Title: PROCESS FOR THE PREPARATION OF A MACROCYCLE

Abstract: The present invention relates to a new process for the preparation of macrocyclic HCV protease inhibitor compounds of the formula (XXII) wherein R1 is an amino protecting group and X is halogen by way of a ring closing metathesis approach.
PROCESS FOR THE PREPARATION OF A MACROCYCLE

The present invention relates to a new process for the preparation of macrocyclic HCV protease inhibitor compounds of the formula

![Chemical Structure](attachment:image1.png)

wherein $R_1$ is an amino protecting group and $X$ is halogen.

Particularly the HCV protease inhibitor compound of the formula

![Chemical Structure](attachment:image2.png)

has been nominated for preclinical development.

Key step in the synthesis of the macrocyclic compounds of formula XXII is a ring closing metathesis (RCM) reaction of a diene compound in the presence of a suitable ring closing metathesis catalyst.

According to PCT Publication WO 2005/037214 or PCT Publication WO 2007/015824 a diene compound of the formula
is subjected to RCM in the presence of a Nolan or Hoveyda catalyst to form the macrocyclic ester of formula

The substitution of the hydroxy function is according the state of the art performed in a subsequent step.

It was found that the RCM as disclosed in the art suffer from a low performance of the reaction due to modest yields, low catalyst selectivity and the need to run the reaction with very low substrate concentrations, which translates into low efficiency and high costs.

Object of the present invention therefore was to find an improved process which is applicable on technical scale and which is able to overcome the disadvantages known in the art.

It was found that this object could be reached with the process of the present invention as outlined below.

The process for the manufacture of a macrocyclic compound of formula
wherein $R^1$ is an amino protecting group and $X$ is a halogen atom, comprises one or more of the steps

a) subjecting a diene compound of formula

$$\text{II}$$

wherein $R^1$ and $PG$ are amino protecting groups, $R^2$ is $Ci_4$-alkyl and is $X$ is halogen to ring; closing metathesis reaction in the presence of a ruthenium (II) carbene complex catalyst to form a macrocyclic ester of the formula

$$\text{I}$$

wherein $R^1$ and $PG$ are amino protecting groups, $R^2$ is $Ci_4$-alkyl and $X$ is halogen;

b) hydrolyzing the macrocyclic ester of formula I and removing the protecting group $PG$ to form the macrocyclic acid of the formula
wherein R₁ is an amino protecting group and X is halogen;
c) forming the macrocyclic sulfonamide of formula

d) treating the macrocyclic sulfonamide of formula XXI with a sodium base to form the macrocyclic compound of formula XXII.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "amino protecting group" refers to any substituents conventionally used to hinder the reactivity of the amino group. Suitable amino protecting groups are described in Green T., "Protective Groups in Organic Synthesis", Chapter 7, John Wiley and Sons, Inc., 1991, 309-385. Suitable amino protecting groups for R₁ are Fmoc, Cbz, Moz, Boc, Troc, Teoc or Voc. Preferred amino protecting group, as defined for R₁ is Boc. Suitable amino protecting group for PG is C₁-₆-alkylcarbonyl, arylcarbonyl or Cl-₆-alkoxycarbonyl, but preferably benzoyl.
The term "halogen" refers to fluorine, chlorine, bromine and iodine. The preferred halogen as a rule is chlorine, while the preferred halogen for X is fluorine.

In a preferred embodiment the moiety of the formula

\[
\begin{align*}
X \equiv & \text{halogen} \\
& \text{as a rule is chlorine, while the preferred halogen for X is fluorine.}
\end{align*}
\]

5 stands for

\[
\begin{align*}
& \text{halogen} \\
& \text{as a rule is chlorine, while the preferred halogen for X is fluorine.}
\end{align*}
\]

The term "Ci-6-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to six carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and pentyl or hexyl and its isomers.

The term "C1-4-alkyl" as used in herein for R² refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to four carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl, preferably to ethyl.

The term "C2-6-alkenyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent unsaturated aliphatic hydrocarbon radical of two to six carbon atoms, preferably two to four carbon atoms. This term is further exemplified by radicals as vinyl, propenyl, butenyl, pentenyl and hexenyl and their isomers. Preferred alkenyl radical is vinyl.

The term "C2-6-alkynyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent unsaturated aliphatic hydrocarbon radical of two to six carbon atoms, preferably two to four carbon atoms. This term is further exemplified by radicals as ethynyl, propynyl, butynyl, pentynyl or hexynyl their isomers.

The term "halogen-Ci_6-alkyl" refers to a halogen substituted Ci_6-alkyl radical wherein halogen has the meaning as above. Preferred "halogen-Ci_6-alkyl" radicals are the fluorinated Ci_6-alkyl radicals such as CF₃, CH₂CF₃, CH (CF₃)₂, CH (CH₃) (CF₃), C₄F₉.

The term "Ci-6-alkoxy" refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to six carbon atoms, preferably 1 to 4 carbon atoms attached to an oxygen atom. Examples of "alkoxy" are methoxy, ethoxy, propoxy, isopropoxy, butoxy,
isobutoxy, tert-butoxy and hexyloxy. Preferred are the alkoxy groups specifically exemplified herein.

The alkyl chain of the alkoxy group can optionally be substituted, particularly mono-, di- or tri-substituted by alkoxy groups as defined above, preferably methoxy, or ethoxy or by aryl groups, preferably phenyl. Preferred substituted alkoxy group is the benzyloxy group.

The term "Ci-6-alkyl carbonyl" refers to Ci-6-alkyl substituted carbonyl group, preferably to a Ci-4-alkycarbonyl group. It includes for example acetyl, propanoyl, butanoyl or pivaloyl. Preferred alkyl carbonyl group is acetyl.

The term "Ci-6-alkylthio" refers to the group Ci-6-alkyl-S-, preferably Ci-4-alkyl e.g. methylthio or ethylthio. Preferred are the alkylthio groups specifically exemplified herein.

The term "arylthio" refers to a group aryl-S-, preferably to phenylthio.

The term "Ci-6-alkylsulfonyl" refers to a Ci-6-alkyl substituted sulfonyl group, preferably to methylsulfonyl.

The term "Ci-6-alkylsulfinyl" refers to a Ci-6-alkyl substituted sulfinyl group, preferably to methylsulfinyl.

The term "SO₂- aryl" refers to a sulfonyl substituted aryl radical. Preferred SO₂-aryl radical is SO₂-phenyl.

The term "SO₂-NR’R” “ refers to a sulfonyl group substituted with an amino group NR’R” wherein R’ and R” independently of each other have the meaning of hydrogen or Ci-6-alkyl or R’ and R” together with the N atom form a carbocycle, eg. - (CH₂)₄- or -(CH)₄-. Preferred SO₂-NR’R” radical is SO₂-N (CH₃)₂.

The term "mono- or di-Ci-6-alkyl-amino" refers to an amino group, which is mono- or disubstituted with Ci-6-alkyl, preferably Ci-4-alkyl. A mono-Ci-6-alkyl-amino group includes for example methylamino or ethylamino. The term "di-Ci-6-alkyl-amino" includes for example dimethylamino, diethylamino or ethylmethylamino. Preferred are the mono- or di-Ci-4-alkylamino groups specifically exemplified herein. It is hereby understood that the term "di-Ci-6-alkyl-amino" includes ring systems wherein the two alkyl groups together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocycle which also may carry one further hetero atom selected from nitrogen, oxygen or sulfur.

The term "cycloalkyl" denotes a "C₃₋₇-cycloalkyl" group containing from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.
The term "aryl" relates to the phenyl or naphthyl group, which can optionally be mono-, di-, tri- or multiply-substituted by halogen, hydroxy, CN, halogen-C_i6-alkyl, NO_2, NH_2, N(H,alkyl), N(alkyl)2, carboxy, aminocarbonyl, alkyl, alkoxy, alkylcarbonyl, Ci_6-alkylsulfonyl, SO_2-aryl, SO_3H, SC(V)alkyl, SO_2-NR'R", aryl and/or aryloxy. Preferred aryl group usually is phenyl, however the preference for aryl may differ as indicated hereinafter for certain substituents.

The term "aryloxy" relates to an aryl radical attached to an oxygen atom. The term "aryl" has the meaning as defined above. Preferred aryloxy group is phenyloxy.

The term "arylalkyl" relates to an aryl radical attached to an alkyl group. The term "aryl" has the meaning as defined above. Preferred arylalkyl group is benzyl.

The term "arylcarbonyl" relates to an aryl radical attached to a carbonyl group. The term "aryl" has the meaning as defined above. Preferred arylcarbonyl group is benzoyl.

The term "heteroaryl" relates to a heterocyclic aryl radical containing 1 to 3 heteroatoms in the ring with the remainder being carbon atoms. Suitable heteroatoms include, without limitation, oxygen, sulfur, and nitrogen. Exemplary heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl, benzofuranyl, quinolinyl, and indolyl. Like the aryl group the heteroaryl group can optionally be mono-, di-, tri- or multiply-substituted by halogen, hydroxy, CN, NO_2, NH_2, N(H,alkyl), N(alkyl)2, carboxy, aminocarbonyl, alkyl, alkoxy, alkylcarbonyl, Ci_6-alkylsulfonyl, SO_2-aryl, SO_3H, SO_2-aryl, SO_2-aryl, SC(V)alkyl, SO_2-NR'R", aryl and/or aryloxy.

The diene starting compound of formula XV can be prepared following the scheme 1 below:
For example thevinylcyclopropanecarboxylate $\text{X}$ is treated withsulfuric acid to form $\text{XI}$, then coupled with Boc-(2S,4R)-hydroxyproline to form $\text{XII}$. Carbamate formation at the free OH group with 4-fluoroisoindoline leads to $\text{XIII}$ and removal of the Boc-protecting group and addition of the (5)-2-tert-Butoxycarbonylamino-non-8-enoic acid side chain can then provide diene $\text{XV}$.

The introduction of the N-substitution and the formation of the diene of formula II can be accomplished according to scheme 2 below:
Scheme 2:

For example diene XV is treated with a carboxylic acid anhydride in the presence of an alkali or alkali earth halogenide such as lithium chloride to introduce Ci-6-alkylcarbonyl substituents like acetyl or with a dialkyl dicarbonate in the presence of a base such as with 4-dimethylamino pyridine to introduce Ci-6-alkoxycarbonyl substituents like Boc.

The diene compounds of the formula
wherein R\textsuperscript{1} and PG are amino protecting groups, R\textsuperscript{2} is C\textsubscript{4}-alkyl and is X is halogen are compounds not known in the art and accordingly represent a further embodiment of the present invention.

Preferred are diene compounds of formula II wherein R\textsuperscript{1} is Boc, R\textsuperscript{2} is ethyl; PG is C\textsubscript{6}-alkylcarbonyl, arylcarbonyl or C\textsubscript{6}-alkoxycarbonyl and the moiety of the formula

Even more preferred is a diene compound of formula II wherein PG is benzoyl.

**Step a)**

Step a) requires the transformation of the diene compound of formula II via RCM reaction into the macrocyclic ester of formula I.

