Title: METATHESIS REACTION INVOLVING THE UNSATURATED SIDE CHAIN OF AN ALPHA, ALPHA-DISUBSTITUTED AMINO ACID

Abstract: The invention relates to a process for amino acid synthesis, i.e., the preparation of side chain unsaturated α,α-disubstituted-α-amino acid derivatives with formula (1) wherein: * denotes a stereogenic C-atom; PG represents an N-protecting group or the C-terminal part of an optionally protected amino acid or peptide chain; X represents an optionally substituted amino group or an alkoxy group; R¹ represents an optionally substituted alkyl group; R² represents R³ or R⁴; if R¹ = R² then R³ = R⁴ and if R¹ = R³ then R² = R⁴; R¹, R², R³ and R⁴ each independently represent H, an optionally substituted (cyclo)alkyl, heterocyclic, acyl, alkoxyalkyl, cyano, di-alkylphosphoryl, oxiranyl group, or a CHO group optionally protected as its acetal, or a group derived from an O-protected carbohydrate, or R¹ and R³ may form together with the C-atom to which they are attached an optionally substituted hydrocarbon ring, with the proviso that R², R³ and R⁴ do not all represent H at the same time. R⁴ represents H, an alkyl group or an aryl group; n represents an integer larger than or equal to 0, via a cross metathesis reaction between the corresponding amino acid derivative precursor and an (eventually substituted) alkene.
METATHESIS REACTION INVOLVING THE UNSATURATED SIDE CHAIN OF AN ALPHA, ALPHA-DISUBSTITUTED AMINO ACID

The invention relates to a process for the preparation of side chain unsaturated $\alpha,\alpha$-disubstituted-$\alpha$-amino acid derivatives with formula 1

\[
\begin{align*}
\text{PG} & \quad \text{HN} \\
& \quad \text{O} \\
& \quad \text{X} \\
& \quad \text{R}^1 \quad \text{R}^4 \\
& \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^5 \\
& \quad \text{n}
\end{align*}
\]

(1)

wherein:

* denotes a stereogenic C-atom

PG represents an N-protecting group or the C-terminal part of an optionally protected amino acid or peptide chain;

X represents an optionally substituted amine group or an alkoxy group;

$R^1$ represents an optionally substituted alkyl group or aryl group;

$R^1$ represents $R^2$ or $R^3$; if $R^1 = R^2$ then $R^1 = R^5$ and if $R^1 = R^3$ then $R^1 = H$;

$R^2$, $R^3$ and $R^5$ each independently represent H, an optionally substituted (cyclo)alkyl, (hetero)aryl, acyl, alkoxycarbonyl, cyano, di-alkylphosphonyl, oxiranyl group, a CHO group optionally protected as its acetal, or a group derived from an O-protected carbohydrate, or $R^2$ and $R^5$ may form together with the C-atom to which they are attached an optionally substituted hydrocarbon ring, with the proviso that $R^2$, $R^3$ and $R^5$ do not all represent H at the same time.

$R^4$ represents H, an alkyl group or an aryl group;

$n$ represents an integer larger than or equal to 0,

in which process the corresponding $\alpha,\alpha$–disubstituted-$\alpha$-amino acid derivative with formula 2
wherein *, PG, X, R\(^1\) and n are as defined above and R\(^6\) and R\(^7\), each independently represent H or an alkyl group, is contacted with a compound with formula 3

\[ (1) \]

wherein R\(^2\), R\(^3\) and R\(^5\) are as defined above, in the presence of a metathesis catalyst.

Cross-metathesis reactions starting from \(\alpha\)-H-\(\alpha\)-amino acids are known in the art and for instance described in Biagini et al., J. Chem. Soc., Perkin Trans. 1, (1998), p.2485 ff. As described in Biagini et al. increasing steric bulk leads to decreased metathesis activity. It was therefore to be expected that due to sterical hindrance, it would not be possible to perform intermolecular cross-metathesis reactions starting from \(\alpha\),\(\alpha\)-disubstituted-\(\alpha\)-amino acids or derivatives thereof.

Surprisingly it appeared that in the process according to the invention cross-metathesis reactions occurred with reasonable yields of the products of formula 1. The invention thus provides a generally applicable process for the preparation of multifunctional chiral \(\alpha\),\(\alpha\)-disubstituted-\(\alpha\)-amino acid building blocks.

Side chain unsaturated \(\alpha\),\(\alpha\)-disubstituted-\(\alpha\)-amino acid derivatives with formula 1 are precursors of building blocks in a number of important pharmaceuticals, for instance Efomoritine in Vaniga\(^a\) as for instance described in USP-4,413,141 and USP-4,330,559; CNS-agents, such as metabotropic glutamate receptor (ant)agonists as for instance described in WO-A-95/15940; lipophilic Trichogin GA IV peptabiol as for instance described in J. Pept. Sci (1998) 4,389; cell proliferation stimulators, as for instance described in WO-A-95/15336; nitric oxide synthetase inhibitors as for instance described in USP-5,981,511, WO-A-2000/44731 and WO-A-
2000/63195; and LTA4 hydrolase inhibitors as for instance described in WO-A-
2000/58864. The invention now provides a process that is particularly suited for making
such \( \alpha,\alpha \)-disubstituted-\( \alpha \)-amino acid derivatives. As in the process of the present
invention no racemisation occurs, the process is particularly suited for the preparation
of enantiomerically enriched compounds with formula 1, starting from enantiomerically
enriched compounds with formula 2, for instance compounds with formula 1 and/or 2
with an \( ee \) higher than 80\%, preferably higher than 90\%, most preferably higher than
95\%.

