 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
chloropropyl]carbamate (I)



15 To an ice-cooled 1.0 M solution of triisobutylaluminum in
hexane (10.5 ml, 10.5 mmol) was added 0.76 ml (10 mmol) of 2-
propanol, and the mixture was stirred at room temperature for
30 minutes. After dilution of the mixture with 10 ml of
20 toluene, 0.759 g (2.5 mmol) of t-butyl [1(S)-benzyl-2-oxo-3-
chloropropyl]carbamate was added and the resultant mixture
was stirred at room temperature for 2 hours. Hydrolysis with
1 N hydrochloric acid, extraction with ethyl acetate and
concentration gave 0.840 g of pale-yellow crystals. The
crystals obtained were subjected to quantitative analysis by
HPLC and the yield and selectivity were determined.

25 Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
chloropropyl]carbamate 97.4%; t-butyl [1(S)-benzyl-2(R)-
hydroxy-3-chloropropyl]carbamate 2.6%. Selectivity: (1S,2S)
form/(1S,2R) form = 97.4/2.6.

30 Example 2 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
chloropropyl]carbamate (I)

35 To a 1.0 M solution of triisobutylaluminum in hexane
(10.5 ml, 10.5 mmol) was added 0.47 g (2.5 mmol) of
triisopropoxyborane, and the mixture was heated at 170°C for 2
hours. After cooling to 80°C, the pressure was reduced to 10
mmHg to thereby cause the excess triisobutylborane to distill
off. After cooling to room temperature and dilution with 20

1 ml of toluene, 0.744 g (2.5 mmol) of t-butyl [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate was added and the resultant mixture was stirred at room temperature for 3 hours. Hydrolysis with 1 N hydrochloric acid, extraction with ethyl acetate and concentration gave 0.995 g of pale-yellow crystals. The crystals obtained were subjected to quantitative analysis by HPLC and the yield and selectivity were determined.

Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate 80.1%; t-butyl [1(S)-benzyl-2(R)-hydroxy-3-chloropropyl]carbamate 3.4%. Selectivity: (1S,2S) form/(1S,2R) form = 95.9/4.1.

Example 3 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (I)

A hexane solution of diethylaluminum ethoxide (about 1 M, 10.4 ml, 10.4 mmol) was diluted with 18 ml of toluene, then 1.489 g (5 mmol) of t-butyl [1(S)-benzyl-2-keto-3-chloropropyl]carbamate was added, and the mixture was stirred at room temperature for 24 hours. After quenching with 1 N hydrochloric acid, the mixture was extracted with ethyl acetate. Concentration of the extract gave 2.560 g of pale-yellow crystals. The crystals obtained were subjected to quantitative analysis by HPLC and the yield and selectivity were determined.

Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate 55.7%; t-butyl [1(S)-benzyl-2(R)-hydroxy-3-chloropropyl]carbamate 8.3%. Selectivity: (1S,2S) form/(1S,2R) form = 87/13.

Example 4 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (I)

Acetone (581 mg, 10 mmol) was added to 9.9 ml (10 mmol) of a toluene solution of DIBAH (1.02 M) at room temperature and the mixture was stirred at room temperature for 1 hour.

1 Then, 1.489 g (5 mmol) of t-butyl [1(S)-benzyl-2-oxo-3-
chloropropyl]carbamate was added and the resultant mixture
was stirred at room temperature for 2 hours. After hydrolysis
5 extracted with ethyl acetate. Concentration of the extract
gave 1.635 g of pale-yellow crystals. The crystals obtained
were subjected to quantitative analysis by HPLC and the yield
and selectivity were determined.

Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
10 chloropropyl]carbamate 82.6%; t-butyl [1(S)-benzyl-2(R)-
hydroxy-3-chloropropyl]carbamate 4.1%. Selectivity: (1S,2S)
form/(1S,2R) form = 95.2/4.8.

Example 5 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-
15 chloropropyl]carbamate (I)

2-Propanol (1.53 ml, 20 mmol) was added to 9.8 ml (10
mmol) of a toluene solution of DIBAH (1.02 M) at room
temperature and the mixture was stirred at room temperature
for 1 hour. Thereto was added 1.489 g (5.0 mmol) of t-butyl
20 [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate, and the resultant
mixture was stirred at room temperature for 2 hours, followed
by hydrolysis with 1 N hydrochloric acid under cooling with
ice. Extraction with ethyl acetate and concentration gave
1.61 g of pale-yellow crystals. Purification by silicagel
25 column chromatography (hexane/ethyl acetate) gave 1.386 g of
t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate
(yield: 92.5%) and 33 mg of t-butyl [1(S)-benzyl-2(R)-hydroxy-
3-chloropropyl]carbamate (yield: 2.2%). [(1S,2S) form/(1S,2R)
form = 97.7/2.3].

