SYNTHESIS OF TTX INTERMEDIATES

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The present invention relates to the synthesis of intermediates which are useful in TTX synthesis and to the preparation thereof.
SYNTHESIS OF TTX INTERMEDIATES

FIELD OF THE INVENTION

[0001] The present invention relates to the synthesis of TTX intermediates and their analogs.

BACKGROUND OF THE INVENTION

[0002] Tetrodotoxin (TTX), octahydro-12-(hydroxymethyl)-2-imino-5,9,7,10a-dimethano-1,13-dioxocino[6,5-d]pyrimidine-4,7,10,11,12-pentol is a powerful neurotoxin which selectively binds to the sodium channel proteins inhibiting their cell membrane function. Tetrodotoxin was isolated for the first time in 1909 from the ovaries of puffer fish and was named after the puffer fish “tetradontidae” family. Despite being a small molecule, it has an extremely complex structure characterized by a dioxaadamantane skeleton, a guanidine residue which is part of a hemiaminal and an orthoacid bridge.

It must also be highlighted that TTX is normally present as a mixture of two possible tautomers: an orthoester and a hydroxylactone (Scheme 1). The ratio of both tautomers depends on the medium in which the TTX is present.


Tetrodotoxin blocks sodium diffusion through the sodium channel, preventing depolarization and propagation of action potentials in nerve cells. The TTX-Na channel binding site is extremely tight (Kd=10^{-10} nM). Therefore it is an essential tool in pharmacological studies related to sodium channel proteins.

Furthermore, tetrodotoxin, due to its analgesic properties, is a promising new drug candidate in the field of pain management.


Tetrodotoxin analogs are those described in U.S. Pat. No. 5,846,975 (included herein by reference). From column 3 line 40 to column 6 line 40 U.S. Pat. No. 5,846,975 describes a general formula of known TTX analogs, for example, anhydrous tetrodotoxin, tetradoxin, methoxytetrodotoxin, ethoxytetrodotoxin, deoxytetrodotoxin and tetrodonic acid, 6-epi-tetrodotoxin, 11-deoxytetrodotoxin as well as hemilactile type TTX derivatives (e.g. 4-epi-TTX, 6-epi-TTX, 11-deoxy-TTX, 4-epi-11-deoxy-TTX, TTX-8-O-hemimucin, deoxytetrodotoxin, 11-nor-TTX-6(S)-ol, 11-nor-TTX-6(R)-ol, 11-nor-TTX-6,6-diol, 11-oxo-TTX and TTX-11-carboxylic acid), lactone type
TTX derivatives (e.g. 6-epi-TTX (lactone), 11-deoxy-TTX (lactone), 11-nor-TTX-6(S)-ol (lactone), 11-nor-TTX-6(R)-ol (lactone), 11-nor-TTX-6,6-diol (lactone), 5-deoxy-TTX, 5,11-dideoxy-TTX, 4-epi,5,11-dideoxy-TTX, 1-hydroxy-5, 11-dideoxy-TTX, 5,6,11-trideoxy-TTX and 4-epi-5,6,11-trideoxy-TTX) and 4,9-anhydrous type TTX analogs (e.g. 4,9-anhydro-TTX, 4,9-anhydrous-6-epi-TTX, 4,9-anhydrous-11-deoxy-TTX, 4,9-anhydro-TTX-8-O-hemisuccinate, 4,9-anhydro-TTX-11-O-hemisuccinate). The typical TTX analogs possess only \( \frac{1}{6} \) to \( \frac{1}{4} \) of the TTX toxicity in mice, based upon bioassay in mice. It has been observed that these derivatives produce joint action and do not interact adversely.


[0014] Hydroxylated lactams serving as starting material for the derivatives of the present invention are prepared in international application PCT/EP2005/005149.

[0015] In view of all of the above there is an existing need of providing an alternative inexpensive and efficient synthesis of tetrodotoxin and analogs thereof, which can be used for the industrial production of sufficient amounts of these compounds. Furthermore, new analogues with useful biological and pharmacological properties will be readily available by means of new synthetic strategies.

**SUMMARY OF THE INVENTION**

[0016] The authors of the invention, on their continuous effort to discover an industrially viable synthesis, have discovered that the intermediates of the invention are promising intermediate products for synthesizing TTX and analogs thereof. Therefore, a first aspect of the invention relates to a compound of formula (II), stereoisomers, salts or solvates thereof.