The amino acid derivative substrate to be used in the process

according to the invention is an \( \alpha,\alpha \)-disubstituted-\( \alpha \)-amino acid derivative with formula
2. PG represents an N-protecting group, for instance an acylgroup with e.g. 1-10 C-
atoms, in particular a formyl, acetyl or substituted acetyl group, in particular
chloroacetyl, phenacyl, methoxyacetyl or trifluoroacetyl; an alkoxy carbonyl group with
e.g. 1-20 C-atoms, in particular benzoxycarbonyl (Cbz), t-butoxycarbonyl (Boc) or 9-
fluorenylmethoxycarbonyl (Fmoc); tosyl (Ts); \( \text{NH}_2\text{C(O)}\); or any other protecting group
used in peptide coupling chemistry, as for instance described in J. Podlech et al. in
2002, pp41-165, or PG can be the C-terminal part of a (protected) amino acid or
peptide chain.

\( X \) represents an optionally substituted amino group (NR\(^8\)R\(^9\)) or an
alkoxy group, for instance an alkoxy group with 1-6 C-atoms, preferably methoxy,
ethoxy or t-butoxy. R\(^8\) and R\(^9\) each independently may represent H, an optionally
substituted (cyclo)alkyl group, for instance a C1-C20 (cyclo)alkyl group, in particular a
methyl, ethyl and/or benzyl group or can be the N-terminal part of a (protected) amino
acid or peptide chain; or R\(^8\) and R\(^9\) may form together with the N atom to which they
are attached an optionally substituted for instance 3-8 membered, preferably 5-6
membered ring, which may contain 1 or more, for instance 1-3, hetero atoms, for
instance N or O; an aryl group, for instance a C6-C20 aryl group, for instance phenyl.

R\(^1\) represents an optionally substituted (cyclo)alkyl or aryl group,

preferably a C1-C10 alkyl group, in particular a methyl, ethyl, propyl, or (substituted)
phenyl group. The alkyl group in R\(^1\) may contain one or more substituents. Suitable
substituents are for example a halogen, a hydroxy group, a C1-C6 alkoxy group or an
optionally substituted phenyl group. A special subgroup of R\(^1\) represents the optionally
protected side chains of proteinogenic amino acids. Preferably R\(^1\) represents an alkyl
group with 1-3 C-atoms, optionally substituted with, for instance, one or more OH
groups or halogens, for instance one or more F. Suitable examples of $R^4$ are, for
instance, methyl, ethyl, propyl, benzyl, fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl and hydroxymethyl.

$R^4$ represents an optionally substituted (cyclo)alkyl or aryl group,
preferably a C1-C10 alkyl group, in particular a methyl, ethyl, propyl, or (substituted)
phenyl group. The alkyl or aryl group in $R^4$ may contain one or more substituents.
Suitable substituents are for example a halogen, a hydroxy group, a C1-C6 alkoxy
group or an optionally substituted phenyl group. Preferably $R^4$ represents an alkyl
group with 1-3 C-atoms, optionally substituted with, for instance, one or more OH
groups or halogens, for instance one or more F. Suitable examples of $R^4$ are, for
instance, methyl, ethyl, propyl, benzyl, fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl and hydroxymethyl.

The integer n is larger than or equal to 0, preferably n = 1-8, in

particularly 1,2,3, or 4.

$R^6$ and $R^7$, each independently, represent H or an alkyl group with for
instance 1-5 C-atoms, preferably 1-3 C-atoms. Most preferably $R^6$ and/or $R^7$ is H.
Preferably, at least one of the substituents $R^8$ or $R^9$ in the compound of formula 2 is
different from $R^1$ and $R^5$ in the compound of formula 1, and thus, preferably the

compound of formula 1 is not identical to the compound of formula 2. In case that $R^6 =
R^1$ and $R^7 = R^9$ (or vice versa $R^6 = R^1$ and $R^7 = R^9$), the compound of formula 1 is
identical to the compound of formula 2, and thus the reaction between compound 2 and
compound 3 into compound 1 may be regarded as a "no-reaction reaction".