The RCM reaction is as outlined above performed with a ruthenium (II) carbene complex catalyst selected from compounds of the formula
wherein $L$, $L^1$ and $L^2$ are neutral ligands;

$X^1$ and $X^2$ independently of each other are anionic ligands;

$Y$ is hydrogen, $C_{1-6}$-alkyl, $C_2$-alkenyl or aryl, or $Y$ and $R^8$ taken together to form a $(CH=CR)$ - or a $(CH_2)_n$ bridge with $n$ having the meaning of 2 or 3 and $R$ is as defined for $R^4$;

$Y^1$ and $Y^2$ independently of each other are hydrogen, $C_{1-6}$-alkyl, $C_2$-alkenyl, $C_2$-alkynyl, $C_{1-6}$-alkythio, aryl, arylthio, $C_{1-6}$-alkylsulfonyl, $C_{1-6}$-alkylsulfinyl,

or

$Y^1$ and $Y^2$ taken together form a cycle of the type
with G being hydrogen or aryl;

or

Y and Y² together form a cumulenyl group of type

5

\[
\begin{align*}
&\text{Vla} \\
G - \text{C}^t - \text{Vla} \\
&\text{or} \\
&Y_\Lambda \text{ and } j \text{Y together form a cumulenyl group of type} \\
&\text{VIb VIc} \\
&Y^3 \text{ is hydrogen, Ci-6-alkyl,} \\
&\text{Ci-6-alkylsulfonyl, Ci-6-alkylsulfanyl;} \\
&\text{Y}^4 \text{ and Y}^5 \text{ independently of each other is hydrogen, Ci-6-alkyl, C3-8-cycloalkyl,} \\
&C_2-6-alkenyl, C_2-6-alkynyl, Ci-6-alkoxy, C_2-6-alkynoxy, aryloxy, \\
&Ci-6-alkoxycarbonyl, Ci-6-alkylthio, aryl, arylothio, Ci-6-alkylsulfonyl, Ci-6-alkylsulfanyl; \\
&R^a_1, R^a_2 \text{ and } R^a_3 \text{ independently of each other are C}_{1,6}-alkyl, C_3-7-cycloalkyl, aryl, heteroaryl or } R^a_1 \text{ and } R^a_2 \text{ or } R^a_2 \text{ and } R^a_3 \text{ or } R^a_1 \text{ and } R^a_3 \text{ form together a 1,5-bridged cyclooctyl group;} \\
&R^b \text{ is Ci-6-alkyl, C}_2-6-alkenyl, halogen- Ci-6-alkyl, C_2-6-alkynyl, aryl,} \\
&Ci-6-alkoxycarbonyl, Ci-6-alkylcarbonyl, mono-Ci-6-alkyl-or di-Ci-6-alkylamino,} \\
&Ci-6-alkylaminocarbonyl, Ci-6-alkylthio, Ci-6-alkylthiocarbonyl, Ci-6-alkylsulfonyl, Ci-6-alkylsulfanyl or} \\
&arylalkyl; \\
&R^3, R^4, R^5, R^6, R^7 \text{ and R}^8 \text{ independently of each other have the meaning of hydrogen, } C_{1,6}-\text{alkyl, halogen-Ci-6-alkyl, C}_2-6-\text{alkenyl, C}_2-6-\text{alkynyl, halogen-Ci-6-alkyl, Ci-6-alkoxy,} \\
&C_2-6-alkynoxy, C_2-6-alkynoxy, Ci-6-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro,} \\
&Ci-6-alkoxycarbonyl, amino, mono-Ci-6-alkyl-or di-Ci-6-alkylamino, halogen, thio,} \\
&Ci-6-alkylthio, arylothio, Ci-6-alkylsulfonyl, Ci-6-alkylsulfanyl, arylosulfonyl,} \\
&SO_3\text{H, Ci-6-alkylcarbonyl amino, aryl carbonyl amino, Ci-6-alkyl sulfonyl amino, aryl sulfonyl} \\
amino, halogen-Ci-6-alkyl sulfonyl amino, SO_3\text{Ci-6-alkyl or } OSi(Ci-6-alkyl)\text{3 and SO}_2\text{-NRR}'
wherein R’ and R” independently of each other have the meaning of hydrogen, aryl or C_i-6-alkyl or R’ and R'’ together with the N atom form a carbocycle;

a, b, c and d independently of each other have the meaning of hydrogen, C_i-6-alkyl, halogen-C_i-6-alkyl, C_2-6-alkenyl, C_2-6-alkynyl, halogen-C_i-6-alkyl, C_i-6-alkoxy, C_2-6-alkenyloxy, C_2-6-alkynloxy, C_6-alkylcarbonyl, aryl, hydroxy, aryloxy, nitro, Ci-6-alkoxycarbonyl, amino, mono-C_i-6-alkyl-or di-C_i-6-alkylamino, halogen, thio, Ci-6-alkythio, arylthio, Ci-6-alkylsulfonyl, Ci-6-alkylsulfanyl, arylsulfonyl, SO3H, Ci-6-alkylcarbonyl amino, aryl carbonyl amino, Ci-6-alkyl sulfonyl amino, aryl sulfonyl amino, halogen-Ci-6-alkyl sulfonyl amino, S0_3Ci-6-alkyl or OSi(Ci-6-alkyl)3 and SO_2NR’R” wherein R’ and R” independently of each other have the meaning of hydrogen, aryl or C_i-6-alkyl or R’ and R’” together with the N atom form a carbocycle;

Arene stands for phenyl or naphthyl optionally mono-, di-, tri- or multiply-substituted by halogen, hydroxy, cyano, halogen-C_i-6-alkyl, NO2, amino, mono-Ci-6-alkyl-or di-Ci-6-alkylamino, carboxy, amino carboxyl, C_i-6-alkyl, Ci-6-alkoxy, Ci-6-alkylcarbonyl, C_i-6-alkylsulfonyl, aryloxy SO_2-aryl, SO_3H, SO_3-C_i-6-alkyl , SO_2-NR’R” wherein R and R” independently of each other are hydrogen or C^Valkyl;

R_1^a is hydrogen, hydroxy, Ci-6-alkyl, C_i-6-alkoxy, C_2-6-alkenylxloxy, C_3-8-cycloalkyloxy, halogen- Ci-6-alkoxy, aryloxy, Ci-6-alkylthio, arylthio, or -NR \cdot R” wherein R’ and R” independently of each other are hydrogen, d-6-alkyl, C_3-8-cycloalkyl, aryl, aryl-Ci-6-alkyl or wherein R’ and R” together with the N atom form a 5 to 8 member carbocycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

R_2^a and R_3^a are independently of each other H, C^V-alkyl, C_3-8-cycloalkyl, aryl, C_{7,18}^- arylalkyl or

R_1^a and R_2^a or R_3^a together form a 5 to 12 member carbocycle

The ligand L is a neutral ligand preferably selected from

\[ P(R^a_1)(R^a_2)(R^a_3) \].

\[ \begin{array}{ccc}
\text{VII} & \text{VIII} & \text{IX} \\
\end{array} \]
wherein \(R^{10}\) and \(R^{11}\) independently of each other are \(\text{Ci}-6\text{-alkyl, aryl, C}_2\text{-6-alkenyl or 1-adamantyl and}\n\)
\(R^{9a-d}\) are independently of each other hydrogen, \(\text{Ci}_6\text{-alkyl, C}_2\text{-6-alkenyl or aryl, or R}^{9b}\) and \(R^{9c}\) or \(R^{9a}\) and \(R^{9d}\) taken together form \(\text{a-(CH}_2\text{)}_4\text{-bridge;}\n\)
or \(R^{9a}\) and \(R^{9d}\) in formula IX both have the meaning of halogen, preferably of chlorine;
\(R^{a1-a3}\) are as outlined above, but preferably cyclohexyl or phenyl.

In a preferred embodiment \(R^{10}\) and \(R^{11}\) are \(\text{Ci}-6\text{-alkyl or a phenyl group which is mono-, di- or tri-substituted with Ci}_6\text{-alkyl.}\n\)
\(R^{10}\) and \(R^{11}\) more preferably have the meaning of \(\text{t-butyl, 1-adamantyl, isopropyl, 2-methylphenyl, 2, 6-diisopropylphenyl or 2, 4, 6-trimethylphenyl, most preferably 2, 4, 6-trimethylphenyl.}\n
In a preferred embodiment \(R^{9a}\) and \(R^{9c}\) are methyl or phenyl and \(R^{9b}\) and \(R^{9d}\) are hydrogen, or \(R^{9a}\) and \(R^{9c}\) or \(R^{9b}\) and \(R^{9d}\) are taken together to form a -\(\text{-(CH}_2\text{)}_4\)-bridge with \(n\) having the meaning of 3 or 4. Its hereby understood that if chiral carbon atoms are present, both the racemic and the enantiomERICally pure form are comprised.

In a further preferred embodiment \(R^{9ad}\) is hydrogen.

In a further preferred embodiment \(L\) is

\[
\begin{align*}
\text{Vila} & \quad \text{Villa} \\
\end{align*}
\]

wherein \(R^{10}\) and \(R^{11}\) are as described above.

The anionic ligands \(X^1\) and \(X^2\) are preferably selected from a halogenide or a pseudo halogenide such as cyanide, a rhodanide, a cyanate, an isocyanate, acetate or trifluoroacetate may be selected.

Preferred anionic ligand for \(X^1\) and \(X^2\) is a halogenide, whereas chloro is the most preferred anionic ligand.

\(Y\) preferably is hydrogen;

\(Y^1\) and \(Y^2\) are the same or different and preferably stand for hydrogen, \(d\)-\(\text{6-alkyl, C}_2\text{-6-alkenyl, Ci}_6\text{-alkylthio, phenyl, phenylthio, or}\n\)
Y\(^1\) and Y\(^2\) taken together form a cycle of the type

![Diagram](image)

with G being hydrogen or phenyl;

Y\(^3\) preferably is hydrogen.

Y\(^4\) and Y\(^5\) are the same or different and preferably stand for hydrogen, C\(^\wedge\)-alkyl, aryl or arylthio.

R\(b\) is as outlined above, but preferably stands for C\(_{1-6}\)-alkyl and halogen-C\(_{1-6}\)-alkyl.

The preferred meaning for a, b and d is hydrogen.

The preferred meaning for c is hydrogen, halogen, nitro, C\(_{1-6}\)-alkyl carbonyl amino, aryl carbonyl amino, aryl sulfonyl amino, alkyl sulfonyl amino, halogen-C\(_{1-6}\)-alkyl sulfonyl amino, SO\(_2\)-NR'\(\cdot\)R" wherein R' and R" independently of each other have the meaning of hydrogen, C\(_1\), C\(_{1-6}\)-alkyl, aryl or R' and R" together with the N atom form a carbocycle.

More preferred c means hydrogen, Cl, nitro, SO\(_2\)-NR'\(\cdot\)R".

Preferred meaning for Arene is benzene, p-cymene, mesitylene or, p-xylene.

The following catalysts represent preferred ruthenium (II) carbene complex catalysts

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<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical 1" /></td>
<td>[RuCl$_2$(PCy$_3$)$_2$(benzylidene)]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical 2" /></td>
<td>[RuCl$_2$(PCy$_3$)(ImH$_2$Mes)(benzylidene)]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical 3" /></td>
<td>[RuCl$_2$(=CH(2-iPrOPh))(PCy$_3$)]</td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical 4" /></td>
<td>[RuCl$_2$(=CH(2-iPrOPh))(ImH$_2$Mes)]</td>
</tr>
<tr>
<td><img src="image5.png" alt="Chemical 5" /></td>
<td>[RuCl$_2$(PCy$_3$)$_2$(3-phenylindenyl-1-idene)]</td>
</tr>
<tr>
<td><img src="image6.png" alt="Chemical 6" /></td>
<td>[RuCl$_2$(PCy$_3$)(ImH$_2$Mes)(3-phenylindenyl-1-idene)]</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>$[\text{RuCl}_2(3\text{-phenyldienyl-1-idene})(\text{ImMes})(\text{PCy}_3)]$</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>$[\text{RuCl}_2(3\text{-phenyldienyl-1-idene})(\text{ImMes})(\text{PPh}_3)]$</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>$[\text{RuCl}_2(\text{-CH(2-iPrO, 5-ClPh)})(\text{ImH}_2\text{Mes})]$</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>$[\text{RuCl}_2(\text{-CH(7-CF}_3, 5\text{-Cl-8-quinoline)})-(\text{ImH}_2\text{Mes})]$</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure 5" /></td>
<td>$[\text{RuCl}_2(\text{-CHSPh}) (\text{ImH}_2\text{Mes})(\text{PCy}_3)]$</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure 6" /></td>
<td>$[\text{RuCl}_2(3\text{-phenyldienyl-1-idene)- (isobutylphobane)}_2]$</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CHPh})(\text{ImH}_2\text{Mes})(\text{m-Br-Pyr})_2])</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CH}(\text{o-OCH(CH}_3\text{)(C=O)}\text{CH}_3\text{)}\text{Ph})(\text{ImH}_2\text{Mes})])</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CH}(\text{o-OCH(\text{Me})CO}_2\text{Me})\text{Ph})(\text{ImH}_2\text{Mes})])</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CH}(\text{o-OCH(\text{Me})CO}_2\text{H})\text{-Ph})(\text{ImH}_2\text{Mes})])</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CH}(\text{o-OCH(\text{Me})CONe}_2\text{Ph})(\text{ImH}_2\text{Mes})])</td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td>([\text{RuCl}_2(=\text{CH}(\text{o-OCH(\text{Me})CONH}_2)\text{-Ph})(\text{ImH}_2\text{Mes})])</td>
</tr>
</tbody>
</table>
Even more preferred are:

\[ \text{[RuCl}_2(\text{ImMes})(\text{p-cymene})] \]

\[ \text{[RuCl}_2(\text{CH(o-OCH(Me)CO-N-Morpholine)Ph})(\text{ImH}_2\text{Mes})] \]

\[ \text{[RuCl}_2(\text{CH(o-OCH(Me)CO-N-Pyrrolidine)Ph})(\text{ImH}_2\text{Mes})] \]

\[ \text{[RuCl}_2(\text{CH(o-OCMe_2CO-N-Pyrrolidine)Ph})(\text{ImH}_2\text{Mes})] \]

\[ \text{[RuCl}_2(\text{CH(o-OCH}_2\text{CO-N-Pyrrolidine)Ph})(\text{ImH}_2\text{Mes})] \]

\[ \text{[RuCl}_2(\text{PCy}_3)(\text{ImH}_2\text{Mes})(\text{benzyldene})] \]

\[ \text{[RuCl}_2(\text{C}=\text{CH(l-IPrOPh))})(\text{ImH}_2\text{MeS})] \]

\[ \text{[RuCl}_2(\text{PCy}_3)(\text{ImH}_2\text{Mes})(3\text{-phenylindenyl-1-idene})] \]

\[ \text{[RuCl}_2(3\text{-phenylindenyl-1-idene})(\text{ImMes})(\text{PCy}_3)] \]

\[ \text{[RuC^=CH(O-OCH(Me)CO}_2\text{Me)PhXImH}_2\text{MeS}] \]
-20-

[RuCl₂C=CH(O-OCH(Me)CONEt₂)Ph](ImH₂MeS)],

[RuCl₂(=CH(o-OCH(Me)CO- N-Morpholine)Ph)(ImH₂Mes)],

[RuCl₂(=CH(o-OCH(Me)CO- N-Pyrrolidine)Ph)(ImH₂Mes)],

[RuCl₂(=CH(o-OCMe₂CO-N-Pyrrolidine)Ph) (ImH₂MeS)] and

[RuCl₂(=CH(o-OCH₂CO- N-Pyrrolidine)Ph)(ImH₂Mes)].

The RCM reaction is usually performed in an organic solvent, preferably in an aromatic organic solvent such as in benzene, toluene or mesitylene or in halogenated aromatic solvents such as in polyfluorinated benzenes or toluenes like α,α,α-trifluoro toluene, octafluoro toluene, 1,2-difluorobenzene or hexafluoro benzene. Also halogenated hydrocarbons such as dichloromethane or dichloroethane are suitable solvents. The solvents may be used as single solvent or as a mixture of different solvents. In addition a co-solvent selected from an aliphatic hydrocarbon such as pentane, hexane or heptane may be used as well.

The reaction temperature is as a rule selected in a range of 20°C to 140°C, preferably 40°C to 100°C and even more preferred 50°C to 90°C.

The molar substrate to catalyst ratio S/C is usually selected in a range of 20 to 10000, but preferably in a range of 150 to 4000.

The exact substrate concentration is not critical, it can be chosen in a very wide range between 0.1 and 25%. From a technical standpoint it is preferable to use a substrate concentration between 5 and 15%.

It is convenient to run the reaction either under bubbling of an inert gas through the reaction mixture or under a slight vacuum.

The macrocyclic ester of formula I can be isolated by applying methods known to the skilled in the art such as by column chromatography or by crystallization. The metathesis reaction mixture can also, after a simple extractive work-up, be brought directly into the next step.

In order to remove most catalyst from the solution of the macrocyclic ester I the reaction mixture can be treated with a complexing agent such as ethylenediamine and to extract the resulting soluble ruthenium species into acidic water. The amount of ethylenediamine is not critical; it can be used in a 1:1 to 100:1 molar ratio relative to the catalyst, preferentially in 20:1 to 70:1 molar ratio.
The macrocyclic esters of the formula

wherein \( R^1 \) and PG are amino protecting groups, \( R^2 \) is \( C_{i-4}\)-alkyl and X is halogen are compounds not known in the art and thus represent a further embodiment of the present invention.

In a preferred macrocyclic ester of formula I \( R^1 \) is Boc, \( R^2 \) is ethyl, PG is \( C_{1.6-} \)-alkylcarbonyl, arylcarbonyl or \( C_{i-6}\)-alkoxycarbonyl and the moiety of the formula

stands for

In a further preferred macrocyclic ester of formula I PG is benzoyl.

Step b)

Step b) requires the hydrolysis of the ester and the removal of the protection group PG of the macrocyclic ester of formula I and the formation of the macrocyclic acid of formula XX.

In a preferred embodiment the macrocyclic ester of the formula...
wherein $R^1$ is Boc, $R^2$ is ethyl, $PG$ is d-6-alkylcarbonyl, arylcarbonyl or C$_{1-6}$-alkoxycarbonyl and the moiety of the formula stands for

is used. In an even more preferred embodiment $PG$ is benzoyl.

The hydrolysis and the removal of the protection group $PG$ can usually be accomplished by treatment with an aqueous alkali hydroxide solution such as with an aqueous sodium hydroxide solution in solvents like tetrahydrofuran, methanol or ethanol or mixtures thereof at a temperature of 0°C to 40°C.

In the case of $PG = C_{i-6}$-alkoxycarbonyl its removal can usually be accomplished by treatment with an acid, such as with hydrochloric acid, sulfuric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid. As the acid treatment may remove the Boc-group $R^1$ as well reintroduction of this Boc group $R^1$ may be necessary for performing the subsequent synthesis steps.

After neutralization of the reaction mixture, usually with hydrochloric acid, the macrocyclic acid of formula XX can be isolated by way of extraction with a suitable solvent such as with dichloromethane. Crystallization in a suitable solvent, preferably in tetrahydrofuran leads to a crystalline product with a purity of over 98% (HPLC, area).
In a further preferred embodiment of the invention the macrocyclic acid of formula XX can be obtained directly without isolation of the intermediate products from the intermediate of formula XIVa.

Scheme 3:

\[ \text{XIVa} \]

\[ \text{XX} \]

\( R^1, R^2 \) and \( X \) have the meaning as mentioned above.

Step c)

Step c) requires the coupling of the macrocyclic acid of formula XX with cyclopropyl sulfonamide to form the macrocyclic sulfonamide of formula XXI.

In a preferred embodiment the macrocyclic acid of the formula

\[ \text{XXb} \]

is used.

In a first step the macrocyclic acid of formula XX is reacted with acetic acid anhydride in the presence of an inorganic base, such as with an alkali carbonate like sodium carbonate and a suitable organic solvent such as with tetrahydrofuran into an azlactone intermediate of the formula
wherein $R^1$ is an amino protecting group and $X$ is halogen.

The reaction is expediently performed at a temperature of $10^\circ$C to $50^\circ$C.

As a rule the azlactone intermediate will not be isolated but in situ further reacted with cyclopropyl sulfonamide in the presence of an inorganic base, such as with an alkali carbonate like potassium carbonate to the macrocyclic sulfonamide of formula XXI.

The reaction in this second step is expediently performed at a temperature of $50^\circ$C to $70^\circ$C.

Upon completion of the reaction the reaction mixture can be treated with water. After separation and removal of the water phase the organic phase may further be diluted with a suitable organic solvent such as with ethyl acetate or toluene and washed e.g. with an aqueous sulphuric acid and water.

Isolation of the macrocyclic sulfonamide of formula XXI can then be accomplished by a solvent switch to ethanol followed by addition of the ethanolic solution to water thereby causing precipitation of the desired product.

However, in a preferred embodiment the macrocyclic sulfonamide of formula XXI will not be isolated, but the organic phase which has been treated as hereinbefore described will be freed of residual water by way of a continuous azeotropic distillation.

The mixture can then directly be used for subsequent step d).

**Step d)**

Step d) requires the treatment of the macrocyclic sulfonamide of formula XXI with a sodium base to form the end product, i.e. the macrocyclic compound of formula XXII.

In a preferred embodiment the macrocyclic sulfonamide of the formula
is used.

As a rule the water free mixture obtained from step c) is treated with a sodium base such as sodium hydroxide, preferably an aqueous solution thereof, sodium methylate or sodium ethoxide, preferably with sodium methylate in the presence of methanol at a temperature of 0°C and 50°C.

Upon completion of the reaction the reaction mixture can be treated with a mixture of a suitable organic solvent such as ethyl acetate and water where after the crystals of the sodium compound of formula XXII, preferably the compound of formula XXIIb can be collected in good purity and yield.
Abbreviations:

r.t. = room temperature

ImH$_2$MeS = 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene
ImMes = 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolylidene
ImH$_2$Pr = 1,3-bis-(2,6-diisopropylphenyl)-2-imidazolidinylidene
RCM = ring closing metathesis
S/C = molar substrate-to-catalyst ratio

Mes = 2,4,6-Trimethylphenyl

a% = HPLC area%

Diene XV: 4-Fluoro-1,3-dihydro-isouindole-2-carboxylic acid, (3i?,55)-l-[((5)-2-tert-butoxy-carbonylamino-non-8-enoyl]-5-[(S)-2,5-ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester.

N-acetyl-Diene lib: 4-Fluoro-1,3-dihydro-isouindole-2-carboxylic acid (3i?,55)-5-[acetyl-((S)-2,5-ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl]-1-((S)-2-tert-butoxycarbonylamino-non-8-enoyl)-pyrrolidin-3-yl ester

N-propionyl-Diene He: 4-Fluoro-1,3-dihydro-isouindole-2-carboxylic acid (3i?,55)-l-((5)-2-tert-butoxycarbonylamino-non-8-enoyl)-5-[(S)-2,5-ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

N-BOC -Diene Ha: 4-Fluoro-1,3-dihydro-isouindole-2-carboxylic acid ($3R,55$)-1-((S)-2-tert-butoxycarbonylamino-non-8-enoyl)-5-[(S)-2,5-ethoxycarbonyl-((S)-2-tert-butoxycarbonyl-2-vinyl-cyclopropyl)-aminocarbonyl]-pyrrolidin-3-yl ester

N-Benzoyl-Diene Hd:
4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3i?,55)-5-[benzoyl-((li?,25)-l-
ethoxycarbonyl-2-vinyl-cyclopropyl)-carbamoyl]-l-((5)-2-tert-butoxycarbonylamino-non-8-
enoyl)-pyrrolidin-3-yl ester

N-Acetyl-RCM-Ester Ib: (Z)-(15',4i?,65',14,S',18i?)-3-Acetyl-14-tert-butoxycarbonylamino-18-(4-
fluoro-1,3-dihydro-isoindole-2-carbonyloxy)-2,15-dioxo-3,16-diaza-
tricyclo[14.3.0.0^4^6]nonadec-7-ene-4-carboxylic acid ethyl ester.

The atom numbering is shown below:

![Structure diagram]

N-Propionyl-RCM-Ester Ic: (Z)-(1S,4R,6S,14S,18i?)-14-tert-Butoxycarbonylamino-18-(4-fluoro-1,3-dihydro-isoindole-2-
carbonyloxy)-2,15-dioxo-3-propionyl-3,16-diaza-tricyclo[14.3.0.0^4^6]nonadec-7-ene-4- 
carboxylic acid ethyl ester.