[0017] The preparation of the compounds of formula (II) allows efficiently functioning positions 4a and 5 of TTX according to the TTX numbering while at the same time introduces carbon 4. Additionally, it opens the door to the synthesis of more advanced intermediates in the TTX synthesis, such as the compounds of formula (III), (IV), (V), (VI), (VII), (VIII), (IX), (Xa), (XI), (XII), (XIII), and (XIV) each of which forms an additional aspect of the invention.
Additional aspects of the invention are methods for synthesizing said compounds of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (Xa), (XI), (XII), (XIII) and (XIV) as well as their use as intermediates in the synthesis of TTX and analogs thereof. These compounds, as well as their more particular embodiments are called “compounds of the invention” throughout the present invention.

These intermediates of the invention form advanced intermediates in the TTX synthesis. Additionally, the synthesis also allows obtaining TTX analogs by means of modifying the different positions in a flexible manner. Methods similar to those described in other documents mentioned above (for example, in the Sato or Isobe publications) allow constructing the orthoester and the guanidinium ring from the compounds of the invention.

**Detailed Description of the Invention**

**Definitions**

Except in the examples, the numbering followed to designate the positions in the compounds of the invention has been the following:

[0021] In other words, this is the numbering referred to when it is indicated that the number of a specific position is “according to the TTX numbering”.

[0022] In the present document the following terms have the indicated meanings:

- **Alkyl** refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing no saturation, having 1-12, preferably one to eight, more preferably one to six carbon atoms, and which is bound to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, etc.
“Alkenyl” refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing at least one unsaturation, having 2-12, preferably two to eight, preferably two to six carbon atoms, and which is bound to the rest of the molecule by a single bond.

“Alkylidene” refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, having 1-12, preferably one to eight, more preferably one to six carbon atoms, and which is bound to the rest of the molecule by a double bond, e.g., methylene (—CH2—) or ethyldene (—CH2CH)=.

“Alkynyl” refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, conjugated or not, having two to twelve, preferably two to eight, preferably two to six carbon atoms, and which is bound to the rest of the molecule by a single bond, such as —C—H, —CH=CH—, —C—CH3, —CH2=CH2, —C—CH2=CH2.

“Aryl” or “Ar” refers to an aromatic hydrocarbon radical such as phenyl, naphthyl or anthracenyl.

“Aryalkyl” refers to an aryl group bound to the rest of the molecule through an aryl group such as benzyl and phenethyl.

“Cycloalkyl” refers to cyclic hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing no unsaturation, having 3 to 8 carbon atoms, bound to the rest of the molecule by a single bond.

“Alkoxy” refers to a radical of the formula —Oalkyl, e.g., methoxy, ethoxy, propoxy, etc.

“Aryloxy” refers to a radical of formula —Oaryl.

“Heterocyclyl” refers to a stable 3 to 15-membered ring consisting of carbon atoms and one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, preferably a 4 to 8-membered ring with one or more heteroatoms, preferably a 4- or 6-membered ring with one or more heteroatoms. For the purposes of this invention, the heterocycle can be a monocyclic, bicyclic or tricyclic ring system, which can include fused ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or completely saturated or aromatic. Examples of said heterocycles include, but are not limited to, azepines, benzimidazoles, benzoxazoles, furan, isothiazole, imidazole, indole, pyridine, piperazine, pyrimidine, indazole, tetrahydrofurans.

“Amino” refers to a radical of formula —NH2, —NR, —NR2*, wherein R* and R** independently represent a group selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aroyl, unsubstituted or unsubstituted aryl, substituted or unsubstituted aralkyl.

“Hydroxyl protecting group” refers to a group blocking the OH function for subsequent reactions and can be removed under controlled conditions. Hydroxyl protecting groups are well known in the art, representative protecting groups are:

- silyl ethers of formula —Si(R′)3, such as trimethylsilyl ether, triethylsilyl ether, tert-butyldimethylsilyl ether, tert-butyldiphenylsilyl ether, triisopropylsilyl ether, diethylisopropylsilyl ether, triphenylsilyl ether, di-tert-butyldimethylsilyl ether;
- alkyl and arylalkyl ethers such as methyl ether, tert-butyl ether, benzyl ether, p-methoxybenzyl ether, 3,4-dimethoxybenzyl ether, trityl ether, allyl ether;
- alkoxyethyl and arylalkoxy ethers of formula —CH2—O—R′, such as methoxymethyl ether, 2-methoxyethoxymethyl ether, benzoxymethyl ether, p-methoxybenzylalkoxy ethyl ether, 2-(trimethylsilyl)ethoxyethoxymethyl ether, tetrahydropropylyl and related ethers; methylthiomethyl ether;
- esters of formula —C(=O)R′ such as acetate ester, benzoate ester, pivalate ester, methoxyacetate ester, chloroacetate ester, levulinic ester;
- carbonates of formula —C(=O)—O—R′ such as benzyl carbonate, p-nitrobenzyl carbonate, tert-butyl carbonate, 2,2,2-trichloroethyl carbonate, 2-(trimethylsilyl)ethyl carbonate, allyl carbonate; and
- sulphonates such as SO3 py.