A second starting material to be used in the process according to the
invention is a compound of formula 3. The compound of formula 3 may be in its (Z) as
well as its (E) form or mixtures thereof. Provided that $R^2$, $R^3$ and $R^5$ do not all represent
H at the same time, $R^2$, $R^3$ and $R^5$, each independently may represent H; an optionally
substituted (cyclo) alkyl group, for instance an (cyclo) alkyl group with 1-10 C-atoms, in

particular methyl, ethyl, propyl, butyl or pentyl; an optionally substituted (hetero)aryl
group, for instance an (hetero)aryl group with 3-18 C-atoms, in particular phenyl,
naphthyl or thienyl; a CHO group, (optionally protected as its (cyclic) acetal); a group
derived from an O-protected carbohydrate with for instance 8-50 C-atoms; an acyl
group, for instance an acyl group with 2-10 C-atoms, in particular acetyl or benzoyle; an
alkoxycarbonyl group with for instance 2-10 C-atoms; a cyano group; a
dialkoxyphosphonyl group, for instance a group with 2-10 C-atoms, in particular
dimethyl or diethylphosphonyl; or an oxirane group, or \( \mathbf{R}^2 \) and \( \mathbf{R}^5 \) may form together with the C-atom to which they are attached and optionally substituted hydrocarbon ring. The alkyl, (hetero)aryl, acyl, alkoxy carbonyl or oxirane groups are optionally substituted with for instance one or more substituents chosen from halogen (F, Cl, Br), alkyl, aryl, OR\(^{10} \) (with \( \mathbf{R}^{10} \) = optionally substituted (cyclo)alkyl or aryl, C(O)\( \mathbf{R}^{11} \) with \( \mathbf{R}^{11} \) = optionally substituted (cyclo)alkyl or aryl, trialkysilyl, NHC(O)\( \mathbf{R}^{12} \) (amides with \( \mathbf{R}^{12} \) = optionally substituted (cyclo)alkyl or aryl, or carbamates with \( \mathbf{R}^{12} \) = alkoxy e.g. t-butoxy or benzylxoy), \( \mathbf{N}_3 \), \( \mathbf{CN} \), CO\( \mathbf{R}^{13} \), with \( \mathbf{R}^{13} \) = optionally substituted (cyclo)alkyl or aryl, the substituents preferably have 1-20 C-atoms. The (hetero)aryl groups may contain one or more S, O, or N atoms.

\( \mathbf{R}^2 \), \( \mathbf{R}^3 \) and \( \mathbf{R}^5 \), each independently may represent a group derived from an O-protected carbohydrate, for instance, a carbohydrate substituent which is fully O-protected and which -in its anomic (C-1) position- is directly linked to the alkenyl group of the compound of formula 3 or which may be linked to the alkenyl group via a linker group consisting of a carbon chain. In these cases, the group derived from an O-protected carbohydrate (\( \mathbf{R}^2 \), \( \mathbf{R}^3 \) and/or \( \mathbf{R}^5 \)) is belonging to the class of C-glycosides. Alternatively, the fully O-protected carbohydrate substituent(s) may for instance also be linked to the alkenyl group of the compound of formula 3 via an O- or N-heteroatom or via a linker group consisting of a carbon chain and a O- or N-heteroatom, for example by cross metathesis reaction with O-protected 1-O-allyl-\( \alpha \)-D-glucopyranose or O-protected N-acetyl-N-allyl-\( \alpha \)-D-glucosamine. Examples of C-glycosides comprise for example D-galactose, D-glucose, D-mannose, L-fucose; sugars of shorter chain-length, for example ribose, arabinose, xylose; sugars with NHAc substituents, for example glucosamine,galactosamine; and furanosides.

Protective groups on the heteroatoms can be, for example, alkyl groups (methyl, benzyl, 4-methoxybenzyl (PMB)), esters (acyl, benzoyl) or silyl groups (trimethylsilyl (TMS), t-butyldimethylsilyl (TB DMS), triethylsilyl (TES), t-butyldipropylsilyl (TBDPS). An example of a compound with formula 3 containing an O-protected carbohydrate group is e.g. 3-(2,3,4,6-tetra-O-benzyl-\( \alpha \)-D-galactopyranosyl)-1-propene.

Preferably \( \mathbf{R}^3 = \mathbf{H} \), in particular \( \mathbf{R}^3 = \mathbf{R}^5 = \mathbf{H} \), or \( \mathbf{R}^3 \) is the same as \( \mathbf{R}^2 \) and \( \mathbf{R}^5 = \mathbf{H} \) (or \( \mathbf{R}^5 \) is the same as \( \mathbf{R}^3 \) and \( \mathbf{R}^2 \) is \( \mathbf{H} \)), as otherwise a mixture of compounds with \( \mathbf{R}^1 = \mathbf{R}^2 \) (or \( \mathbf{R}^5 \) and compounds with \( \mathbf{R}^1 = \mathbf{R}^3 \) is obtained. However, if a non-symmetric compound with formula 3 is more easily available, also such non-symmetric compound with formula 3 may be advantageously applied. \( \mathbf{R}^2 \) and \( \mathbf{R}^5 \) may form
together with the C-atom to which they are attached an optionally substituted, for
instance 3-8 membered, hydrocarbon ring with for instance 3-20 C-atoms. Suitable
substituents are, for example, the substituents mentioned above for R², R⁵ and/or R⁷.