30 An NMR spectrum of the thus-obtained product t-butyl
[1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate is shown in
Fig. 1 and an IR spectrum of the same in Fig. 2.

$[\alpha_D^{25}] = -3.44$ (c = 1.05, MeOH)

Melting point: 168.5 to 169.5°C.

1 Example 6 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (I)

 Benzhydrol (3.68 g, 20 mmol) was added to 9.9 ml (10 mmol) of a toluene solution of DIBAH (1.02 M) at room
5 temperature, followed by addition of 20 ml of toluene. After stirring the mixture at room temperature for 1 hour, 1.489 g (5 mmol) of t-butyl [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate was added and the resultant mixture was stirred at room
10 temperature for 2 hours. After hydrolysis with 1 N hydrochloric acid, the reaction mixture was extracted with ethyl acetate and the organic layer obtained was subjected to quantitative analysis by HPLC and the yield and selectivity were determined.

 Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate 99.1%; t-butyl [1(S)-benzyl-2(R)-hydroxy-3-chloropropyl]carbamate 0.9%.

 Selectivity: (1S,2S) form/(1S,2R) form = 99.1/0.9.

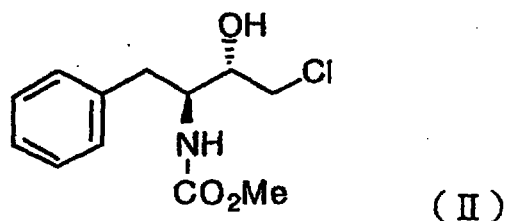
20 Example 7 Production of t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (I)

 Cyclohexanol (2.0 g, 20 mmol) and 10 ml of toluene were added to 9.8 ml (10 mmol) of a toluene solution of DIBAH (1.02 M) at room temperature and the mixture was stirred at room temperature for 1 hour. Thereto was added 1.489 g (5.0
25 mmol) of t-butyl [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate, and the resultant mixture was stirred at room temperature for 2 hours, followed by hydrolysis with 1 N hydrochloric acid with ice cooling. Extraction with ethyl acetate and concentration gave 1.53 g of pale-yellow crystals. The
30 crystals obtained were subjected to quantitative analysis by HPLC and the yield and selectivity were determined.

 Yields: t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate 93.4%; t-butyl [1(S)-benzyl-2(R)-hydroxy-3-chloropropyl]carbamate 2.9%.

35 Selectivity: (1S,2S) form/(1S,2R) form = 97.0/3.0.

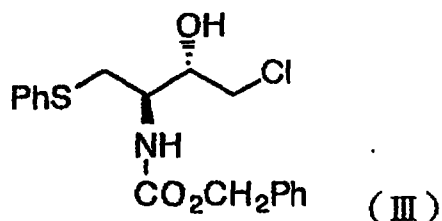
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Example 8 Production of methyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (II)



10 The procedure of Example 1 was followed using 1.28 g (5 mmol) of methyl [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate in lieu of t-butyl [1(S)-benzyl-2-oxo-3-chloropropyl]carbamate, to give 1.314 g of pale-yellow crystals. Recrystallization from hexane/ethyl acetate/ethanol gave 1.063 g of methyl
15 [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (yield: 78.0%). Analysis of the mother liquor by HPLC revealed the presence of 60.0 mg of methyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate (yield: 4.5%) and 36.1 mg of methyl [1(S)-benzyl-2(R)-hydroxy-3-chloropropyl]carbamate (yield:
20 2.8%). Selectivity with respect to the total reaction products: (1S,2S) form/(1S,2R) form = 96.7/3.3.

An NMR spectrum of the thus-obtained product methyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate is shown in Fig. 3 and an IR spectrum of the same in Fig. 4.