N-BOC- RCM-Ester-Ia: (Z)-(1S,4R,6S,14S,1SR)-14-tert-Butoxycarbonylamino-18-(4-fluoro-1,3-dihydro-isoindole-2-
carbonyloxy)-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^4^6]nonadec-7-ene-3,4-dicarboxylic acid 3-
tert-butyl ester 4-ethyl ester.

N-Benzoyl-RCM-Ester Id: (Z)-(1S,4R,6S,14S,18i?)-3-Benzoyl-14-tert-butoxycarbonylamino-18-(4-fluoro-1,3-dihydro-
isoindole-2-carbonyloxy)-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^4^6]nonadec-7-ene-4-carboxylic acid ethyl ester.

RCM-Carboxylic Acid XXb: (Z)-(1S,4R,6S,14S,1ZR)-14-tert-Butoxycarbonylamino-18-(4-fluoro-1,3-dihydro-isoindole-2-
carbonyloxy)-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^4^6]nonadec-7-ene-4-carboxylic acid.

RCM-Ester XVI:
(Z)-(1S,4R,6S,1AS,1%R)-14-tert-Butoxycarbonylamino-18-(4-fluoro-1,3-dihydro-isoindole-2-carbonyloxy)-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^4^6]nonadec-7-ene-4-carboxylic acid ethyl ester.
Table of Catalysts tested:

<table>
<thead>
<tr>
<th>Catalyst Number</th>
<th>Catalyst Structure</th>
<th>Chemical Short Name</th>
</tr>
</thead>
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<tr>
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<td><img src="" alt="Image" /></td>
<td>[RuCl₂(PC₃)(benzylidene)]&lt;br&gt;CAS No. 172222-30-9; a)</td>
</tr>
<tr>
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</tr>
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</tr>
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<tr>
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<td>[RuCl₂(PC₃)(3-phenylindenyl-1-idene)]&lt;br&gt;CAS No. 250220-36-1; c)</td>
</tr>
<tr>
<td>5008</td>
<td><img src="" alt="Image" /></td>
<td>[RuCl₂(PC₃)(ImH₂Mes)(3-phenylindenyl-1-idene)]&lt;br&gt;CAS No. 536724-67-1; c)</td>
</tr>
</tbody>
</table>
5016 \[\text{MesN} \quad \text{Nmes} \quad \text{Cl} \quad \text{Ru} = \text{Ph} \quad \text{Cl} \quad \text{PCy}_2\] \[\text{[RuCl}_2(3\text{-phenylindenyl-1-idene})(\text{ImMes})(\text{PCy}_3)]\] CAS No. 254972-49-1; d)

5017 \[\text{MesN} \quad \text{Nmes} \quad \text{Cl} \quad \text{Ru} = \text{Ph} \quad \text{Cl} \quad \text{PPh}_3\] \[\text{[RuCl}_2(3\text{-phenylindenyl-1-idene})(\text{ImMes})(\text{PPh}_3)]\] CAS No. 254972-47-9; d)

5024 \[\text{MesN} \quad \text{Nmes} \quad \text{Cl} \quad \text{Ru} = \text{O} \quad \text{Cl} \quad \text{C}_2\] \[\text{[RuCl}_2(=\text{CH(2-iPrO, 5-ClPh)})(\text{ImH}_2\text{Mes})]\] CAS No. 918870-68-5; b)

5025 \[\text{MesN} \quad \text{Nmes} \quad \text{Cl} \quad \text{Ru} = \text{F}_2\text{C} \quad \text{Cl} \quad \text{N}_2\] \[\text{[RuCl}_2(=\text{CH(7-CF}_3, 5-\text{Cl-8-quinoline})\text{-}(\text{ImH}_2\text{Mes})]\] e)

5040 \[\text{MesN} \quad \text{Nmes} \quad \text{Cl} \quad \text{Ru} = \text{S} \quad \text{Cl} \quad \text{PCy}_3\] \[\text{[RuCl}_2(=\text{CHSPh})(\text{ImH}_2\text{Mes})(\text{PCy}_3)]\] g)

5041 \[\text{Cl} \quad \text{Ru} = \text{Ph} \quad \text{Cl} \quad \text{P}\] \[\text{[RuCl}_2(3\text{-phenylindenyl-1-idene)-(isobutylphobane)}_2]\] CAS No. 894423-99-5; c)
| 5047 | \[
\text{[RuCl}_2\text{(=CHPh)(ImH}_2\text{Mes})(\text{m-Br-Pyr})_2]\]
CAS No. 477218-66-9; a) |
| 5055 | \[
\text{[RuCl}_2\text{(=CH((o-OCH(CH}_3\text{))(C=O)CH}_2\text{)Ph)(ImH}_2\text{Mes})]\]
Prepared according to WO 2008/034552 A1 |
| 5056 | \[
\text{[RuCl}_2\text{(=CH(o-OCH(Me)CO}_2\text{Me)Ph)(ImH}_2\text{Mes})]\]
CAS No. 837392-94-6
| 5057 | \[
\text{[RuCl}_2\text{(=CH(o-OCH(Me)CO}_2\text{H)Ph)(ImH}_2\text{Mes})]\]
CAS No. 959710-27-1
| 5058 | \[
\text{[RuCl}_2\text{(=CH(o-OCH(Me)CONEt}_2\text{)Ph)(ImH}_2\text{Mes})]\]
f) |
| 5059 | \[
\text{[RuCl}_2\text{(=CH(o-OCH(Me)CONH}_2\text{)Ph)(ImH}_2\text{Mes})]\]
f) |
a) Commercially available from Sigma-Aldrich Chemie GmbH, Postfach, CH-9471 Buchs, Switzerland:

b) Commercially available from Zannan Pharma Ltd. 4299 Jindu Road, Bid. 3, Shanghai, 201 108, P.R. China and Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA 01950-4098, USA.

c) Commercially available from Umicore & Co., Rodenbacher Chaussee 4, D-63403 Hanau, Germany and Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA 01950-4098, USA.

d) Commercially available from Degussa AG, Rodenbacher Chaussee 4, D-63403 Hanau, Germany.

e) Prepared according to WO2008/000644 Al.
f) Prepared according to EP Appl. No. 08154367.0, filed April 11, 2008.
g) Commercially available from Strem Chemicals, Inc., Postfach 1215, KEHL, 77672, Germany.

Preparation of diene compounds Ha to Hd:

5 Example A

To a solution of the diene XV (40.0 g, 53.80 mmol, 92.1% content) in 330 ml of tetrahydrofuran were added under argon 22.70 ml (163.5 mmol) of triethylamine, 6.90 g (161.6 mmol) of lithium chloride and 15.0 ml (159 mmol) of acetic anhydride and the mixture was stirred at 60°C (internal temperature) during 6 h, after which time only 2 area% of diene XV had remained unreacted. The slightly cloudy reaction mixture was cooled, filtered and the precipitate washed with tetrahydrofuran. The combined filtrates were rotary evaporated to dryness (40°C/180 mbar). The oily residue was dissolved in 500 ml of ethyl acetate and extracted with 300 ml of hydrochloric acid 0.5 M. The aqueous phase was back-extracted with a total of 1 L ethyl acetate. The combined organic phases were washed with 300 ml of hydrochloric acid, 300 ml of deionized water, then dried with 70 g of sodium sulfate and filtered. The filtrate was treated with decolorizing charcoal, filtered and rotary evaporated. The oily residue was purified by column chromatography (1 kg silica gel 0.040-0.063 mm) and eluted with a mixture of heptane and ethyl acetate using a gradient from 9:1 to 3:2. Collection of the fractions containing the desired product in comparable purity and evaporation to dryness to constant weight (40°C/16 mbar/3 h) afforded 27.6 g of diene-acetate lib as a white solid with 96 area% according to HPLC and 85% according to NMR.

HPLC method: same as Example 1. Retention times: diene XV 8.66 min, diene-acetate lib 10.1 min.

MS [MH]+ 657.4 u, 727.4 [MNH₂]⁺.

NMR (selected peaks, δ CDCl₃): (CH₃C=O) 2.26 (s, 3H), (CH₂=CH₂) 1.22 (t, 3H), (CH₃-CH₂) 4.13 (m, 2H), (t-Bu) 1.33 (s, 9H).

IR: Carbonyl signals at 1710 cm⁻¹ (strong, broad), 1632 cm⁻¹ (medium, broad).
Example B

To a solution of the diene XV (15.3 g, 22 mmol) in 120 mL of tetrahydrofuran were added under argon 6.8 g (67 mmol) of triethylamine, 2.9 g (67 mmol) lithium chloride and 6.4 g (49 mmol) of propionic acid anhydride. The mixture was heated to 80°C for 10 h 30 min and then cooled to room temperature at which it was stirred for another 1 h. After this time in-process control showed 99.6 % (HPLC) conversion. To the mixture 100 mL water and 3.5 mL aqueous HCl (37%) were added. The biphase mixture was extracted with ethyl acetate, the aqueous layer was separated off and the organic layer was washed with 100 mL of brine. The aqueous layers were back extracted with 200 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness. 26.8 g of an oily brown residue was obtained. The oily residue was purified by column chromatography (600 g silica gel 0.040-0.063 mm) and eluted with a mixture of hexane and ethyl acetate using a gradient from 7:3 to 7:4.

Collection of the fractions containing the desired product in comparable purity and evaporation to dryness afforded 16.8 g of Hc as a colorless solid with a purity of 97.6 area % according to HPLC.

HRMS, [MH]+ 785.41315.

NMR (δ, DMSO-D6, 150°C): 1.09 (t, 3H), 1.15 (t, 3H), 1.30 (s, 9H), 1.3-1.4 (m, 6H), 1.52 (m, IH), 1.60-1.69 (m, IH), 1.74-1.82 (m, IH), 1.92-1.95 (m, IH), 1.99-2.04 (m, 2H), 2.21-2.27 (m, IH), 2.41 (m, IH), 2.48-2.56 (m, IH), 2.61-2.71 (m, IH), 3.81 (m, IH), 3.89 (d, br, IH), 4.09 (q, 2H), 4.17 (q, br, IH), 4.66 (s, 4H), 4.90 (m, IH), 4.96 (m, IH), 5.14 (m, IH), 5.16-5.33 (m, 3H), 5.74-5.85 (m, 2H), 6.0 (s, br, IH), 7.01 (M, IH), 7.11 (d, IH), 7.30 (m, IH).

IR (selected absorptions, cm⁻¹): 3294, 2980, 2934, 1705, 1631, 1596, 1518, 996, 911, 776.
Example C:

To a solution of the diene XV (15.3 g, 22 mmol) in 90 mL of ethyl acetate were added under argon 0.82 g (6.7 mmol) of 4-dimethylamino pyridine. The mixture was cooled to 0°C and 6.9 g (31 mmol) of di-tert-butyl dicarbonate were added within 5 minutes. The reaction mixture was heated to 23°C an stirred at this temperature for 225 minutes. After this time only 3.8 area% of diene XV had remained unreacted. To the mixture 50 mL of 0.1 N aqueous HCl were and 50 mL of ethyl acetate were added. The aqueous phase was separated and extracted with 100 mL of ethyl acetate. The organic layer was washed with 50 mL of water, dried over sodium sulfate, filtered and concentrated. 21.1 g of a brown oily residue was obtained. The oily residue was purified by column chromatography (silica gel 0.040-0.063 mm) and eluted with a mixture of hexane and ethyl acetate using a gradient from 8:2 to 7:3. Collection of the fractions containing the desired product in comparable purity and evaporation to dryness afforded 17.3 g of N-BOC-diene Ha as a yellowish solid with 98.5 area% according to HPLC.

HRMS, [MH]+ 785.41315.