Preferably, the compound of formula 2 differs from the compound of
formula 3. Intermolecular cross metathesis reactions between different starting
materials 2 and 3 are preferred in the process of the present invention. In one preferred
embodiment, at least one of the substituents R⁶ or R⁷ in the compound of formula 2 is
different from R² and R⁵ in the compound of formula 3. In another preferred
embodiment, at least one of the substituents R⁶ or R⁷ in the compound of formula 2 is
different from R⁵ and H in the compound of formula 3.

The compounds to be prepared with the process of the present
invention are chiral compounds, either as a racemic mixture of the enantiomers or in
enantiomerically enriched form. If an enantiomerically enriched compound is aimed at,
the starting material with formula 2 should also be in enantiomerically enriched form.

Such enantiomerically enriched compounds may be prepared in a manner known per
se, for instance via asymmetric synthesis, enzymatic resolution, classical resolution via
diastereomeric salt formation, asymmetric transformation or using a chiral auxiliary as
for instance described in C. Cataviela, Tetrahedron; Assym. (1998) 9, 3517-3599; J.
Jacques, A. Collet, S.H. Wilen; “Enantiomers, Racemates and Resolutions”, Wiley
Drauz, H. Waldmann (Eds.), VCH, Weinheim (2002), pp 398-412; “Stereoselective

Suitable metathesis catalysts to be used in the process of the present
invention are, for example, metal carbene complexes with the general formula
R¹⁴R¹⁵C=MLₙXₘ wherein M represents a metal, for instance Mo, Ru, W, Os or Ta,
preferably Ru, or Mo, R¹⁴ and R¹⁵ each represent H, an optionally substituted, for
instance C₁-C₂₀, alkyl, alkenyl, alkynyl, aryl, carboxylate, alkoxy, alkenoxylo,
alkynyloxy, alkoxycarbonyl, alkylthio, alkysulfuryl or alkysulfinyl group.

Suitable substituents for the groups in R¹⁴ and R¹⁵ are for example halogens, alkyl, for
instance C₁-C₅ alkyl, alkoxy, for instance C₁-C₅ alkoxy or aryl, for instance C₆-C₁₀
aryl. The n and m are integers, for instance 0, 1 or 2, each L represents a neutral
ligand and each X represents an anionic ligand. Suitable ligands L are, for example,
phosphine (PC₃), THF, N,N'-dimesityl-imidazol-2-ylidene (mesityl = 2,4,6-
trimethylphenyl (=Mes)), N,N'-dimesityl-dihydroimidazol-2-ylidene. Suitable ligands X
are, for example, halogenides (Cl, Br), alkoxydes (neopentanolate, 1,1-bis-
(trifluoromethyl)ethoxy), aryloxides (in particular disubstituted phenolates (i-Pr, Br), bismaphtholates), anilides (derived from 2,6-di-isopropylaminoiline). Such catalysts, e.g. a Schrock catalyst, Blechert modification of the Hoveyda catalyst, first and second generation Grubbs catalyst, are for instance described in A. Fürstner, Angew. Chem (2000) 37, 3013-3043 and in WO-A-02/00590. Preferably a catalyst is used wherein M = Ru, X = Cl, m = 2, L = PCy₃, N,N'-dimesityldihydroimidazol-2-ylidene, R¹⁴ = H, R¹⁵ = Ph.

The temperature at which the compound with formula 2 is contacted with the compound of formula 3 is not very critical and preferably is between 0-120 °C, most preferably between 20 and 80 °C.

The process of the invention may be performed in the presence of a solvent. Suitable solvents that can be used in the process of the present invention are for instance ethers, for example MTBE; (aromatic) hydrocarbons, for example toluene; halogenated hydrocarbons, for example dichloromethane. A preferred solvent is toluene.

If desired, subsequently the double bond in the side chain of the (Z) and/or (E) side chain unsaturated α,α-disubstituted-α-amino acid derivative with formula 1 may be hydrogenated using methods known in the art, for instance by hydrogenation with H₂ or a H-donor (e.g. ammonium formate) in the presence of a hydrogenation catalyst e.g. Pd/C or platinum oxide.

The invention will be elucidated by the following examples without being restricted thereby.

**Example 1: Screening of the cross-metathesis reaction of different amino acid derivatives with styrene**

\[
\text{PG, } R_1 (\bigcirc)_n X + \text{styrene} \xrightarrow{\text{catalyst b}} \text{PG, } R_1 (\bigcirc)_n X
\]

Standard procedure for the screening of protecting groups and amino acid derivatives: To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) and 0.25
mmol amino acid derivative under an argon atmosphere in 2.5 ml of freshly distilled oxygen free toluene or dichloromethane, 115 μl (1.00 mmol) styrene was added. The mixture was stirred for 17 hours at room temperature under argon. The reaction mixture was analyzed by GC-MS.

Reaction conditions were not optimized.