In all the above formula R′ represents a group selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aroyl and substituted or unsubstituted arylalkyl. Additional examples of hydroxyl protecting groups can be found in reference books such as Greene and Huts “Protective Groups in Organic Synthesis”, John Wiley & Sons, Inc., New Jersey, 2007.

“Amino protecting group” refers to a group blocking the NH function for subsequent reactions and can be removed under controlled conditions. Amino protecting groups are well known in the art, representative protecting groups are carbamates, e.g. carbamates of formula —C(=O) OR′; amides, e.g. amides of formula —C(=O)R′, such as substituted or unsubstituted acetates; or silyl moieties of formula —Si(R′)3; wherein R′ is as defined above. Different alkoxy moieties can also serve as amino protecting groups. Said alkyl groups can optionally be substituted with one or more substituents such as halogen, hydroxyl, alkoxyl, alkoxyethyl ethers, carboxy, cyano, carbonyl, acyl, alkoxy carbonyl, amino, nitro, mercapto and alkylthio. Additional examples of amino protecting groups can be found in reference books such as Greene and Huts “Protective Groups in Organic Synthesis”, John Wiley & Sons, Inc., New Jersey, 2007.

References herein to substituted groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions with one or more suitable groups, e.g., halogen such as fluorne, chlorine, bromine and iodine, cyano; hydroxy; nitro; azido; alkanoyl such as a C1—C alkanoyl such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to 12 carbon atoms or 1 to 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkyaryl groups including groups having one or more unsaturated bonds and 2 to 12 carbons or 2 to 6 carbon atoms; alkoxyl groups having one or more oxygen bonds and 1 to 12 carbon atoms or 1 to approximately 6 carbon atoms; alkoxy such as phenoxyl; alkylthio groups including those moieties having one or more thioether bonds and 1 to about 12 carbon atoms or 1 to 6 carbon atoms; alkylsulfanyl groups including those moieties having one or more sulfanyl bonds and 1 to 12 carbon atoms or 1 to 6 carbon atoms; alkylsulfanyl groups including those moieties having one or more sulfanyl bonds and 1 to 12 carbon atoms or 1 to 6 carbon atoms; alkoxyalkyl groups such as those groups having one or more N atoms and 1 to 12 carbon atoms or 1 to 6 carbon atoms; carboxylic aryl having 6 or more carbons, particularly phenyl or naphthyl and arylalkyl such as benzyl. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and each substitution is independent of the other.
Unless otherwise stated, it is understood that the compounds of the invention also include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds of formula (I), (III), (IV), (V), (VI), (VII), (VIII), (IX), (Xa), (XI), (XII), (XIII) or (XIV) wherein a hydrogen has been substituted with a deuterium or tritium, and/or the substitution of a carbon with $^{13}$C- or $^{14}$C-enriched carbon, and/or $^{15}$N-enriched nitrogen and/or the substitution of an oxygen with $^{18}$O, are within the scope of this invention.

Compounds of the Invention

As indicated above, aspects of the present invention are the compounds of formula (I), (III), (IV), (V), (VI), (VII), (VIII), (IX), (Xa), (XI), (XII), (XIII) or (XIV), stereoisomers, salts or solvates thereof.
wherein

R₁ is selected from hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl and NReRF₆, wherein Re and RF are each independently selected from H, OH, OP₆ or substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted amino and halogen;

R₂ is selected from hydrogen, OH, or OP₆ or

R₁ and R₂ together form a group selected from -O, alkyldiene and -(CH₂-O-Pr-O-);

E is selected from the group consisting of fluorine, chlorine, bromine, iodine, -SeR₁₄, -O-NR₁₃, -SR₁₄, PO(O-alkyl)₂ and PO(O-arlyl), wherein

R₁₃ is selected from the group consisting of aryl and alkyl;

R₄ is selected from the group consisting of aryl, alkyl, -PO(O-alkyl)₂, PO(O-arlyl), -C(O)O-alkyl and -C(O)O-aryl;

R₆ and R₁₀ are each independently selected from hydrogen, OH, OP₆ and -O, or together form a -O-Pr-O- group;