25
Example 9 Production of benzyl [1(R)-phenylthiomethyl-2(S)-hydroxy-3-chloropropyl]carbamate (III)



35 2-Propanol (26.44 g, 440 mmol) was added to 216 ml (220 mmol) of a toluene solution of DIBAH (1.02 M) at room

1 temperature and the mixture was stirred at room temperature
for 1 hour. Thereto was added 39.6 g (108.9 mmol) of t-
benzyl [1(R)-phenylthiomethyl-2-oxo-3-chloropropyl]carbamate,
and the resultant mixture was stirred at room temperature for
5 3 hours, followed by hydrolysis with 500 ml of 1 N
hydrochloric acid with ice cooling. After extraction with 300
ml of ethyl acetate, the extract was washed in sequence with
500 ml of 2% aqueous sodium hydrogencarbonate and 200 ml of
2% aqueous sodium chloride, dried over with anhydrous
10 magnesium sulfate and concentrated to give 75.6 g of a pale-
yellow solid. The solid obtained was crystallized out from
toluene/hexane to give 32.9 g of benzyl [1(R)-phenylthiomethyl
-2(S)-hydroxy-3-chloropropyl]carbamate (yield 82.7%).
Analysis of the mother liquor by HPLC revealed the presence
15 of 2.03 g of benzyl [1(R)-phenylthiomethyl-2(S)-hydroxy-3-
chloropropyl]carbamate (yield 5.1%) and 1.753 g of benzyl
[1(R)-phenylthiomethyl-2(R)-hydroxy-3-chloropropyl]carbamate
(yield 4.4%). Selectivity with respect to the total of the
reaction products: (1R,2S) form/(1R,2R) form =95.2/4.8. An
20 NMR spectrum of the thus-obtained product benzyl [1(R)-
phenylthiomethyl-2(S)-hydroxy-3-chloropropyl]carbamate is
shown in Fig. 5 and an IR spectrum of the same in Fig. 6.

Example 10 Production of benzyl alcohol

25 2-Propanol (1.53 ml, 20 mmol) was added to 9.8 ml (10
mmol) of a toluene solution of DIBAH (1.02 M) at room
temperature and the mixture was stirred at room temperature
for 1 hour. Thereto was added 0.531 g of benzaldehyde, and
the resultant mixture was stirred at room temperature for 2
30 hours and then hydrolyzed with 1 N hydrochloric acid with ice
cooling. Extraction with ethyl acetate and concentration
gave 615 mg of benzyl alcohol as an oil. HPLC analysis of
the oil obtained revealed a conversion of 99.9% and a yield of
78.0%.

1 Example 11 Production of 1-phenyl-2-chloroethanol

 The procedure of Example 10 was followed using 0.773 g (5
mmol) of phenacyl chloride in lieu of benzaldehyde, to give
809 mg of 1-phenyl-2-chloroethanol as an oil. Conversion
5 rate: 97.5%; yield 80.4%.

 Example 12 Production of α -phenethyl alcohol

 2-Propanol (1.53 ml, 20 mmol) was added to 9.9 ml (10
mmol) of a toluene solution of DIBAH (1.02 M) at room
10 temperature and the mixture was stirred at room temperature
for 1 hour. Thereto was added 0.601 g of acetophenone, and
the resultant mixture was stirred at room temperature for 6
hours, followed by hydrolysis with 1 N hydrochloric acid with
ice cooling. Extraction with ethyl acetate and concentration
15 gave 1.001 g of α -phenethyl alcohol as an oil. Conversion
55%, yield 47.7%.

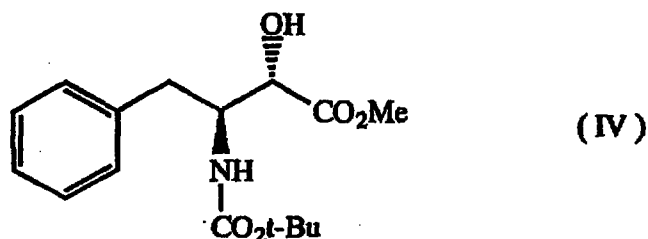
 Example 13 Production of α -phenethyl alcohol

 Benzhydrol (3.68 g, 20 mmol) was added to 9.9 ml (10
20 mmol) of a toluene solution of DIBAH (1.02 M) at room
temperature and the mixture was stirred at room temperature
for 1 hour. Thereto was added 0.601 g (5 mmol) of
acetophenone, and the resultant mixture was stirred at room
temperature for 2 hours, followed by hydrolysis with 1 N
25 hydrochloric acid with ice cooling. Extraction with ethyl
acetate and concentration gave an oil, which was subjected to
quantitative analysis by HPLC. Thus was confirmed the
formation of α -phenethyl alcohol in 42.3% yield (conversion
53.3%).