<table>
<thead>
<tr>
<th>amino acid derivative**</th>
<th>PG</th>
<th>X</th>
<th>R¹</th>
<th>n</th>
<th>solvent*</th>
<th>Conversion**</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL-Ac-Mag-Ome</td>
<td>Ac</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>DL-Boc-Mag-OMe</td>
<td>Boc</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>60%</td>
</tr>
<tr>
<td>DL-Cbz-Mag-OMe</td>
<td>Z</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>70%</td>
</tr>
<tr>
<td>DL-Formyl-Mag-OMe</td>
<td>CHO</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>70%</td>
</tr>
<tr>
<td>DL-Ts-Mag-Ome</td>
<td>4-Ts</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>80%</td>
</tr>
<tr>
<td>DL-Boc-Mag-NH₂</td>
<td>Boc</td>
<td>NH₂</td>
<td>CH₃</td>
<td>1</td>
<td>2 or 2</td>
<td>+</td>
</tr>
<tr>
<td>DL-Formyl-Mag-NH₂</td>
<td>CHO</td>
<td>NH₂</td>
<td>CH₃</td>
<td>1</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>DL-Formyl-Mag-NH-Bn</td>
<td>CHO</td>
<td>NHCH₂Ph</td>
<td>CH₃</td>
<td>1</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>DL-Boc-Mag-Ala-OMe</td>
<td>Boc</td>
<td>Ala-OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>L-Formyl-Mbhag-OMe</td>
<td>CHO</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>3</td>
<td>1</td>
<td>70%</td>
</tr>
</tbody>
</table>

* solvent 1: toluene, solvent 2: CH₂Cl₂

**Mag = α-methyl-α-allylglycine; Mbhag = α-methyl-α-bis-homo-allylglycine

*** + = conversion to product observed

Example 2: Screening of the cross-metathesis reaction of DL-Formyl-Mag-OMe with different olefinic substrates

Standard procedure for the screening of olefinic substrates on DL-
Formyl-Mag-OMe:

To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) under an argon atmosphere in 1.5 ml of freshly distilled oxygen free toluene, a stock solution of DL-Formyl-Mag-OMe (1 ml, 0.25M) and 4 eq. of olefinic substrate was added. The mixture was stirred for 17 hours at room temperature under argon. The reaction mixture was analyzed by GC-MS.

Reaction conditions were not optimized.

<table>
<thead>
<tr>
<th>Olefine</th>
<th>R² = R¹</th>
<th>R³ = R⁴</th>
<th>R⁵</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl chloride*</td>
<td>CH₂Cl</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Allyl bromide</td>
<td>CH₂Br</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Allyl alcohol</td>
<td>CH₂OH</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Allyl acetate</td>
<td>CH₂OAc</td>
<td>H</td>
<td>H</td>
<td>50%</td>
</tr>
<tr>
<td>Allyl cyanide</td>
<td>CH₃CN</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Allyloxytrimethylsilane</td>
<td>CH₂OSiMe₃</td>
<td>H</td>
<td>H</td>
<td>20%</td>
</tr>
<tr>
<td>Diethyl allylmalonate</td>
<td>CH₂CH(CO₂Et)₂</td>
<td>H</td>
<td>H</td>
<td>50%</td>
</tr>
<tr>
<td>Allyltrimethylsilane</td>
<td>CH₂SiMe₃</td>
<td>H</td>
<td>H</td>
<td>20%</td>
</tr>
<tr>
<td>2-Vinyl-1,3-dioxolane</td>
<td></td>
<td>H</td>
<td>H</td>
<td>70%</td>
</tr>
<tr>
<td>Acrolein diethylacetal</td>
<td>CH(OEt)₂</td>
<td>H</td>
<td>H</td>
<td>60%</td>
</tr>
<tr>
<td>Cis-1,4-diacetoxy-2-butene</td>
<td>H</td>
<td>CH₂OAc</td>
<td>CH₂OAc</td>
<td>25%</td>
</tr>
<tr>
<td>2-Vinylpyridine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinylcyclopentane</td>
<td>c-C₅H₁₀</td>
<td>H</td>
<td>H</td>
<td>50%</td>
</tr>
<tr>
<td>1-Octene</td>
<td>n-C₆H₁₃</td>
<td>H</td>
<td>H</td>
<td>70%</td>
</tr>
<tr>
<td>Acrylic acid ethyl ester</td>
<td>CO₂Et</td>
<td>H</td>
<td>H</td>
<td>90%</td>
</tr>
<tr>
<td>Styrene</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>70%</td>
</tr>
<tr>
<td>Methyl vinyl ketone</td>
<td>C(O)CH₃</td>
<td>H</td>
<td>H</td>
<td>30%</td>
</tr>
<tr>
<td>Diethyl vinylphosphonate</td>
<td>PO₃Et₂</td>
<td>H</td>
<td>H</td>
<td>80%</td>
</tr>
<tr>
<td>3-(2,3,4,6-tetra-O-benzyl-o-D-glucopyranosyl)-1-propene</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

* 8 eq. of olefinic substrate
Example 3: Screening of the cross-metathesis reaction of DL-Boc-Mag-NH₂ with different olefinic substrates

Standard procedure for the screening of olefinic substrates on DL-Boc-Mag-NH₂:

To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) and 57.1 mg of DL-Boc-Mag-NH₂ under an argon atmosphere in 2.5 ml of freshly distilled oxygen free toluene, 4 eq. (1.00 mmol) of olefinic substrate was added. The mixture was stirred for 17 hours at room temperature under argon. The reaction mixture was analyzed by GC-MS.