W is selected from the group consisting of -H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl and substituted or unsubstituted alkenyl;

Ra and Rb are each independently selected from H, OH, OP₆, Se-aryl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, substituted or unsubstituted amino and halogen;

Pr is a hydroxyl protecting group;

Z is -COOH or -CHR₄R₅, wherein R₄ is hydrogen, and R₅ is OH or OP₆; or R₄ and R₅ together form -O;

X is -(CH=O) or -CN;

Y is selected from the group consisting of -OR₆, -SR₆, Se-aryl, -N(R₆)₂, +N(R₆)₃ and -NHR₆;

R₆ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl and substituted or unsubstituted heterocyclyl;

R₁₃ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy, substituted or unsubstituted amino and halogen;

X is %H(:O) or %N;

Y is selected from the group consisting of '-0R₄, -CON(R₁₆), CHO, CH₂OH, CH₂N(R₁₇), Se-Aryl, Se(-O)-aryl, said aryl being able to be optionally substituted, -S-R₁₆, -S(-O)-R₁₆, -CH(OAr)₂, -CH(NH)R₁₆CN and -CH(OAr)₂CN;

R₁₆ is in each case independently selected from the group consisting of hydrogen, alkyl and aryl; two R₁₆ groups being able to form a linear or branched alkyldiene group, optionally substituted with one or more carbonyl groups; and

R₁₅ is independently in each case -OH or -OP₆.

The compounds of the invention are intermediate products especially interesting for synthesizing TTX, providing a flexible pathway to its different analogs.

The invention also provides salts of the compounds of the invention with biologically and pharmacologically acceptable inorganic and organic acids, non-limiting examples of which are sulfates; halohydrate salts; phosphates; lower alkane sulfonates; arylsulfonates; salts of C₃-C₂₀ aliphatic mono-, di- or tribasic acids which can contain one or more double bonds, an aryl nucleus or other functional groups such as hydroxyl, amino, or keto; salts of aromatic acids in which the aromatic nuclei may or may not be substituted with groups such as hydroxyl, lower alkyl, amino, mono- or di-(lower alkyl)-amino-sulfonamido. There are also included within the scope of the invention quaternary salts of the tertiary nitrogen atom with lower alkyl halides or sulfates, and oxygenated derivatives of the tertiary nitrogen atom, such as N-oxides. The persons skilled in the art will select the pharmaceutically acceptable salts when preparing dosage formulations.

The term "solvate" according to this invention must be understood as meaning any form of active compound according to the invention which has another molecule (most likely a polar solvent) bound to it through a non-covalent bond. Examples of solvates include hydrates and alcoholates, e.g. methanolae.

The present invention also comprises the different stereoisomers of the compounds of the invention. A "stereoisomer" in the present patent application refers to compounds formed by the same atoms bound by the same bonding sequence but which have different three-dimensional structures that are not exchangeable.

Particular embodiments of the compounds of the invention are made up of the compounds of formula (Ia), (Ib), (Ic), stereoisomers, salts or solvates thereof
[0070] wherein $E$, $R_9$, $R_{10}$, $R_{a}$, $R_b$ and $W$ are as have been defined above.

[0071] According to a particular embodiment $W$ is arylalkyl, preferably $W$ is $C_{6}H_{5}C_{6}H_{4}$-aryl, wherein $R_c$ and $R_d$ are each independently selected from $H$, $OH$, $OPr$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted alkylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted amino and halogen. In a particular embodiment $R_e$ is other than hydrogen and $R_d$ is hydrogen. According to an additional embodiment $R_c$ and $R_d$ are both hydrogen.

[0072] According to a particular embodiment $R_a$ is hydrogen and $R_b$ is selected from the group consisting of halogen, preferably bromine, $OH$, $OPr$ and $Se$-aryl. In another embodiment $R_a$ and $R_b$ are both hydrogen.

[0073] According to a particular embodiment, $Y$ is selected from $OH$, alkoxyl, ammonium and $-NE(=O)(C==O)$-aryl.

[0074] According to a particular embodiment, $E$ is bromine or iodine, preferably bromine.

[0075] According to a particular embodiment, $R_8$ and $R_{10}$ together form a group of formula $-O-Si(R_1)(R_{12})-O-Si(R_1)(R_{12})-O-$, wherein $R_1$ and $R_{12}$ are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic. According to a particular embodiment, $R_{11}$ and $R_{12}$ are isopropyl, for example in the compounds of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (Xa), (XI), (XII), (XIII) or (XIV).