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 Example 14 Production of methyl 2(S)-hydroxy-3(S)-(t-
butoxycarbonylamino)-4-phenylbutyrate (IV)

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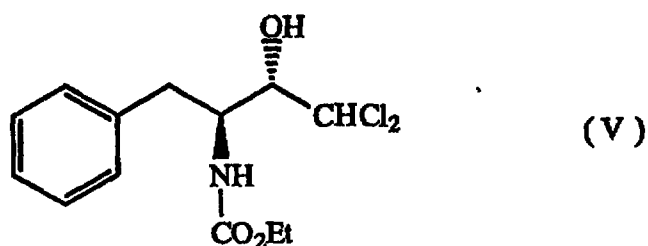


Benzhydrol (0.737 g, 4 mmol) was added to 2 ml (2.04 mmol) of a toluene solution of DIBAH (1.02 M) at room temperature and the mixture was stirred at room temperature for 1 hour. Thereto was added 0.307 g (1 mmol) of methyl 3(S)-(t-butoxycarbonylamino)-2-oxo-4-phenylbutyrate, and the resultant mixture was stirred at room temperature for 2 hours, followed by hydrolysis with 1 N hydrochloric acid with ice cooling. Extraction with ethyl acetate, concentration of the extract and purification of the thus-obtained oil by preparative TLC gave 217 mg of a mixture of methyl 2(S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-phenylbutyrate and methyl 2(R)-hydroxy-3-(S)-(t-butoxycarbonylamino)-4-phenylbutyrate. Upon HPLC analysis, the diastereoselectivity was found to be (2S,3S)/(2R,3S) = 94/6.

Yields: methyl 2(S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-phenylbutyrate 65.9%; methyl 2(R)-hydroxy-3-(S)-(t-butoxycarbonylamino)-4-phenylbutyrate 4.2%.

An NMR spectrum of the thus-obtained product methyl 2(R,S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-phenylbutyrate is shown in Fig. 7 and an IR spectrum of the same in Fig. 8.

Example 15 Production of ethyl [1(S)-benzyl-3,3-dichloro-2(S)-hydroxypropyl]carbamate (V)



2-Propanol (920 mg, 1.5 mmol) was added to 0.73 ml (0.74 mmol) of a toluene solution of DIBAH (1.01 M) at room temperature and the mixture was stirred at room temperature for 1 hour. Thereto was added 100 mg (0.33 mmol) of ethyl [1(S)-benzyl-3,3-dichloro-2-oxopropyl]carbamate, and the resultant mixture was stirred at room temperature for 3.5 hours, then at 40°C for 2 hours and, further, at room temperature for 15 hours, followed by hydrolysis with 1 N hydrochloric acid with ice cooling. Extraction with ethyl acetate and concentration of the extract gave an oil, which was purified by preparative TLC to give 66.7 mg (0.22 mmol) of a mixture of ethyl [1(S)-benzyl-3,3-dichloro-2(S)-hydroxypropyl]carbamate and ethyl [1(S)-benzyl-3,3-dichloro-2(R)-hydroxypropyl]carbamate. The diastereoselectivity as determined by HPLC was (1S,2S)/(1S,2R) =95/5.

Yields: ethyl [1(S)-benzyl-2(S)-hydroxy-3,3-dichloropropyl]carbamate 62.7%; ethyl [1(S)-benzyl-2(R)-hydroxy-3,3-dichloropropyl]carbamate 33%.

An NMR spectrum of the thus-obtained product ethyl [1(S)-benzyl-3,3-dichloro-2(R,S)-hydroxypropyl]carbamate is shown in Fig. 9 and an IR spectrum of the same in Fig. 10.

Reference Example 1 Production of t-butyl [1(S)-benzyl-2(S),3-epoxypropyl]carbamate

A 0.976-g portion of the product obtained in Example 1, namely t-butyl [1(S)-benzyl-2(S)-hydroxy-3-chloropropyl]carbamate, was suspended in 8 ml of acetone, then 2 ml of 10% sodium hydroxide was added, and the mixture was stirred at

1 room temperature for 1 hour. The aqueous layer was separated
and the organic layer was concentrated to dryness to give t-
butyl [1(S)-benzyl-2(S),3-epoxypropyl]carbamate. After
purification by preparative TLC, the optical purity (99.8% ee)
5 was confirmed using a chiral column.