Reaction conditions were not optimized.

<table>
<thead>
<tr>
<th>Olefine</th>
<th>R² = R¹</th>
<th>R³ = R⁴</th>
<th>R⁵</th>
<th>conversion</th>
</tr>
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<tbody>
<tr>
<td>Allyl acetate</td>
<td>CH₃OAc</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Allyloxytrimethylsilane</td>
<td>CH₂OSiMe₃</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>2-Vinyl-1,3-dioxolane</td>
<td></td>
<td>H</td>
<td>H</td>
<td>75%</td>
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<tr>
<td>Acrolein diethylacetal</td>
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<td>H</td>
<td>+</td>
</tr>
<tr>
<td>Cis-1,4-diacetoxy-2-butene</td>
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<td>CH₃OAc</td>
<td>CH₃OAc</td>
<td>+</td>
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<tr>
<td>Vinylcyclopentane</td>
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<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
<td>1-Octene</td>
<td>n-C₆H₁₃</td>
<td>H</td>
<td>H</td>
<td>+</td>
</tr>
<tr>
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<td>H</td>
<td>H</td>
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<td>C(Ο)CH₃</td>
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<td>+</td>
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<tr>
<td>Diethyl vinylphosphonate</td>
<td>PO₃Et₂</td>
<td>H</td>
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Example 4: Screening of the cross-metathesis reaction of DL-Formyl-Mag-OMe with styrene or 2-vinyl-1,3-dioxolane using different metathesis catalysts

Standard procedure for the screening of metathesis catalysts a-d:
To a solution of (5 mol%) metathesis catalyst a-d under an argon atmosphere in 1.5 ml of freshly distilled oxygen free toluene, a stock solution of DL-Formyl-Mag-OMe (1 ml, 0.25M) and 115 μl (1.00 mmol) styrene or 2-vinyl-1,3-dioxolane was added. The mixture was stirred for 17 hours at room temperature under argon. The reaction mixture was analyzed by GC-MS.

Procedure for the screening of metathesis catalyst e:
To a solution of 9.5 mg (5 mol%) metathesis catalyst e and 57.1 mg of DL-Boc-Mag-OMe (0.24 mmol) under an argon atmosphere in 2.5 ml of freshly distilled oxygen free toluene, 115 μl (1.00 mmol) styrene was added. The mixture was stirred for 17 hours at room temperature under argon. The reaction mixture was analyzed by GC-MS.

Reaction conditions were not optimized.
<table>
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<th>conversion</th>
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<td></td>
<td>$R^3 = R^5 = H$</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>CHO</td>
<td>Ph</td>
<td>+</td>
</tr>
<tr>
<td>b</td>
<td>CHO</td>
<td>Ph</td>
<td>70%</td>
</tr>
<tr>
<td>c</td>
<td>CHO</td>
<td>Ph</td>
<td>50-60%</td>
</tr>
<tr>
<td>d</td>
<td>CHO</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>e</td>
<td>Boc</td>
<td>Ph</td>
<td>+</td>
</tr>
</tbody>
</table>

**Example 5**

To 114 mg (0.50 mmol) DL-Boc-Mag-NH$_2$ and 21.2 mg (5 mol%) metathesis catalyst (b) under an argon atmosphere, 5 ml of freshly distilled oxygen free toluene and 100 µl (2.00 mmol) 2-vinyl-1,3-dioxolane was added. The mixture was stirred for 17 hours at room temperature under a gentle argon stream. The toluene was removed under reduced pressure. Column chromatography (EtOAc/heptane 7:3) yielded 110.6 mg (74%) of cross-metathesis product as a mixture of (E) and (Z) isomers.

$^1$H-NMR, $\delta_H$ (300 MHz, CDCl$_3$): 6.38 (1H, b s, NH), 5.90-5.72 (1H, m, CH$_2$-CH=CH), 5.65-5.50 (1H, d, CH=CH-CH), 5.31 (1H, b s, NH), 5.31-5.21 (1H, d, O$_2$CH), 4.01-3.88 (4H, m, OC$_2$H$_4$O), 2.82-2.58 (2H, m, $\beta$-CH$_2$), 1.49 (3H, s, $\alpha$-CH$_3$), 1.43 (9H, s, Boc).
Example 6:

To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) under an argon atmosphere in 1.5 ml of freshly distilled oxygen free toluene, a stock solution of DL-Boc-Mag-OMe (1 ml, 0.25M) and 159 µl (1.00 mmol) allytrimethylsilane was added. The mixture was stirred for 17 hours at room temperature under a gentle argon stream. The toluene was removed under reduced pressure. Column chromatography (EtOAc/heptane 2:1) yielded 58.0 mg (70%) of cross-metathesis product as a mixture of (E) and (Z) isomers.

$^1$H-NMR, δ (300 MHz, CDCl₃): 5.54-5.44 (1H, m, CH=CH), 5.12-5.02 (2H, m + b s, CH=CH + NH), 3.70 (3H, s, OMe), 2.51-2.42 (2H, m, β-CH₂), 1.50-1.40 (15H, 3 x s, α-Me + CH₂Si + Boc), 0.02 (9H, s, Si(Me)₃).