NMR (δ, DMSO-D6, 120°C): 1.15 (t, 3H), 1.28 (s, 9H), 1.25-1.40 (m, 6H), 1.47 (s, 9H), 1.52 (m, IH), 1.62 (m, IH), 1.79 (m, IH), 2.01 (m, 2H), 2.23 (m, IH), 2.29 (m, IH), 1.48-2.55 (m, 2H), 3.82 (m, IH), 4.0 (m, IH), 4.06 (m, 2H), 4.14 (m, IH), 4.66 (s, 4H), 4.90 (m, IH), 5.30 (m, 6H), 5.78 (m, 2H), 6.25 (s, br, IH), 7.03 (m, IH), 7.12 (d, IH), 7.31 (m, IH). IR (selected absorptions, cm⁻¹): 3289, 1719, 1634, 1523, 1019, 997, 776.
Example D:

To a solution of the diene XV (30.0 g, 41.67 mmol) in 200 ml of toluene were added under argon in an ice bath 7.20 ml (79.2 mmol) of benzoyl chloride. Then a 2 M solution of lithium tert-butoxyde in tetrahydrofuran (38.5 ml, 77.0 mmol) was added within 5 minutes and the reaction mixture was stirred at the same temperature for 30 minutes. After this time only 4.6 area% of diene XV had remained unreacted. After dropwise addition of a 2 M sodium hydroxide solution (50 ml, 100 mmol) the organic phase was separated, extracted with 50 mL each of water, 1 M hydrochloric acid and water, dried with sodium sulphate and evaporated to dryness. The resulting brown oily residue was purified by column chromatography (silica gel 0.040-0.063 mm) and eluted with a mixture of heptane and ethyl acetate using a gradient from 3:1 to 1:1. Collection of the fractions containing the desired product in comparable purity and evaporation to dryness afforded 26.8 g (78.2%) of N-benzoyl-diene Hd as a yellowish solid with 96.0 area% according to HPLC.

HRMS: [MH] + 789.3858.

IR (nujol, cm⁻¹, selected signals): 1708, 1640 (C=O)
RCM Examples:
Comparison example A (RCM with no N-substitution)

To a solution of 6.60 g (5.00 mmol) of diene XV (as a 51.4% solution in toluene) in 390 ml of toluene was added at 70°C under vacuum (pressure = ca. 0.26 bar) by dropping funnel a solution of 3.59 mg (0.005 mmol) of catalyst 5058 in 20 ml of toluene. The catalyst was added during ca. 1 h. Under these conditions a small amount of toluene (19 ml) distilled off in the course of the reaction. After 2 h of total reaction time 17 µl (0.252 mmol) of ethylene diamine were added at ambient pressure, the reaction mixture was concentrated under vacuum, washed with 0.5 M aqueous solution of hydrochloric acid, treated with decolorizing charcoal and evaporated to dryness. RCM-ester XVI was isolated as an off-white solid (3.58 g) with 84.2 a% purity (75.7% content, 82.5% yield).

Example 1 (S/C 20)

In a glove-box (O₂ < 2 ppm) a solution of 60.0 mg (0.070 mmol, corrected by content) of N-acetyl-diene lib and 2.32 mg (0.0035 mmol) of catalyst 5024 in 1.7 ml of toluene (washed with aqueous hydrochloric acid and distilled under argon) was stirred at 60°C in a 15 ml screw-capped flask. After 1.5 h one drop of ethylenediamine was added and the mixture was stirred for ca. 30 min outside of the glove box. After addition of 1 ml of 1 M aqueous solution of hydrochloric acid the biphasic mixture was stirred for ca. 5 min. A 0.5 ml aliquote of the organic
phase was removed and evaporated to dryness; the oily residue was dissolved in 1 ml of acetonitrile and analyzed by HPLC. Conversion was 99.6 area%, the desired product (N-acetyl-RCM-ester Ib) had 89 area % purity.

HPLC method for the determination of conversion and selectivity: Waters XBridge C18 column, 4.6 x 150 mm, solvent A: water/acetonitrile 95/5, solvent B: acetonitrile, solvent C: buffer Bu₄N+HSO₄ pH 3 (1 g in 1 l water/ acetonitrile 9:1), gradient from A/B/C 50/40/10 to 10/80/10 within 6.5 min, then 14 min isocratic, 40°C, 210 nm, 1 ml/min. Retention times: toluene 6.0 min, diene-acetate lib 10.0 min, N-acetyl-RCM-ester Ib 8.65 min (identified by HPLC/MS, [MH]+ 699.4 u), peaks of dimeric by-products at 13.3, 13.8 and 15.6 min (HPLC-MS: [MH]+ 1396 and 1423 u).

Only the sum of the dimer peaks is given in the tables and experiments.

Examples 2a-2o

The examples in Table 1 were carried out using the same procedure and conditions as in Example 1, but in the presence of various catalysts.

Table 1

<table>
<thead>
<tr>
<th>Reaction Nr.</th>
<th>Catalyst Nr.</th>
<th>N-Acetyl-Diene lib (area%)</th>
<th>N-Acetyl-RCM-ester Ib (area%)</th>
<th>Dimers (area%)</th>
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<td>2a</td>
<td>5000</td>
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<td>4.4</td>
</tr>
<tr>
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<td>&lt;0.1</td>
<td>81</td>
<td>2.9</td>
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<td>11.3</td>
<td>61</td>
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<td>73</td>
<td>0.3</td>
</tr>
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<td>55</td>
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<tr>
<td>2j</td>
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<td>89</td>
<td>1.6</td>
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<td>2l</td>
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<td>90</td>
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<td>2m</td>
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<td>0.6</td>
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<td>5062</td>
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</tr>
<tr>
<td>2o</td>
<td>5065</td>
<td>0.5</td>
<td>89</td>
<td>3.0</td>
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</table>
Example 3 (S/C 18):

In a glove-box (O₂ < 2 ppm) a solution of 60.0 mg (0.070 mmol, corrected by content) of N-propionyl-diene Hc and 2.49 mg (0.0038 mmol) of catalyst 5024 in 1.7 ml of toluene (washed with aqueous hydrochloric acid and distilled under argon) was stirred at 60°C in a 15 ml screw-capped flask. After 1.5 h one drop of ethylenediamine was added and the mixture was stirred for ca. 30 min outside of the glove box. After addition of 1 ml of 1 M aqueous solution of hydrochloric acid the biphasic mixture was stirred for ca. 5 min. A 0.5 ml aliquote of the organic phase was removed and evaporated to dryness; the oily residue was dissolved in 1 ml of acetonitrile and analyzed by HPLC. Conversion was >99.5 area%, the desired product (N-propionyl-RCM-ester Ic) had 86 area % purity.

HPLC method for the determination of conversion and selectivity: same as Example 1. Retention times: toluene 6.0 min, N-propionyl-diene Hc 10.7 min, N-propionyl-RCM-ester Ic 9.2 min (identified by HPLC/MS, [MH]+ 713.3 u), peaks of dimeric by-product at 17.4 min. (MS: [MH]+ 1426.6 u), peaks of unknown by-products at 12.3 min (MS: 768), 14.0 and 16.7 (complex MS spectrum).

NMR: (δ DMSO-D₆, 120°C): 1.07 (t, 3H), 1.14 (t, 3H), 1.23 (s, 9H), 1.26-1.48 (m, 6H), 1.71-1.80 (m, IH), 1.84-1.90 (m, 2H), 1.96-2.03 (m, IH), 2.11-2.23 (m, 2H), 2.34-2.44 (m, IH), 2.61-2.68 (m, 2H), 2.70-2.82 (m, IH), 3.86 (m, IH), 4.02-4.22 (m, 5H), 4.66 (s, 4H), 5.08 (t, IH), 5.30 (m, 2H), 5.49 (m, IH), 6.22 (s, br, IH), 7.03 (m, IH), 7.12 (m, IH), 7.31 (m, IH).

IR (selected absorptions, cm⁻¹): 3286, 1711, 1627, 1523, 1366, 1249, 778.
Examples 4a-4o

The examples in Table 2 were carried out using the same procedure and conditions as in Example 3, but in the presence of various catalysts.

Table 2

<table>
<thead>
<tr>
<th>Reaction Nr.</th>
<th>Catalyst Nr.</th>
<th>N-Propionyl-Diene IIC (area%)</th>
<th>N-Propionyl-RCM-ester Ic (area%)</th>
<th>Dimers (area%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>5000</td>
<td>19.6</td>
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<tr>
<td>4b</td>
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<td>87.8</td>
<td>2.0</td>
</tr>
<tr>
<td>4c</td>
<td>5002</td>
<td>18.9</td>
<td>26.9</td>
<td>2.4</td>
</tr>
<tr>
<td>4d</td>
<td>5003</td>
<td>&lt;0.1</td>
<td>85.5</td>
<td>2.0</td>
</tr>
<tr>
<td>4e</td>
<td>5006</td>
<td>18.6</td>
<td>22.8</td>
<td>1.5</td>
</tr>
<tr>
<td>4f</td>
<td>5017</td>
<td>1.4</td>
<td>73.6</td>
<td>1.7</td>
</tr>
<tr>
<td>4g</td>
<td>5025</td>
<td>35.6</td>
<td>10.7</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4h</td>
<td>5040</td>
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<td>40.8</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4i</td>
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<td>37.9</td>
<td>4.1</td>
</tr>
<tr>
<td>4j</td>
<td>5047</td>
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<td>1.0</td>
</tr>
<tr>
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<td>2.1</td>
</tr>
<tr>
<td>4l</td>
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<td>1.8</td>
</tr>
<tr>
<td>4m</td>
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</tr>
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<td>4n</td>
<td>5062</td>
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<td>&lt;0.1</td>
</tr>
<tr>
<td>4o</td>
<td>5065</td>
<td>&lt;0.1</td>
<td>83.7</td>
<td>1.9</td>
</tr>
</tbody>
</table>
**Example 5: (S/C 533. cone. ca. 14%)**

A solution of 15.7 g (20 mmol) of N-BOC-diene Ha in 115 ml of toluene was heated to 60°C. At this temperature 14.3 mg of catalyst 5024 dissolved in 5.9 mL of toluene was dosed within 1 h to the reaction mixture; an in process control showed complete conversion after dosing was completed (Ha n.d.). During the reaction the mixture was purged with nitrogen (150 ml/min). To the reaction mixture 118 mg of ethylene diamine was added. It was cooled to room temperature and 40 mL of 0.5 N aqueous HCl were added. The phases there separated and the aqueous layer was extracted with 100 mL of toluene. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to dryness to obtain 18.5 g of raw product. Purification was achieved by column chromatography (silica gel 0.040-0.063 mm) with a mixture of hexane and ethyl acetate using a gradient of 8:2 then 7:3 and 6:4. Fractions containing the desired product in comparable purity were collected, concentrated and recrystallized from ethyl acetate. Drying under reduced pressure afforded 11.6 g of colorless crystals (98.6 area % HPLC) and 2.9 g of residue from concentrated mother liquor (95.5 area % HPLC) giving a yield of 93 %.

**HRMS, [MH]** + 757.38174

**NMR** (selected peaks, δ, DMS-D6, 120°C): 1.15 (t, 3H), 1.24 (s, 9H), 1.29-1.46 (m, 6H), 1.49 (s, 9H), 1.62 (m, IH), 1.73 (m, 2H), 1.99-2.24 (m, 4H), 2.50-2.60 (m, 2H), 3.87 (m, IH), 4.06 (q, 2H), 4.17 (m, 2H), 4.67 (s, 4H), 5.20 (m, IH), 5.30 (m, IH), 5.33 (m, IH), 5.46 (m, IH), 6.20 (d, br, IH), 7.03 (m, IH), 7.12 (d, IH), 7.31 (m, IH).

IR (selected absorptions, cm⁻¹): 3361, 1739, 1692, 1519, 1370, 1175, 792.