Reference Example 2 Production of α -phenethyl alcohol

Acetophenone (0.601 g) was dissolved in 15 ml of 2-
propanol, 2.04 g of aluminum triisopropoxide was added, and
10 the mixture was stirred at 25°C for 4 hours. After
hydrolysis with 1 N hydrochloric acid, the mixture was
extracted with ethyl acetate. Concentration gave 0.564 g of
an oil, which was analyzed by HPLC (conversion 0.6%, yield
0.4%).

15

Reference Example 3 Reduction of methyl 3(S)-(t- butoxycarbonylamino)-2-oxo-4-phenylbutyrate with Al(O-iPr),

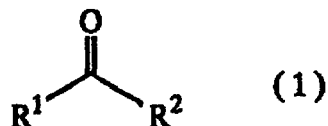
Methyl 3(S)-(t-butoxycarbonylamino)-2-oxo-4-
phenylbutyrate (307 mg) was dissolved in 6 ml of 2-propanol,
20 204 mg (2 mmol) of Al(O-iPr), was added, and the mixture was
stirred at room temperature for 1 hour and then at 50°C for
further 15 hours. However, the formation of the reduction
product methyl 2(R,S)-hydroxy-3(S)-(t-butoxycarbonylamino)-4-
phenylbutyrate was scarcely observed.

25

INDUSTRIAL APPLICABILITY

Being constituted as mentioned above, the present
invention makes it possible to reduce carbonyl compounds to
the corresponding hydroxy compounds in a simple and easy
30 manner at a lower temperature with high stereoselectivity.
Thus, for example, the invention makes it possible to produce
aminohalohydrin derivatives, which are intermediates in the
production of useful medicinal compounds, from aminohaloketone
derivatives derived from phenylalanine and the like, under
35 mild conditions with very high stereoselectivity.

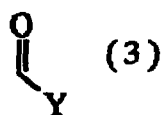
1. A process for reducing carbonyl compounds which comprises reacting a carbonyl compound of the general formula (1)



wherein R^1 and R^2 each independently represents a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 30 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 30 carbon atoms, a cyano group, a hydrogen atom, a group of the general formula (2)

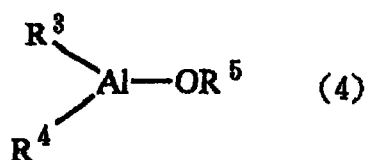


in which X represents a halogen atom and n represents an integer of 0 to 2, or a group of the general formula (3)

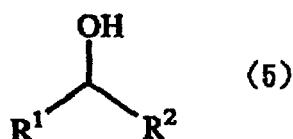


in which Y represents an alkoxy group, an aralkyloxy group, a substituted or unsubstituted amino group or an alkylthio group, provided that one of R^1 and R^2 is a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 30 carbon atoms or a substituted or unsubstituted aryl group containing 6 to 30 carbon atoms, with an organoaluminum compound of the general formula (4)





wherein R³ and R⁴ each independently represents a substituted or unsubstituted alkyl group containing 1 to 10 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms or a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms and R⁵ represents a substituted or unsubstituted primary alkyl group containing 1 to 20 carbon atoms, a substituted or unsubstituted secondary alkyl group containing 1 to 20 carbon atoms, a substituted or unsubstituted primary aralkyl group containing 7 to 30 carbon atoms or a substituted or unsubstituted secondary aralkyl group containing 7 to 30 carbon atoms, to provide the corresponding alcohol compound of the general formula (5)



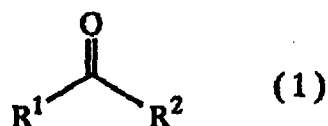
wherein R¹ and R² are as defined above.

2. The process for reducing carbonyl compounds according to Claim 1, wherein the organoaluminum compound of general formula (4) is diisobutylaluminum isopropoxide or diisobutylaluminum diphenylmethoxide.

3. A process for reducing carbonyl compounds which comprises reacting a carbonyl compound of the general formula (1)



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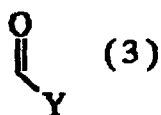


5

wherein R^1 and R^2 each independently represents a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 30 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 30 carbon atoms, a cyano group, a hydrogen atom, a group of the general formula (2)



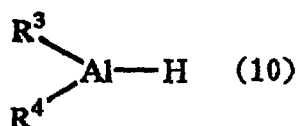
15 in which X represents a halogen atom and n represents an integer of 0 to 2, or a group of the general formula (3)