Example 7:

To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) under an argon atmosphere in 1.5 ml of freshly distilled oxygen free toluene, a stock solution of DL-Boc-Mag-OMe (1 ml, 0.25M) and 159 µl (1.00 mmol acrolein diethylacetal was added. The mixture was stirred for 17 hours at room temperature under a gentle argon stream. The toluene was removed under reduced pressure. Column chromatography (EtOAc/heptane 2:1) yielded 57.0 mg (66%) of cross-metathesis product as a mixture of (E) and (Z) isomers.
\(^1\)H-NMR, \(\delta_H\) (300 MHz, CDCl\(_3\)): 5.66-5.50 (1H, m, CH\(_2\)-CH=CH), 5.15+5.14 and 4.80+4.78 (1H, d, CH=CH-CH), 3.75 (3H, s, OMe), 3.71-3.39 (4H, d m, OCH\(_2\)), 2.73-2.53 (2H, m, \(\beta\)-CH\(_2\)), 1.49 (3H, s, \(\alpha\)-CH\(_3\)), 1.40 (9H, s, Boc), 1.23-1.15 (6H, m, 2 x CH\(_2\)-CH\(_3\)).

Example 8:

To a solution of 10.6 mg (5 mol%) metathesis catalyst (b) under an argon atmosphere in 1.5 ml of freshly distilled oxygen free toluene, a stock solution of DL-Boc-Mag-OMe (1 ml, 0.25M) and 115 \(\mu\)l (1.00 mmol styrene was added. The mixture was stirred for 17 hours at room temperature under a gentle argon stream. The toluene was removed under reduced pressure. Column chromatography (EtOAc/heptane 1:4) yielded 51.1 mg (64%) of cross-metathesis product as a mixture of (E) and (Z) isomers.

\(^1\)H-NMR, \(\delta_H\) (300 MHz, CDCl\(_3\)): 7.35-7.19 (5H, m, Ph), 6.48 + 6.42 (1H, d, CH=CH-Ph), 6.10-6.00 (1H, m, CH\(_2\)-CH=CH), 5.19 (1H, b s, NH), 3.75 (3H, s, OMe), 2.87-2.71 (2H, m, \(\beta\)-CH\(_2\)), 1.57 (3H, s, \(\alpha\)-CH\(_3\)), 1.43 (9H, s, Boc).

Example 9
A suspension of 2.00 g (15.5 mmol) (S)-α-methyl-α-allylglycine in 25 ml of methanol was cooled to 0 °C and SOCl₂ (3.2 ml) was added dropwise. The mixture was allowed to reach room temperature and then refluxed for 17 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 250 ml CH₂Cl₂, 4.24 g of Cbz-OSu and 4.5 ml of Et₃N were added and the reaction mixture was stirred for 17 h at room temperature. The mixture was evaporated to dryness under reduced pressure and after column chromatography (EtOAc/heptane 1:4) 3.59 g of Cbz-(S)-Mag-OMe was isolated. Yield over two steps is 84%.

¹H NMR, δH (300 MHz, CDCl₃): 7.35-7.28 (5H, m, Ph), 5.71-5.57 (1H, m, CH=CH₂), 5.50 (1H, b s, NH), 5.11-5.04 (4H, m, OCH₃ + CH=CH₂), 3.74 (3H, s, OMe), 2.80-2.54 (2H, m, α-CH₂), 1.60 (3H, s, α-CH₃).

Example 10

A solution of 1.60 g (5.8 mmol) of Cbz-(S)-Mag-OMe under an argon atmosphere in 60 ml of freshly distilled oxygen free toluene was stirred at 95 °C. Then, 2.88 ml of 2-vinyl-1,3-dioxolane (5 equiv) and in total 245 mg (5 mol%) of the metathesis catalyst (b) was added in portions of 49 mg (1 mol%). The mixture was stirred for 24 h under an argon atmosphere. The reaction mixture was evaporated to dryness under reduced pressure and after column chromatography (EtOAc/heptane 1:2) a mixture of the dimer of 2-vinyl-1,3-dioxolane and E/Z mixture of cross metathesis product was obtained; 1.92 g, ratio by H-NMR: product/dimer = 1 : 0.98. Yield cross metathesis product estimated from the ¹H-NMR ratio: 48%.
Example 11

To a solution of 1.92 g metathesis products of the previous example (containing 2.8 mmol of cross metathesis product) in 50 ml of methanol under an argon atmosphere, 4% (w/w) Pd/C 5 wt% (79 mg) was added. The argon was replaced by hydrogen (1 bar atmosphere). The reaction mixture was stirred for 22 h at room temperature. The Pd/C was removed by filtration over Celite and the filtrate was evaporated to dryness. After column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 9:1) 537 mg of (S)-2-methyl-5-(1,3-dioxolan-2-yl)norvaline methyl ester was obtained. Yield: 89%