[0076] According to a particular embodiment, $R_1$ is alkyl-OPr. According to another particular embodiment, $R_1$ and $R_2$ together form $-O$, alkylidenec $-O$, alkylidene $-O$, $Pr-O-$. According to a particular embodiment, $R_1$ and $R_2$, in the compounds of formula (X), (Xa), (XI), (XII), (XIII) or (XIV), for example, together form $-CH_2-O-Pr-O-$, wherein $Pr$ is $[(R_1)(R_{12})]$, wherein $R_1$ and $R_{12}$ are as have been defined above, preferably methyl. In another particular embodiment $R_1$ is hydrogen and $R_2$ is OH or OPr.

[0077] In a particular embodiment, $X$ is $CN$.

Synthesis of the Compounds of the Invention

[0078] An aspect of the present invention is a method for synthesizing a compound of formula (II), stereoisomers, salts or solvates thereof, comprising a sequence A which comprises (ai) reacting a compound of formula (I) in the presence of a cyanide ion source, and (aaii) reacting the intermediate obtained in the presence of an electrophile, or a sequence B which comprises (aii) reacting a compound of formula (I) in the presence of an electrophile, and (aii) reacting the intermediate obtained in the presence of a cyanide ion source.

[0079] wherein $R_8$, $R_{10}$, $R_a$, $R_b$ and $W$ are as have been defined above.

[0080] The methods for obtaining the compounds of formula (I), starting materials of the present invention, are described in patent applications PCT/EP2005/005149 and PCT/EP2005/005146, of the same inventors.

[0081] In Sequence A, step (aii) provides a Michael addition on position 4a of the cyclohexene ring of the compound of formula (I). The intermediate enolate of formula (Ia) is produced as a result of said attack.
[0082] The electrophile can be added directly in the reaction medium after the reaction with cyanide ion source, without the need of isolating said intermediate enolate of formula (Ia). Alternatively, said enolate can be trapped and isolated before its reaction with the electrophile.

[0083] In sequence B, the electrophile is first added to provide the corresponding derivative of position 5 (lb)

\[
\begin{align*}
\text{(lb)} & \quad 0 \quad E \quad R_9 \quad R_{10} \quad R_a \quad N - O \quad R_b \quad W \quad O \\
\end{align*}
\]

Michael addition on said derivative is then performed with the cyanide ion. According to a particular embodiment, the derivative of formula (lb) is isolated and then subjected to reaction (bii) in the presence of a cyanide ion source. According to a particular embodiment, the reaction (bii) is also performed in the presence of a base, for example, an organic base such as a trialkylamine (e.g. triethylamine).

[0085] Alternatively, the compounds of formula (I) can be reacted in the presence of a cyanide ion source and, instead of reacting the intermediate obtained in the presence of an electrophile, the intermediate enolate can be reacted with a proton source. Compounds of formula (X), stereoisomers, salts or solvates thereof are obtained as a result.

\[
\begin{align*}
\text{(X)} & \quad R_2 \quad R_1 \quad R_9 \\
\end{align*}
\]

[0086] wherein R_{1}, R_{2}, R_{9}, R_{10}, R_{a}, R_{b} and W are as defined above.

[0087] The different definitions for R_{1} and R_{2} radicals in the compounds of formula (X) can be obtained by following the methods described in the section “Other Reactions” below.

[0088] Of these compounds, the compounds of formula (Xa) described above are a novel subgroup especially useful for synthesizing the TTX. As can be seen, these compounds of formula (Xa) allow arriving, in a few steps, to the compounds of formula (XI), (XII), (XIII) or (XIV), all of them are also novel advanced intermediates for synthesizing TTX compounds.

[0089] In another embodiment, the compounds of formula (X) can be obtained by means of sequence A giving rise to the compounds of formula (II), followed by treatment with base (for example, a trialkylamine such as triethylamine) giving rise to the removal of group E. For example, it is possible to treat a compound of formula (Ia) with NBS to produce the resulting compound of formula (II) wherein E is bromine, which compound can be converted into a compound of formula (X) by means of treatment with triethylamine.

\[
\begin{align*}
\text{(Ia)} & \quad R_2 \quad R_1 \quad R_9 \quad R_{10} \quad R_a \quad N - O \quad R_b \quad W \quad O \\
\text{(II)} & \quad R_2 \quad R_1 \quad R_9 \quad R_{10} \quad R_a \quad N - O \quad R_b \quad W \quad O \\
\text{(X)} & \quad R_2 \quad R_1 \quad R_9 \\
\end{align*}
\]

[0090] According to a particular embodiment, Pr in a compound of formula (Xe) is \( -O\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}(R_{11}R_{12})\text{Si}

[0093] In another embodiment, the reaction can be performed in the presence of KCN (J. Am. Chem. Soc. 1958, 80, 4677-4680). The conditions already described in the art comprise a mixture of KCN with one of the following reaction systems: Et₃O/H₂O (Tetrahedron Letters, 2001, 42, 6259-6262; THF/rt. (Carbohydrate Research 1994, 254, 133-140) or CH₃Cl₂/H₂O/rt., with or without NaHCO₃ (J. Chem. Soc. Perkin Trans 1 1985, 1067-1072).