20

in which Y represents an alkoxyl group, an aralkyloxyl group, a substituted or unsubstituted amino group or an alkylthio group, provided that one of R^1 and R^2 is a substituted or unsubstituted alkyl group containing 1 to 30 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 30 carbon atoms or a substituted or unsubstituted aryl group containing 6 to 30 carbon atoms, with a compound prepared in advance from an organoaluminum compound of the general formula (10)

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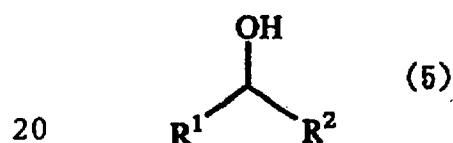
35 wherein R^3 and R^4 each independently represents a substituted



1 or unsubstituted alkyl group containing 1 to 10 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
20 carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 20 carbon atoms, and an alcohol compound of
5 the general formula (11)



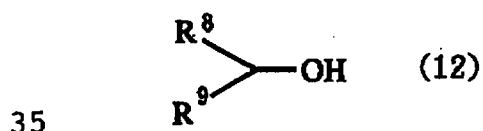
wherein R^5 represents a substituted or unsubstituted primary
10 alkyl group containing 1 to 20 carbon atoms, a substituted or
unsubstituted secondary alkyl group containing 1 to 20 carbon
atoms, a substituted or unsubstituted primary aralkyl group
containing 7 to 30 carbon atoms or a substituted or
unsubstituted secondary aralkyl group containing 7 to 30
15 carbon atoms, to provide the corresponding alcohol compound of
the general formula (5)



wherein R^1 and R^2 are as defined above.

4. The process for reducing carbonyl compounds according
25 to Claim 3, wherein the organoaluminum compound of general
formula (10) is diisobutylaluminum hydride.

5. The process for reducing carbonyl compounds according
to Claim 3 or 4, wherein the alcohol compound of general
30 formula (11) is an alcohol compound of the general formula
(12)





1
in which R⁸ and R⁹ each independently represents a substituted
or unsubstituted alkyl group containing 1 to 10 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
5 20 carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 20 carbon atoms or R⁸ in combination with R⁹
represent a cycloalkyl group.

6. The process for reducing carbonyl compounds according
10 to Claim 5, wherein the alcohol compound of general formula
(12) is isopropanol.

7. The process for reducing carbonyl compounds according
to Claim 5, wherein the alcohol compound of general formula
15 (12) is benzhydrol.

8. The process for reducing carbonyl compounds according
to Claim 1, 2, 3, 4, 5, 6 or 7, wherein the reduction
reaction is carried out at a temperature of -10°C to 30°C.

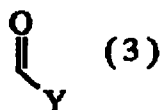
20 9. The process for reducing carbonyl compounds according
to Claim 1, 2, 3, 4, 5, 6, 7 or 8, wherein, in the carbonyl
compound of general formula (1), R¹ is a substituted or
unsubstituted alkyl group containing 1 to 30 carbon atoms, a
25 substituted or unsubstituted aralkyl group containing 7 to 30
carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 30 carbon atoms and R² is a group of the
general formula (2)



in which X represents a halogen atom and n represents an
integer of 0 to 2, or a group of the general formula (3)

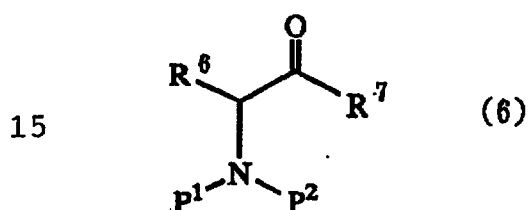


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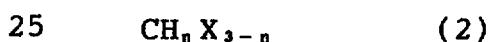


5 in which Y represents an alkoxy group, an aralkyloxy group, a substituted or unsubstituted amino group or an alkylthio group.

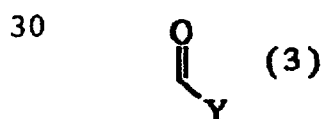
10 10. A process for producing α -aminoalcohol derivatives which comprises reacting an α -aminoketone derivative of the general formula (6)



15 wherein R^6 represents a substituted or unsubstituted alkyl group containing 1 to 20 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or a hydrogen atom, R^7 represents a group of the general formula (2)



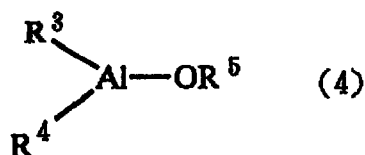
25 in which X represents a halogen atom and n represents an integer of 0 to 2, or a group of the general formula (3)