**Example 6 (S/C 1000. cone. = 8%)**

A solution of 5.00 g (6.67 mmol) of N-acetyl-diene lib in 70 ml of toluene was extracted twice with 15 ml HCl 0.5 mol/l and rotary concentrated to a total weight of 40.2 g (corresponds to a 8% weight/weight concentration). To this solution was added at 70°C under vacuum (pressure = ca. 0.26 bar) by dropping funnel a solution of 4.75 mg (0.0067 mmol) of catalyst 5058 in 10 ml of toluene. The catalyst was added during 1 h. Under these conditions a small amount of toluene
(ca 10 ml) distilled off in the course of the reaction. After 1.5 h of total reaction time 23 µl (0.34 mmol) of ethylenediamine were added at ambient pressure, the reaction mixture was concentrated under vacuum, washed with 0.5 M aqueous solution of hydrochloric acid, treated with 10 ml ethyl acetate and 0.41 g of charcoal and stirred for 30 min, filtered and evaporated to dryness. N-Acetyl-RCM-ester Ib was isolated as yellow foam (5.07 g).

HPLC analysis showed Ib (89.2 area%), 0.2 area% lib and 7.7 area% dimers (identified by HPLC/MS). The content by HPLC with internal standard was 83.5%, which corresponds to 90.8% yield.

HPLC method for content determination: Gemini C6-Phenol column, 4.6 x 150 mm, 3.0 µm, solvent A: water/acetone 95/5, solvent B: buffer Bu₄N+HSO₄⁻ pH 3 (1g in 1 l water/acetone 9:1); solvent C: acetone gradient from A/B/C 25/5/70 to 15/5/80 within 1.0 min, then 4 min isocratic, 45°C, 210 nm, 2.3 ml/min. Retention times: N-acetyl-diene lib 1.88 min, N-acetyl-RCM Ib 2.18 min, int. standard dinitrobenzene (1 g/1 acetone) 10.3 min.

MS: [MH]+ 699.4;

NMR (selected peaks, δ CDCl₃: (CH₂C=O) 2.27 (s, 3H), (CH₂-CH₂) 1.23 (t, 3H), (CH₃-CH₂) 4.14 and 4.22 (m, 1H each), (t-Bu) 1.27 (s, 9H).

IR: carbonyl absorption at 1705 cm⁻¹ (strong, broad).

Example 7 (S/C 600, conc. = 1%)

To a solution of 1.0 g (1.35 mmol) of N-acetyl-diene lib in 114 ml of toluene was added at 70°C under vacuum (pressure = ca. 0.26 bar) by dropping funnel a solution of 1.63 mg (0.0017 mmol) of catalyst 5058 in 4 ml of toluene. The catalyst was added during 1 h. Under these conditions a small amount of toluene (ca 14 ml) distilled off in the course of the reaction. After 2 h of total reaction time 10 µl (0.15 mmol) of ethylenediamine were added at ambient pressure, the reaction mixture was concentrated under vacuum, washed with 0.5 M aqueous solution of hydrochloric acid, stirred with 80 mg of charcoal for 30 min, filtered and evaporated to dryness. N-acetyl-RCM-ester Ib was isolated as white foam (1.07 g).

HPLC analysis showed 2.2 area% toluene, 91.9 area% Ib, 1.5 area% lib and 1.0 area% dimers.

The purity by HPLC with internal standard was 89.0% content, which corresponds to 98% yield.

Examples 8a-8e

The experiments in Table 4 have been carried out in analogy to Example 7, Catalyst No., temperature, reaction time, yield and purity of N-acetyl-RCM ester Ib are given in the table.
Table 3

<table>
<thead>
<tr>
<th>Reaction Nr.</th>
<th>Catalyst No.</th>
<th>T °C</th>
<th>N-acetyl-Diene Ib a%</th>
<th>N-acetyl-RCM-ester Ib a% / %y.</th>
<th>Dimers a%</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>5065</td>
<td>70</td>
<td>1.5</td>
<td>87 / 95</td>
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<td>8b</td>
<td>5008</td>
<td>70</td>
<td>3.3</td>
<td>87 / 92</td>
<td>7.2</td>
</tr>
<tr>
<td>8c</td>
<td>5024</td>
<td>70</td>
<td>1.5</td>
<td>88 / 95</td>
<td>6.7</td>
</tr>
<tr>
<td>8d</td>
<td>5064</td>
<td>70</td>
<td>1.4</td>
<td>87 / 95</td>
<td>7.7</td>
</tr>
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<td>1.8</td>
<td>84 / 89</td>
<td>9.1</td>
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</table>

All reactions were run at S/C 1000 on a 7.0 mmol scale for 1.5 h. Concentration is 8%.
%y. = % yield determined by HPLC with internal standard; a%: HPLC area%.

Example 9 (S/C 1000, cone. = 8%)

To a solution of 5.83 g (7.00 mmol) of N-propionyl-diene Hc in 80 ml of toluene was added at 70°C under vacuum (pressure = ca. 0.26 bar) by dropping funnel a solution of 5.26 mg (0.0070 mmol) of catalyst 5065 in 15 ml of toluene. The catalyst was added during 1 h, then the dropping funnel was rinsed with 15 ml of toluene. Under these conditions a small amount of toluene (ca 10 ml) distilled off in the course of the reaction. After 1.5 h of total reaction time 24 µl (0.35 mmol) of ethylenediamine were added at ambient pressure, the reaction mixture was concentrated under vacuum, washed with 0.5 M aqueous solution of hydrochloric acid, treated with 10 ml dichloromethane and 0.50 g of charcoal and stirred for 30 min, filtered and evaporated to dryness. N-propionyl-RCM-ester Ic was isolated as an off-white foam (5.96 g). HPLC analysis showed Ic (80.4 area %), Hc (2.4 area%) and dimers (4.8 area%, identified by HPLC/MS). The content by HPLC with internal standard was 74.5%, which corresponds to 89% yield. The crude product could be purified, if desired, by column chromatography on silica gel, eluent heptane/ethyl acetate. MS: [MH]⁺ 713.3.

HPLC method for content determination: Gemini C6-Phenol column, 4.6 x 150 mm, 3.0 um, solvent A: water/acetonitrile 95/5, solvent B: buffer Bu₄N⁺HSO₄⁻ pH 3 (lg in 1 l water/acetonitrile 9:1); solvent C: acetonitrile gradient from A/B/C 25/5/70 to 15/5/80 within 1.0 min, then 4 min isocratic, 50°C, 210 nm, 2.3 ml/min. Retention times: N-propionyl-diene Hc 1.93 min, N-propionyl-RCM-ester Ic 2.07 min, int. standard dinitrobenzene (1 g/l acetonitrile) 1.03 min.
Example 10 (S/C 20)

In a glove-box (O<sub>2</sub> < 2 ppm) a solution of 60.0 mg (0.073 mmol, corrected by content) of N-benzoyl-diene Hd and 2.40 mg (0.0038 mmol) of catalyst 5024 in 1.7 ml of toluene (washed with aqueous hydrochloric acid and distilled under argon) was stirred at 60°C in a 15 ml screw-capped flask. After 1.5 h two drops of ethyl vinyl ether were added and the mixture was stirred for ca. 30 min outside of the glove box. After addition of 1 ml of 1M aqueous solution of hydrochloric acid the biphasic mixture was stirred for ca. 5 min. A 0.5 ml aliquote of the organic phase was removed and evaporated to dryness; the oily residue was dissolved in 1 ml of acetonitrile and analyzed by HPLC. Conversion was 99 area%, the desired product (N-benzoyl-RCM-ester Id) had 83 area% purity.

HPLC method for the determination of conversion and selectivity: Gemini C6 Phenyl (by Phenomena, Torrance Ca, USA), 4.6 x 150 mm, solvent A: water/acetonitrile 95/5, solvent B: acetonitrile, solvent C: buffer Bu₄N⁺HSO₄⁻ pH 3 (1 g in 1 l water/ acetonitrile 9:1), gradient from A/B/C 45/50/5 to 10/85/5 within 7.0 min, then 5 min isocratic, 50°C, 210 nm, 2 ml/min. Retention times: toluene 2.5 min, diene-benzoate Hd 6.62 min, N-benzoyl-RCM-ester Id 5.96 min (identified by HPLC/MS, [M-H]⁺ 761.2 u), peaks of dimeric by-products at 6.5 to 9.1 min (HPLC-MS: [M-H]⁺ 1520 and 1576 u). Only the sum of the dimer peaks is given in the tables and experiments.

MS: [MHJ⁺] 761.2 u

NMR: (δ CDCl₃, selected peaks): 1.25 (t, 3H), 1.34 (d, 9H)

Example 11

The examples in Table 4 were carried out using the same procedure and conditions as in Example 10, but in the presence of various catalysts.
Table 4

<table>
<thead>
<tr>
<th>Reaction Nr.</th>
<th>Catalyst Nr.</th>
<th>N-Benzoyl-Diene Id (area%)</th>
<th>N-Benzoyl-RCM-Ester Id (area%)</th>
<th>Dimers (area%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
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<td>52</td>
<td>16</td>
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<td>5</td>
</tr>
<tr>
<td>11c</td>
<td>5002</td>
<td>22</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>11d</td>
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</tr>
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<td>11o</td>
<td>5065</td>
<td>&lt;1</td>
<td>84</td>
<td>7</td>
</tr>
</tbody>
</table>

Example 12 (S/C 135)

To a solution of 3.29 g (4.00 mmol) of N-benzoyl-diene Hd (96% purity) in 44 ml of toluene was added under argon bubbling (33 ml/min) at 60°C 21.3 mg (0.03 mmol) of catalyst 5065. After 4.5 h stirring at this temperature 97 µl of ethyl vinyl ether were added followed by 67 µl (1.0 mmol) of ethylenediamine and the mixture was stirred at room temperature for 10 min. After this time the mixture was extracted with 1 M aqueous solution of hydrochloric acid and with water. The organic phase was treated with decolorizing charcoal, filtered and evaporated to dryness to afford 3.2 g of N-benzoyl-RCM-ester Id as a light brown solid. Crystallization of the crude product from ethanol afforded the desired Id (2.46 g, 81%) as an off-white crystalline solid with 93% purity.

Example 13 (S/C 135)

The examples in Table 5 were carried out using the same procedure and conditions as in Example 12, but in the presence of various catalysts.
Table 5

<table>
<thead>
<tr>
<th>Reaction Nr.</th>
<th>Catalyst Nr.</th>
<th>N-Benzoyl-Diene Id a%</th>
<th>N-Benzoyl-RCM-Ester Id a%</th>
<th>Dimers a%</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>5058</td>
<td>20</td>
<td>64</td>
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<tr>
<td>13b</td>
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<td>69</td>
<td>13.2</td>
</tr>
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<td>13c</td>
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<td>35</td>
<td>50</td>
<td>13.0</td>
</tr>
<tr>
<td>13d</td>
<td>5073</td>
<td>0.5</td>
<td>84</td>
<td>10.6</td>
</tr>
</tbody>
</table>

a%: HPLC area%.

Example 14 (S/C 2000, cone. = 8%)

To a solution of 6.57 g (8.00 mmol) of N-benzoyl- diene Hd in 93 ml of toluene was added at 70°C under vacuum (pressure = ca. 0.26 bar) by dropping funnel a solution of 2.78 mg (0.0039 mmol) of catalyst 5065 in 10 ml of toluene. The catalyst was added during 1 h. Under these conditions a small amount of toluene (ca 10 ml) distilled off in the course of the reaction. After 1.5 h of total reaction time 20 μl (0.20 mmol) of ethyl vinyl ether were added at ambient pressure followed after 1 h by 14 μl (0.20 mmol) of ethylenediamine and the reaction mixture was concentrated under vacuum. After addition of 10 ml of dichloromethane the solution was washed with 0.5 M aqueous solution of hydrochloric acid, treated with 5 ml of dichloromethane and evaporated to dryness. N-benzoyl-RCM-ester Id was isolated as a light tan solid (7.05 g). HPLC analysis showed 84.3 area% Id, 1.42 area% Hd and 10.3 area% dimers. The content by HPLC with internal standard was 70.3%, which corresponds to 81.5% yield.