[0094] In another embodiment, the reaction can be performed in the presence of LiCN. The conditions already described in the art comprise a mixture of LiCN with one of the following reaction systems: Me₂SiCl/THF/rt. (Synthesis, 1986, 12, 1054-1055), DMF/[CH₂Cl₂], PO (Bioorg. Med. Chem. Lett. 1996, 6, 1897-1900), diethyl cyanophosphonate/THF/rt. (Chem. Pharm. Bull. 1986, 34, 4620-4628; Tetrahedron Letters, 1989, 30, 5681-5684) or DMF (Bioorg. Med. Chem. Lett. 2000, 10, 2417-2419).

[0095] Copper cyanide is also a useful cyanide anion source (CuCN/NaHCO₃/H₂O/CH₂Cl₂, Tetrahedron. 1988, 44, 4895-4904).

[0096] In another embodiment, the reaction can be performed in the presence of HCN. The conditions already described in the art comprise a mixture of HCN with one of the following reaction systems: Pyridine/rt. (J. Soc. Chem. Soc. Perkin Trans 1. 1994, 1067-1072), Et₃N/CH₂Cl₂/0°C. (Carbohydrate Research 1986, 155, 236-246) or the in situ generation of HCN mixing Zn(CN)₂ and AlCl₃ (Tetrahedron Asymmetry, 1990, 1, 187-198).

[0097] Therefore, according to an embodiment, the reagent providing a cyanide anion has a formula MCN, wherein M is lithium, potassium, sodium or copper.


[0099] According to an additional embodiment, the reagents providing a cyanide anion are a dialkylaluminium cyanide of formula (alkyl)₂Al—CN or a trialkylsilyl cyanide of formula (alkyl)₃Si—CN, which are available on the market.

[0100] According to a preferred embodiment, the reaction proceeds in the presence of TMSCN or Et₂AlCl.

[0101] According to a particular embodiment, electrophiles useful for the preparation of the compounds of formula (II) are selected of the group consisting of R₁₃S—SR₁₃, for example, Me—S—Me (Yadav, V. K.; Babu, K. G.; Parwez, M. J. Org. Chem. 2004, 69, 3864-3874), or Ph—S—Ph (Morél, G.; Marchand, E.; Ficauca, A. Synthesis 1980, 11, 918-921), R₁₃S—SO₃—R₁₃, for example, Ph—SO₃—Ph (Lythgoe, B.; Waterhouse, I.; J. Chem. Soc. P. T. 1 1979, 2429-2436), CI—PO(O—alkyl), for example, CI—PO(OEt)₂ (Dybowskii, P.; Skowronska, A. Tetrahedron 1991, 32, 4385-4388); CI—O—(O—alkyl), for example, MeO—CO—S—Cl (Sasahara, Y.; Kawamura, S.; Tanade, Y. J. Org. Chem. 1992, 57, 1053-1056); Cl—PO(O—alkyl)₂, for example, Cl—PO(OEt)₂ (Kandil, A. A.; Porter, T. M.; Slesor, K. N. Synthesis 1987, 4, 411-413); ONR₁₃, for example, Ph—NO (Momiyama, N.; Yamamoto, H.; Org. Lett. 2002, 4, 3579-3582); BrSBr₃, for example, BrSBr₃ (Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. J. Am. Chem. Soc. 1981, 103, 4114-4125); or BrSMe (Aoki, I.; Nishihayashi, U.; Sakae, U. Bull. Chem. Soc. Japan 1995, 68, 337-340); R₂Se—SeR₂, for example, Ph-Se—Se-Ph (Wokulnich, P. M.; Baggiofim, E. G.; Hennessy, B. M.; Uskokovic, M. R. Heterocycles 1993, 35, 791-806). These key intermediate products described in document PCT/EP2005/005146 are benzo[d]ienes with the following formula...
wherein the substitution in position Z can create a stereogenic centre. In document PCT/EP2005/005146 a preferred embodiment is that wherein Z is \(-\text{CR}_{a}\text{R}_{b}\)−, wherein Ra and Rb are different and thus create a chiral centre. Thus, according to a preferred embodiment Ra and Rb in the compounds of the invention are different, and a chiral centre is thus created.