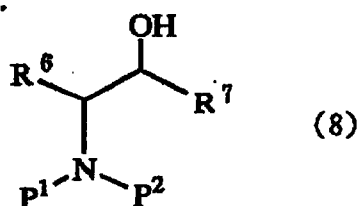
30 in which Y represents an alkoxy group, an aralkyloxy group, a substituted or unsubstituted amino group or an alkylthio group, and P^1 and P^2 each independently represents a hydrogen



1 atom or an amino-protecting group or P^1 in combination with
2 P^2 represent a phthaloyl group, with the exception of the case
3 in which P^1 and P^2 are the same and each is a hydrogen atom,
4 with an organoaluminum compound of the general formula (4)



10 wherein R^3 and R^4 each independently represents a substituted
11 or unsubstituted alkyl group containing 1 to 10 carbon atoms,
12 a substituted or unsubstituted aralkyl group containing 7 to
13 20 carbon atoms or a substituted or unsubstituted aryl group
14 containing 6 to 20 carbon atoms and R^5 represents a
15 substituted or unsubstituted primary alkyl group containing 1
16 to 20 carbon atoms, a substituted or unsubstituted secondary
17 alkyl group containing 1 to 20 carbon atoms, a substituted or
18 unsubstituted primary aralkyl group containing 7 to 30 carbon
19 atoms or a substituted or unsubstituted secondary aralkyl
20 group containing 7 to 30 carbon atoms, to provide the
21 corresponding compound of the general formula (8)



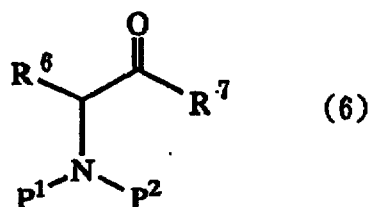
wherein R^6 , R^7 , P^1 and P^2 are as defined above.

30 11. The process for producing α -aminoalcohol
31 derivatives according to Claim 10, wherein the organoaluminum
32 compound of general formula (4) is diisobutylaluminum
33 isopropoxide or diisobutylaluminum diphenylmethoxide.

35 12. A method of producing α -aminoalcohol derivatives



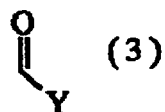
which comprises reacting an α -aminoketone derivative of the general formula (6)



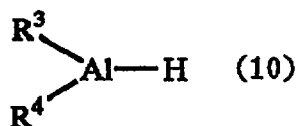
wherein R^6 represents a substituted or unsubstituted alkyl group containing 1 to 20 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms, a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or a hydrogen atom, R^7 represents a group of the general formula (2)



in which X represents a halogen atom and n represents an integer of 0 to 2, or a group of the general formula (3)



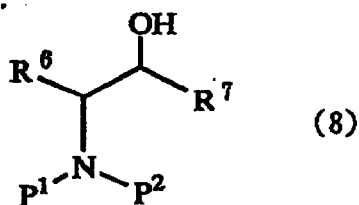
in which Y represents an alkoxyl group, an aralkyloxyl group, a substituted or unsubstituted amino group or an alkylthio group, and P^1 and P^2 each independently represents a hydrogen atom or an amino-protecting group or P^1 in combination with P^2 represent a phthaloyl group, with the exception of the case in which P^1 and P^2 are the same and each is a hydrogen atom, with a compound prepared in advance from an organoaluminum compound of the general formula (10)



1
wherein R³ and R⁴ each independently represents a substituted
or unsubstituted alkyl group containing 1 to 10 carbon atoms,
a substituted or unsubstituted aralkyl group containing 7 to
5 20 carbon atoms or a substituted or unsubstituted aryl group
containing 6 to 20 carbon atoms, and an alcohol compound of
the general formula (11)



10
wherein R⁵ represents a substituted or unsubstituted primary
alkyl group containing 1 to 20 carbon atoms, a substituted or
unsubstituted secondary alkyl group containing 1 to 20 carbon
atoms, a substituted or unsubstituted primary aralkyl group
15 containing 7 to 30 carbon atoms or a substituted or
unsubstituted secondary aralkyl group containing 7 to 30
carbon atoms, to provide the corresponding compound of the
general formula (8)



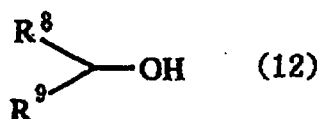
25 wherein R⁶, R⁷, P¹ and P² are as defined above.