Example 15 (Saponification of Id)

A suspension of 6.52 g (6.75 mmol) N-benzoyl-RCM-ester Id in 25 mL of THF, 25 mL of ethanol and 5 mL of water was cooled to 0°C. At an internal temperature of 0.7°C to 4.0°C a solution of 4.0 g (98.01 mmol) sodium hydroxide in 20 mL of water was added within 22 min. The mixture was stirred for 16.5 h at 0°C. At this temperature 12.9 mL (98.96 mmol) aqueous HCl 25% was added. The mixture was concentrated at 45°C/45 mbar to a residual weight of ca. 30 g. To the suspension 5 mL of water was added and extracted with 30 mL of dichloromethane. The organic layer was washed with 25 mL of water and the combined aqueous layers were extracted with 25 mL of dichloromethane. The combined organic layers there concentrated to a residual volume of 15 mL at 60°C/900 mbar. To the concentrate 50 mL of THF is added slowly and again concentrated to a residual weight of ca. 40 g at 60°C/700 mbar). Seeds were added and the suspension was stirred 1 h at room temperature and 1.5 h at 0°C to complete the
crystallization. The crystals were collected on a filter nutsche and washed with 12 mL of THF (precooled to -20°C). The crystals were dried for 5 h at 50°C/10 mbar. 3.55 g of XXb with a purity of 97.2% (yield 81.3%) were obtained.

Example 16

To a solution of the N-acetyl-RCM-ester Ib (2.41 g, 2.88 mmol, 83.5% content) in 20 mL of ethanol was added under argon at ca. 3°C (ice bath) a solution of sodium hydroxide (1.50 g, 36.7 mmol) in water (6.5 mL). The solution was stirred at 5-10°C for 6 h, and then treated with 37%HCl (4.5 mL) at ca. 3°C. The resulting suspension was concentrated and extracted with a mixture of dichloromethane (15 mL) and water (8 mL). The organic phase was evaporated, the oily residue was taken up in THF (25 mL). The resulting suspension was concentrated to a total weight of 12.6 g, stirred for 1 h at 55°C and in an ice bath for 3 h. The precipitate was filtered off, washed with cold THF and dried to constant weight (40°C/5 mbar/3 h) to afford 1.64 g of carboxylic acid XXb as a white solid with 97 area% according to HPLC and 89.2% content. Total content of dimers: 0.9%.

MS: [MH]^+ 627.3
IR: carbonyl absorption at 1706 cm⁻¹ (strong, broad) and 1680 cm⁻¹ (medium, sharp).

Example 17 (telescopied process for the preparation of XXb)

A suspension of 90.2 g (191 mmol) (S)-2-tert-butoxycarbonylamino-non-8-enoic acid dicyclohexylammonium salt (commercially available from Synthetech Oregon, USA) in 373 g of THF was cooled to -5°C and 22.7 g (188 mmol) pivaloylchloride was added within 30 min. The mixture was stirred for 1.5 h at 0°C. At 5-10°C 75.0 g (174 mmol) 4-fluoro-1,3-dihydroisoindole-2-carboxylic acid (3R,5S)-5-((IR,2S)-1-ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester (XIV) was added in five portions followed by 18 g
THF. The suspension was heated to 20-25°C and stirred for 4 h. After complete conversion 225 g of water was added and the solvent was removed at 50°C under reduced pressure. To the residue 649 g of toluene was added and the internal temperature was decreased to 20-25°C. To the suspension 80 g water and 8.57 g (87 mmol) 37% aqueous hydrochloric acid was added. The precipitated dicyclohexylammonium hydrochloride was removed by filtration and the filter cake was washed with 114 g toluene. To the filtrate 26 g toluene was added and phases were separated. The organic phase was treated at 20-25°C with a mixture of 267 g water, 43.0 g (301 mmol) 28% aqueous sodium hydroxide and 2.11 g (35 mmol) ethylene diamine for 30 min. Then phases were separated and the organic layer was washed with a mixture of 267 g water and 21.5 g (151 mmol) 28% aqueous sodium hydroxide. The organic phase was concentrated at 65°C under reduced pressure to a residual volume of 500 mL. The solution was cooled to -3°C and 27.5 g (196 mmol) benzoyle chloride was added. Then 84.6 mL (188 mmol) lithium tert-butoxide in THF was dosed within 1 h. After additional stirring for 15 min a sample showed conversions typically to be < 3% of diene XV. The mixture was heated to 20-25°C and diluted with 337 g toluene. The solution was first washed with a mixture of 210 g water and 33.5 g (235 mmol) 28% aqueous sodium hydroxide, then with a mixture of 210 g water and 16.8 g (118 mmol) 28% aqueous sodium hydroxide and finally with a mixture of 210 g water and 11.6 g (117 mmol) 37% aqueous hydrochloric acid. The organic phase was then dried by concentrating to a residual volume of 650 mL at 65°C under reduced pressure. To the residue 865 g toluene were added and the solution was heated to 75°C jacket temperature. The pressure was reduced to 290-330 mbar and 167 mg (0.235 mmol) of catalyst 5065 dissolved in 35 g toluene and 13 g dichloromethane was added within 30 min. After stirring for additional 15 min a sample showed conversions typically to be < 3% N-benzyol-diene Hd. Then 0.5 g water was added and the mixture was stirred for 10 min. The mixture was concentrated to a residual volume of 200 mL at 75°C and reduced pressure, 415 g THF and 496 g ethanol were added. The internal temperature was decreased to 20-25°C and 106 g water was added. The suspension was cooled to 0-5°C and 340 g (2.38 mol) 28% aqueous sodium hydroxide was added. The internal temperature was raised to 7-10°C and the reaction mixture was stirred for 9-11 h. After this time the conversion was typically < 1% N-benzyol-RCM-ester Id. At an internal temperature of 5-10°C 237 g (2.40 mol) 37% aqueous hydrochloric acid was added. The internal temperature was raised to 40°C and the suspension was concentrated to 700 mL under reduced pressure. At an internal temperature of 30-35°C 108 g water and 620 g dichloromethane was added. The phases were separated and the aqueous phase was extracted with 124 g dichloromethane. The combined organic phases were washed with 94 g water and the aqueous phase was back-extracted with 102 g dichloromethane. The combined organic phases were concentrated to a residual volume of 300 mL at a jacket temperature of 80°C. To the residue 899 g THF were dosed, first an amount what gave a reactor volume of 470 mL and after adding seeds, in such a rate the residual volume of 470 mL could be maintained during continued distillation. After all THF had been added the internal temperature
was decreased to 0-3°C within 1.5 h. The crystals were collected on a filter nutsche and washed with 115 g THF. The product was dried for 3-6 h at 30°C/15 mbar. 79.2 g of colorless crystals of XXb were obtained in an assay of 89% wt which corresponds to a yield of 64%.

**Example 18**

![Diagram](image)

Preparation of sodium ((2R,6S, 13aS, 14aR, 16aS,Z)-6-(tert-butoxycarbonylamino)-2-(4-fluoroisoindoline-2-carbonyloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,15,16a-hexadecahydrocyclopenta[e]pyrrolo [1,2-a][1,4]diazacyclopentadecine-14a-carbonyl) (cyclopropylsulfonylamide (HCV protease inhibitor; compound XXIIb).

To a suspension of 30.0 g (0.043 mol) of carboxylic acid (product of example 11 with an assay of 90.2% (m/m)) and 14.0 g of sodium carbonate in 225 g of tetrahydrofuran was added at 45°C within 30 minutes 7.60 g (0.074 mol) of acetic acid anhydride and the resulting mixture was stirred at 45°C for 8 hours. To the resulting suspension was then added 30.2 g (0.17 mol) of potassium carbonate and 8.0 g (0.065 mol) of cyclopropyl sulfonamide. The mixture was heated to 62°C and stirred at this temperature for 17 hours. The mixture was concentrated to a residual volume of 200 ml and then treated with 200 g of water. The biphasic mixture was stirred for 15 minutes and the layers were then allowed to separate. The lower aqueous phase was removed.
The organic phase was diluted with 90 g of ethyl acetate and washed with 3% sulfuric acid (1x140 g) and water (3x130 g). The organic layer was concentrated to dryness and then diluted with 400 ml of ethyl acetate. Residual amounts of water were removed by a continuous azeotropic distillation with ethyl acetate. The mixture was then treated at 100°C with 20 ml of methanol, followed by 10.0 g of sodium methylate (30% in methanol). From the resulting mixture approx. 300 ml of ethyl acetate/methanol were then distilled off. The mixture was then treated at 34°C within one hour with 300 ml of ethyl acetate and 5 g of water. The resulting mixture was allowed to cool to ambient temperature within 4 hours. The crystals were filtered off, washed with 80 ml of ethyl acetate and dried at 80°C/<30 mbar for 20 hours to afford 30.4 g (87% corrected yield) of the title compound as white crystals with an assay of 92.7 % (m/m).

MS: 732.28 (M+H), 676.23, 632.25.

1H-NMR (400MHz, DMSO-d6): 7.89-7.80 (m, 1H), 7.39-7.31 (m, 1H), 7.21-7.06 (m, 2H), 6.97-6.90 (m, 1H), 5.49-4.41 (m, 1H), 5.31-5.21 (m, 2H), 4.66 (s, br, 4H), 4.45-4.35 (m, 1H), 4.19-4.08 (m, 2H), 3.91-3.81 (m, 1H), 2.68-2.58 (m, 1H), 2.30-2.14 (m, 3H), 2.0-1.2 (m, 12H), 1.17 and 1.14 (2s, 9H), 0.78-0.69 (m, 2H), 0.62-0.53 (m, 2H).
Claims

1. Process for the manufacture of a macrocyclic compound of formula

wherein R₁ is an amino protecting group and X is a halogen atom, comprising one or more of the steps

a) subjecting a diene compound of formula

wherein R₁ and PG are amino protecting groups, R₂ is C_i₄ alkyl and is X is halogen to ring; closing metathesis reaction in the presence of a ruthenium (II) carbene complex catalyst to form a macrocyclic ester of the formula
wherein $R^1$ and $PG$ are amino protecting groups, $R^2$ is $C_l_4$-alkyl and $X$ is halogen;

b) hydrolyzing the macrocyclic ester of formula I and removing the protecting group $PG$ to form the macrocyclic acid of the formula

\[
\text{XX}
\]

wherein $R^1$ is an amino protecting group and $X$ is halogen;

c) forming the macrocyclic sulfonamide of formula

\[
\text{XXI}
\]

wherein $R^1$ is an amino protecting group and $X$ is halogen by coupling the macrocyclic acid of formula XX with cyclopropyl sulfonamide and

d) treating the macrocyclic sulfonamide of formula XXI with a sodium base to form the macrocyclic compound of formula XXII.