Furthermore, document PCT/EP2005/005146 describes as a preferred embodiment compounds wherein the substituent W of the benzospirones above is an arylalkyl group, more preferably wherein W is \(-\text{CR}_{a}\text{R}_{b}\text{Q}\), wherein Ra and Rb in the connector essentially have the same meaning as in the present application, and the substituent Q has \(\pi\) (pi) interactions with those moieties of benzodienone. Thus,

another chiral source arises when Ra and Rb in said connector are different, preferably wherein W is \(-\text{CH}_{a}\text{R}_{b}\)− (e.g., \((\text{S})-1-(\text{1-phenylethoxy})-1\)-azaspiro[3,5]nona-5,8-diene, which is described as compound 5d in document PCT/EP2005/005146). As described in document PCT/EP2005/005146 said configurations provide a stereogenic centre allowing the selectivity or specificity of any other reaction, distinguishing the two double bonds of the benzospirones-mentioned, which are intermediate products in the synthesis of the compounds of the invention. This will open up a pathway to diastereoselective and enantioselective synthesis.

Therefore, by using the chiral materials described in documents PCT/EP2005/005149 and/or PCT/EP2005/005146, the specific stereoisomers and enantiomers of the compounds described in the present invention can be obtained.

To obtain the different compounds of formula (II) or of formula (X) or of formula (XI), the latter or the precursors thereof can be subjected to one or more steps which are selected from the group consisting of:

a) reducing the ketone to hydroxyl group, optionally followed by protecting and/or inverting the configuration of said hydroxyl group;

b) olefinating the ketone to obtain an alkylidene group, optionally followed by dihydroxylation;

c) olefinating the ketone to obtain an alkylidene group, optionally followed by dihydroxylation and subsequent protection of at least one of the hydroxyl groups formed;

d) protecting the ketone;

e) alkylating the ketone; and

f) aminating the ketone.

The ketone of a compound of formula (Ia) for example can be reduced to hydroxyl and to subsequently protect it, or it can be subjected to a Wittig reaction to obtain methylene derivative. The ketone can also be protected (see scheme 2)

Another aspect of the present invention is a method for synthesizing a compound of formula (III) or (XI), stereoisomers, salts or solvates thereof, which comprises reacting a compound of formula (II) or (X), respectively, in the presence of a hydride. The spiranolactam ring is opened by means of this reaction, carbon 10 being able to obtain (according to the TTX numbering) either aldehyde or alcohol depending on the nature of the hydride and of the reaction conditions (for example, by means of choosing the solvent or the number of hydride equivalents). Optionally, the resulting hydroxyl can be protected. Another alternative is oxidizing the aldehyde or alcohol obtained to obtain the corresponding carboxylic acid.
The spirolactam ring is opened in the presence of a hydride, preferably in the presence of an aluminium or boron hydride derivative, for example, 9-BBN, NaBH₄, DIBALH or LiAlH₄ (see for example chapter 19 of “Advanced Organic Chemistry: reactions, mechanisms and structures”, March, J., 5th edition, Wiley-interscience). Other non-limiting hydrides and methods suitable for the present invention are described in Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents. Eds; John Wiley & Sons: New York, 1999: diborane (pages 126-132), BH₃, SMe₂ (pages 48-51), BH₃THF (pages 52-57), (CH₃)₃SnCH(2CH₃)₂BH (pages 160-163) or disopropinocamphor-borane (pages 146-149).

An additional aspect of the invention is a method for synthesizing a compound of formula (IV), stereoisomers, salts or solvates thereof, which comprises

(a) reacting a compound of formula (IIIa) in the presence of a base.

or

(b) when the compound of formula (IV) wherein Ra is —Se-aryl is to be obtained, reacting a compound of formula (IIIb) in the presence of halogen-Se-aryl or aryl-Se-aryl, and a base, preferably a cyclic amino, preferably morpholine.

Methods (a) and (b) for obtaining compounds of formula (IV) can also be used to obtain the compounds of formula (V), depending on the base used. This also forms additional aspects of present invention. In some cases the compounds of formula (V) or the compounds of formula (IV) are exclusively obtained, and in other occasions mixtures of both (see examples 7 and 8 below).