13. The process for producing α -aminoalcohol
derivatives according to Claim 12, wherein the organoaluminum
compound of general formula (10) is diisobutylaluminum
30 hydride.

14. The process for producing α -aminoalcohol
derivatives according to Claim 12 or 13, wherein the alcohol
compound of general formula (11) is an alcohol compound of
35 the general formula (12)



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in which R^8 and R^9 each independently represents a substituted or unsubstituted alkyl group containing 1 to 10 carbon atoms, a substituted or unsubstituted aralkyl group containing 7 to 20 carbon atoms or a substituted or unsubstituted aryl group containing 6 to 20 carbon atoms or R^8 in combination with R^9 represent a cycloalkyl group.

15

15. The process for producing α -aminoalcohol derivatives according to Claim 14, wherein the alcohol compound of general formula (12) is isopropanol.

20

16. The process for producing α -aminoalcohol derivatives according to Claim 14, wherein the alcohol compound of general formula (12) is benzhydrol.

25

17. The process for producing α -aminoalcohol derivatives according to Claim 10, 11, 12, 13, 14, 15 or 16, wherein the reduction reaction is carried out at a temperature of -10°C to 30°C .

30

18. The process for producing α -aminoalcohol derivatives according to Claim 10, 11, 12, 13, 14, 15, 16 or 17, wherein one of P^1 and P^2 in the α -aminoketone derivative of general formula (6) is a hydrogen atom and the other is an amino-protecting alkoxycarbonyl or aralkyloxycarbonyl group.

35

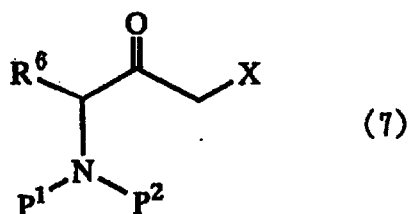
19. The process for producing α -aminoalcohol derivatives according to Claim 10, 11, 12, 13, 14, 15, 16, 17 or 18, wherein the α -aminoalcohol derivative of general

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1 formula (11) is obtained stereoselectively in the erythro
form.

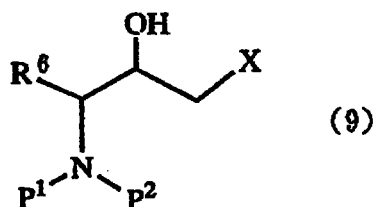
20. The process for producing α -aminoalcohol
5 derivatives according to Claim 10, 11, 12, 13, 14, 15, 16, 17,
18 or 19, wherein the α -aminoketone derivative of general
formula (6) is an α -aminohaloketone derivative of the
general formula (7)

10



15 in which X represents a halogen atom, R^6 represents a
substituted or unsubstituted alkyl group containing 1 to 20
carbon atoms, a substituted or unsubstituted aralkyl group
containing 7 to 20 carbon atoms, a substituted or
unsubstituted aryl group containing 6 to 20 carbon atoms or a
20 hydrogen atom and P^1 and P^2 each independently represents a
hydrogen atom or an amino-protecting group or P^1 in
combination with P^2 represent a phthaloyl group, with the
exception of the case in which P^1 and P^2 are the same and each
is a hydrogen atom, and the α -aminoalcohol derivative of
25 general formula (8) is the α -aminohalohydrin derivative of
the general formula (9)

30



in which X, R^6 , P^1 and P^2 are as defined above.

35

21. The process for producing α -aminoalcohol derivatives



1 according to Claim 20, wherein the α -aminohaloketone
derivative of general formula (7) is optically active
t-butyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
5 methyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
ethyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
ethyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
10 benzyl (R)-(1-benzyl-3-chloro-2-oxopropyl)carbamate,
benzyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
benzyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
t-butyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
15 methyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
methyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
ethyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate or
ethyl (R)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate.

20 22. The process for producing α -aminoalcohol
derivatives according to Claim 20, wherein the
 α -aminohaloketone derivative of general formula (7) is
t-butyl (S)-(1-benzyl-3-chloro-2-oxopropyl)carbamate or
benzyl (S)-(1-phenylthiomethyl-3-chloro-2-oxopropyl)carbamate,
25 the organoaluminum compound of general formula (4) is
diisobutylaluminum hydride and the alcohol compound of general
formula (5) is isopropanol or benzhydrol.

30 23. The process for producing α -aminoalcohol
derivatives according to Claim 20, 21 or 22, wherein the
 α -aminohalohydrin derivative of general formula (9) is
obtained stereoselectively in the erythro form.