\textsuperscript{1}H NMR, δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}): 4.76-4.72 (1H, m, O\textsubscript{2}CH), 3.89-3.71 (4H, m, OC\textsubscript{2}H\textsubscript{4}O), 3.62 (1H, s, OMe), 1.64-1.18 (6H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.23 (3H, s, α-CH\textsubscript{3})
CLAIMS

1. Process for the preparation of a side chain unsaturated \( \alpha,\alpha \)-disubstituted-\( \alpha \)-amino acid derivative with formula 1

\[
\begin{array}{c}
\text{PG} \quad \text{HN} \quad * \\
\text{O} \quad \text{X}
\end{array}
\]

wherein:
* denotes a stereogenic C-atom
PG represents an N-protecting group or the C-terminal part of an optionally protected amino acid or peptide chain;
X represents an optionally substituted amino group or an alkoxy group;
\( \text{R}^1 \) represents an optionally substituted alkyl group or aryl group;
\( \text{R}^1 \) represents \( \text{R}^2 \) or \( \text{R}^3 \); if \( \text{R}^1 = \text{R}^2 \) then \( \text{R}^1 = \text{R}^6 \) and if \( \text{R}^1 = \text{R}^3 \) then \( \text{R}^3 = \text{H} \);
\( \text{R}^2, \text{R}^3 \) and \( \text{R}^6 \) each independently represent \( \text{H} \), an optionally substituted (cyclo)alkyl, (hetero)aryl, acyl, alkoxy carbonyl, cyano, di-alkyl phosphonyl, oxirany group, a CHO group optionally protected as its acetal, or a group derived from an O-protected carbohydrate, or \( \text{R}^2 \) and \( \text{R}^3 \) may form together with the C-atom to which they are attached and optionally substituted hydrocarbon ring, with the proviso that not \( \text{R}^2 = \text{R}^3 = \text{R}^6 = \text{H} \);
\( \text{R}^7 \) represents \( \text{H} \), an alkyl group, or an aryl group;
n represents an integer larger than or equal to 0,
in which process the corresponding \( \alpha,\alpha \)-disubstituted-\( \alpha \)-amino acid derivative with formula 2

\[
\begin{array}{c}
\text{PG} \quad \text{HN} \quad * \\
\text{O} \quad \text{X}
\end{array}
\]
wherein, PG, X, R¹ and n are as defined above and R⁶ and R⁷, each independently represent H or an alkyl group, is contacted with a compound with formula 3

\[ \text{(3)} \]

wherein R², R³ and R⁵ are as defined above, in the presence of a metathesis catalyst.

2. Process according to claim 1, wherein R⁴ = H.

3. Process according to claim 1 or 2, wherein n is 1-8.

4. Process according to any one of claims 1-3, wherein R⁵ = H.

5. Process according to any one of claims 1-4, wherein R⁶ or R² = H.

6. Process according to any one of claims 1-3, wherein R³ = R⁵ and R⁷ = H.

7. Process according to any of claims 1-6 wherein R², R³ and/or R⁵ represent a group derived from an O-protected carbohydrate.

8. Process according to any one of claims 1-7, wherein R¹ represents an alkyl group with 1-3 C-atoms.

9. Process according to any one of claims 1-8, wherein R⁶ and/or R⁷ is H.

10. Process according to any one of claims 1-9, wherein X represents the N-terminal part of an optionally protected amino acid or peptide chain.

11. Process according to any one of claims 1-10, wherein PG represents the C-terminal part of an optionally protected amino acid or peptide chain.

12. Process according to any one of claims 1-11, wherein the side chain unsaturated α,α-disubstituted-α-amino acid derivative is enantiomerically enriched.

13. Process according to any one of claim 1-12, which process further comprises the hydrogenation of the double bond in the side chain of the side chain unsaturated α,α-disubstituted-α-amino acid derivative with formula 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C6/04 C07C227/16 C07K1/00

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO–Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Date of the actual completion of the international search
7 September 2004

Date of mailing of the international search report
21/09/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5816 Patentlaan 2 NL-2280 HT Rijswijk
Tel. (+31-70) 940–2040, Tx. 31 651 epo nl
Fax: (+31-70) 940–3016

Authorized officer
Fausti, S
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<tr>
<td>A</td>
<td>UNDHEIM K ET AL: &quot;Ru(II)-Catalyzed Ring Closing Metathesis in Stereoselective Spiroannulations and Cascade Reactions of Cyclic Dipeptide Substrates&quot; TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 56, no. 28, July 2000 (2000-07), pages 4847-4857, XP04208197 ISSN: 0040-4020 scheme 1(ii); scheme 2(iii); scheme 9(i)</td>
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| A        | HOFFMANN T ET AL: "Rational molecular design and EPC synthesis of a type VI beta-turn inducing peptide mimetic"  
ANGEW. CHEM. INT. ED.; ANGEWANDTE CHEMIE - INTERNATIONAL EDITION SEP 17 2001,  
vol. 40, no. 18,  
17 September 2001 (2001-09-17), pages 3361-3364, XP002258663  
scheme 2(e); page 3362, sentence joining left- and right-hand columns | 1-13 |