2. Process of claim 1, characterized in that the ruthenium (II) carbene complex catalyst is selected from compounds of the formula
wherein $L$, $L^1$ and $L^2$ are neutral ligands;

$X^1$ and $X^2$ independently of each other are anionic ligands;

$Y$ is hydrogen, $d^\alpha$-alkyl, $C_{2-6}$-alkenyl or aryl, or $Y$ and $R^8$ taken together to form a
(CH=CR)- or a -(CH$_2$)$_n$- bridge with $n$ having the meaning of 2 or 3 and $R$ is as defined for $R^4$;

$Y^1$ and $Y^2$ independently of each other are hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl,
$C_{2-6}$-alkynyl, $C_{6}$-alkythio, aryl, arylthio, $C_{1-6}$-alkylsulfonyl, $C_{1-6}$-alkylsulfinyl,
or

$Y^1$ and $Y^2$ taken together form a cycle of the type
with G being hydrogen or aryl;

or

$Y^1$ and $Y^2$ together form a cumulenyl group of type

$$\begin{align*}
\text{Aryl} & \quad \text{C} \\
\text{Aryl} & \quad \text{C} = \text{C} \\
\end{align*}$$

$Y^3$ is hydrogen, C$_6$-alkyl, C$_2$-6-alkenyl, C$_2$-6-alkynyl, C$_6$-alkylthio, aryl, arylthio, C$_6$-alkylsulfonyl, C$_6$-alkylsulfynyl;

$Y^4$ and $Y^5$ independently of each other is hydrogen, C$_6$-alkyl, C$_3$-8-cycloalkyl, C$_2$-6-alkenyl, C$_2$-6-alkynyl, C$_6$-alkoxy, C$_2$-6-alkenyloxy, C$_2$-6-alkynoxy, aryloxy, C$_6$-alkoxycarbonyl, C$_6$-alkylthio, aryl, arylthio, C$_6$-alkylsulfonyl, C$_6$-alkylsulfynyl;

$R^a$, $R^b$, and $R^c$ independently of each other are C$_6$-alkyl, C$_3$-7-cycloalkyl, aryl, heteroaryl or R$^a$ and R$^b$ or R$^c$ and R$^d$ or R$^a$ and R$^b$ and R$^c$ form together a 1,5-bridged cyclooctyl group;

$R^b$ is C$_6$-alkyl C$_{2,6}$-alkenyl, halogen-C$_6$-alkyl, C$_{2,6}$-alkynyl, aryl, C$_6$-alkoxycarbonyl, C$_6$-alkylcarbonyl, mono-C$_6$-alkyl or di-C$_6$-alkylamino, C$_6$-alkylaminocarbonyl, C$_6$-alkylthiocarbonyl, C$_6$-alkylsulfonyl, C$_6$-alkylsulfynyl or aryalkyl;

$R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ independently of each other have the meaning of hydrogen, C$_6$-alkyl, halogen-C$_6$-alkyl, C$_2$-6-alkenyl, C$_2$-6-alkynyl, halogen-C$_6$-alkyl, C$_6$-alkoxy, C$_2$-6-alkenyloxy, C$_2$-6-alkynoxy, C$_6$-alkylcarbonyl, aryloxy, hydroxy, aryloxy, nitro, C$_6$-alkoxycarbonyl, amino, mono-C$_6$-alkyl or di-C$_6$-alkylamino, halogen, thio, C$_6$-alkylthio, arylthio, C$_6$-alkylsulfonyl, C$_6$-alkylsulfynyl, aryloxycarbonyl, SO$_3$H, C$_6$-alkylcarbonyl amino, aryl carbonyl amino, C$_6$-alkyl sulfonyl amino, aryl sulfonyl amino, halogen-C$_6$-alkyl sulfonyl amino, S$_3$-3-C$_6$-alkyl or OSi(C$_6$-alkyl)$_3$ and SO$_2$-NRR$^*$ wherein R$'$ and R$''$ independently of each other have the meaning of hydrogen, aryl or C$_6$-alkyl or R$'$ and R$''$ together with the N atom form a carbo cycle;

a, b, c and d independently of each other have the meaning of hydrogen, C$_6$-alkyl, halogen-C$_6$-alkyl, C$_2$-6-alkenyl, C$_2$-6-alkynyl, halogen-C$_6$-alkyl, C$_6$-alkoxy, C$_2$-6-alkenyloxy, C$_2$-6-alkynoxy, C$_6$-alkylcarbonyl, aryloxy, hydroxy, aryloxy, nitro, C$_6$-alkoxycarbonyl, amino, mono-C$_6$-alkyl or di-C$_6$-alkylamino, halogen, thio, C$_6$-alkylthio, arylthio, C$_6$-alkylsulfonyl, C$_6$-alkylsulfynyl, aryloxycarbonyl, SO$_3$H, C$_6$-alkylcarbonyl amino, aryl carbonyl amino, C$_6$-alkyl sulfonyl amino, aryl sulfonyl
amino, halogen-Ci-6-alkyl sulfonamino, Sθ-Ci-6-alkyl or OSi(Ci-6-alkyl)3 and SO2-NR'R" wherein R' and R" independently of each other have the meaning of hydrogen, aryl or Ci-6-alkyl or R' and R" together with the N atom form a carbocycle;

Arene stands for phenyl or naphthyl optionally mono-, di-, tri- or multiply-substituted by halogen, hydroxy, cyano, halogen-Ci-6-alkyl, NO2, amino, mono-Ci-6-alkyl- or di-Ci-6-alkylamino, carboxy, amino carbonyl, Ci-6-alkyl, Ci-6-alkoxy, Ci-6-alkylcarbonyl, Ci-6-alkylsulfonyl, aryl, aryloxy SO2-aryl, SO3H, SO3-Ci-6-alkyl, SO2-NR'R"wherein R and R" independently of each other are hydrogen or Ci-6-alkyl;

R\textsuperscript{1a} is hydrogen, hydroxy, Ci-6-alkyl, Ci-6-alkoxy, Ci-2-6-alkenyloxy, halogen-Ci-6-alkoxy, aryl, aryloxy, Ci-6-alkylthio, arylthio, or -NR'R" wherein R' and R" independently of each other are hydrogen, Ci-6-alkyl, C\textsubscript{3-8}-cycloalkyl, aryl, aryl-Ci-6-alkyl or wherein R' and R" together with the N atom form a 5 to 8 member carbocycle which may contain nitrogen, oxygen or sulfur as additional hetero atom;

R\textsuperscript{2a} and R\textsuperscript{3a} are independently of each other H, Ci-6-alkyl, C\textsubscript{3-8}-cycloalkyl, aryl, C7\textunderscore i8-arylalkyl or

R\textsuperscript{1a} and R\textsuperscript{2a} or R\textsuperscript{3a} together form a 5 to 12 member carbocycle.

3. Process of claim 2, characterized in that L is

\[ -P(R^{a1})(R^{a2})(R^{a3}) \]

wherein R\textsuperscript{10} and R\textsuperscript{11} independently of each other are Ci-6-alkyl, aryl, C\textsubscript{2-6}-alkenyl or 1-adamantyl and

R\textsuperscript{9a-d} independently of each other are hydrogen, Ci-6-alkyl, C\textsubscript{2-6}-alkenyl or aryl, or R\textsuperscript{9b} and R\textsuperscript{9c} or R\textsuperscript{9a} and R\textsuperscript{9d} taken together form a-(CH\textsubscript{2})\textsubscript{4}-bridge,

or R\textsuperscript{9a} and R\textsuperscript{9d} in formula IX both have the meaning of halogen;

R\textsuperscript{a1,a3} independently of each other are Ci-6-alkyl, C\textsubscript{3-7}-cycloalkyl, aryl, heteroaryl or R\textsuperscript{a1} and R\textsuperscript{a2} or R\textsuperscript{a2} and R\textsuperscript{a3} or R\textsuperscript{a1} and R\textsuperscript{a3} form together a 1,5-bridged cycl\textsubscript{10}octyl group.
4. Process of claim 2, characterized in that $X_1$ and $X_2$ are selected from a halogenide or a pseudo halogenide.

5. Process of claim 2, characterized in that $Y$ is hydrogen;

$Y_1$ and $Y_2$ are the same or different and stand for hydrogen, $\text{Ci-6-alkyl}$, $\text{C2-6-alkenyl}$, $\text{Ci-6-alkylthio}$, phenyl, phenylthio, or

$Y_1$ and $Y_2$ taken together form a cycle of the type

\[
\begin{array}{c}
\text{G} \\
\text{C} \\
\text{Vla}
\end{array}
\]

with $G$ being hydrogen or phenyl;

10

$Y^3$ is hydrogen;

$Y^4$ and $Y^5$ independently of each are hydrogen, $\text{Ci-6-alkyl}$, aryl or arylthio.

6. Process of claim 2, characterized in that $R^b$ is $\text{Ci-6-alkyl}$ and halogen-$\text{Ci-6-alkyl}$;

$a$, $b$ and $d$ are hydrogen and

c is hydrogen, halogen, nitro, $\text{Ci-6-alkyl carbonyl amino}$, aryl carbonyl amino, aryl sulfonyl amino, alkyl sulfonyl amino, halogen-$\text{Ci-6-alkyl sulfonyl amino}$, $\text{SO}_2\text{-NR}^\prime \text{R}''$ wherein $R'$ and $R''$ independently of each other have the meaning of hydrogen, $\text{Ci-6-alkyl}$, aryl or $R'$ and $R''$ together with the N atom form a carbocycle.

7. Process of claim 2, characterized in that Arene is benzene, $p$-cymene, mesitylene or, $p$-xylene.

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8. Process of claim 2, characterized in that $R^{3a}$ is $\text{Ci-6-alkyl}$.

9. Process of claims 1 to 8, characterized in that the ring closing metathesis reaction in step a) is performed in an organic solvent at $20^\circ\text{C}$ to $140^\circ\text{C}$.

10. Process of claims 1 to 9, characterized in that the ring closing metathesis reaction in step a) is performed with a substrate to catalyst ratio in the range of 20 to 10000.
11. Process of claims 1 to 10, characterized in that the ring closing metathesis reaction in step a) is performed with a substrate concentration in the range of 0.1 and 25%.

12. Process of claim 1, characterized in that the hydrolysis in step b) is performed with an aqueous alkali hydroxide solution at a temperature of 0°C to 40°C.

13. Process of claim 12, characterized in that the macrocyclic acid of formula XX obtained in step b) is isolated by way of extraction with dichloromethane and a subsequent crystallization in tetrahydrofuran.

14. Process of claim 1, characterized in that the macrocyclic acid of formula XX is obtained without isolation of the macrocyclic ester of formula I.

15. Process of claim 1, characterized in that the formation of the macrocyclic sulfonamide of formula XXI in step c) is in a first step the reaction of the macrocyclic acid of formula XX with acetic acid anhydride in the presence of an inorganic base and a suitable organic solvent into an azlacton intermediate of the formula

wherein R^1 is an amino protecting group and X is halogen and the subsequent reaction of the azlacton with cyclopropyl sulfonamide in the presence of an inorganic base to the macrocyclic sulfonamide of formula XXI.

16. Process of claim 1, characterized in that the sodium base used for the treatment of the macrocyclic sulfonamide of the formula XXI in step d) is sodium hydroxide, sodium methylate or sodium ethoxide.

17. Process of claims 1 to 16 characterized in that PG is C_6-alkylcarbonyl, arylcarbonyl or C_i_6-alkoxy carbonyl.

18. Process of claim 17 characterized in that PG is benzoyl.

19. Process of claims 1 to 18, characterized in that

R^1 is Boc; R^2 is ethyl and the moiety of the formula
stands for

[Chemical Structure]

20. Macrocyclic ester of the formula

(wherein $R_1$ and $PG$ are amino protecting groups, $R_2$ is C$_4$-alkyl and $X$ is halogen.)

21. Macrocyclic ester of claim 20, wherein

$R_1$ is Boc;

$R_2$ is ethyl;

$PG$ is $\gamma$-alkylcarbonyl, arylcarbonyl or C$_6$-alkoxycarbonyl and the moiety of the formula

stands for

[Chemical Structure]

22. Macrocyclic ester of claim 21, wherein $PG$ is benzooyl.
23. Diene compound of the formula

![Chemical Structure](image)

wherein $R^1$ and $PG$ are amino protecting groups, $R^2$ is $C_{i4}$-alkyl and is $X$ is halogen.

24. Diene compounds of claim 23 wherein $R^1$ is Boc; $R^2$ is ethyl; $PG$ is $C_{i6}$-alkylcarbonyl, arylcarbonyl or $C_{i6}$-alkoxycarbonyl and the moiety of the formula

![Chemical Structure](image)

stands for

![Chemical Structure](image)

25. Diene compound of claim 24 wherein $PG$ is benzoyl.
## A. CLASSIFICATION OF SUBJECT MATTER

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

- C07D209/44
- C07D487/04

## B. RELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols):

- C07D

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
- BEILSTEIN Data
- CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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Further documents are listed in the continuation of Box C.

See patent family annex.

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- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
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**'T'** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**'X'** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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**'Z'** document member of the same patent family

Date of the actual completion of the international search: 1 October 2009

Date of mailing of the international search report: 14/10/2009

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV RIVSWALD
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Mats Valdi viel so, J
### DOCUMENTS CONSIDERED TO BE RELEVANT

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