The compounds of formula (V), for example, formally result from the removal of HBr from a compound of formula (IV). Therefore, harsher conditions (higher temperature, stronger bases, excess of bases, greater reaction times, etc.) would favor the formation of compounds of formula (V). As seen by comparing Examples 7 and 8, a more prolonged exposure to the base (example 8) and/or the excess thereof favors the removal and therefore the formation of the compounds of formula (V). In addition, weaker bases cannot perform the removal and they favor the formation of compounds of formula (IV). Other conditions which can favor the formation of compounds of formula (IV) are the use of less base and shorter reaction times.

According to a particular embodiment, the base selected from the group consisting of phosphazenes (P₁, P₂, P₃ and P₄) and related bases such as Verkade’s base; DBU; DABCO; cyclic aliphatic amines such as pyridine, 4-dimethylaminopyridineperidin or morpholine; trialkylamines such as triethylamine or the disopropylamine. According to a particular embodiment, said amines are supported on polymer supports. According to a particular embodiment the base is DBU.

In a particular embodiment, the compound of formula (V) or of formula (IV) obtained is reacted in an acid medium in the presence of a reagent which is selected from the group comprising of HBr, ORₐ, HSRₐ, Se-aryl, aryl-Se-aryl, HN(Rₐ)₂, N(Rₐ)₃, and —NHRₐ.

wherein

Rₐ is selected from the group consisting of substituted or unsubstituted alky1, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aroyl and substituted or unsubstituted heterocyclyl, and

Rₗ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aroyl, substituted or unsubstituted heterocyclyl, —O-alkyl, —O-aryl, —O-arylalkyl, O—(C—O)—alkyl, —O—(C—O)—arylalkyl.

This embodiment allows exchanging group Y to then obtain different derivatives. The nature of said acid medium is not of special importance and any acid system is suitable. Non-limiting examples of substances which can give rise to an acid medium are p-toluenesulfonic acid (p-TsOH) or the like (for example, camphorsulfonic acid), inorganic acids such as hydrochloric acid or sulfuric acid, or acid materials such as some zeolites. Said acids can be supported on polymer supports.

An additional aspect of the present invention is a method for obtaining a compound of formula (VI), stereoisomers, salts or solvates thereof, which comprises reacting a compound of formula (V) in an acid medium in the presence of a reagent which is selected from the group consisting of HORₐ, HSRₐ, Se-aryl, aryl-Se-aryl, HN(Rₐ)₂, N(Rₐ)₃, and —NHRₐ, wherein Rₐ and Rₗ are as have been defined above.

This reaction can also produce compounds of formula (IX), stereoisomers, salts or solvates thereof, a method which also forms an aspect of the invention. See Example 11 below.

Another aspect of the present invention is a method for obtaining a compound of formula (VII), stereoisomers, salts or solvates thereof, which comprises reacting a compound of formula (V) with a base. Said reaction involves the removal of group Y, and it will therefore be more effective the better the leaving group Y is. In a particular embodiment, the reaction is performed on a compound of formula (V) wherein Y is an ammonium group, i.e., a group of formula —N(Rₐ)₃.

An additional aspect of the present invention is a method for obtaining a compound of formula (VIII), stereoisomers, salts or solvates thereof, which comprises reacting a compound of formula (IV) in an acid medium in the presence of a reagent which is selected from the group consisting of HORₐ, HSRₐ, Se-aryl, aryl-Se-aryl, HN(Rₐ)₂, N(Rₐ)₃, and —NHRₐ, wherein Rₐ and Rₗ are as have been defined above.

In a particular embodiment, the methods described comprise introducing a —Se-aryl group, preferably by means of using phenylselenium bromide in position 9, and optionally its subsequent reaction with a group of formula ORₐ, wherein Rₐ is selected from the group consisting of —(C—O) Rₗ and —NHRₐ, wherein Rₐ is as has been defined above.

An additional aspect of the invention is made up of a method for synthesizing a compound of formula (XII) which comprises reacting a compound of formula (XI) in the presence of a base. According to a particular embodiment and similarly with the synthesis of the compounds of formula (IV), the base can be selected from the group consisting of phosphazenes, DBU, DABCO, cyclic aliphatic amines and trialkylamines, preferably DBU.

An additional aspect of the invention is made up of a method for synthesizing a compound of formula (XIII), which comprises deprotecting the hydroxyls of positions 8 and 10, according to the TTT numbering, removing the Pr group of a compound of formula (XII). For the cases wherein Pr is a silicon-based protective group, for example —Si(Rₐ)₂(O) —O—Si(Rₐ)₂(O), the deprotection can be carried
An additional aspect of the invention comprises a method for synthesizing a compound of formula (XV), which comprises reacting a compound of formula (XII), wherein X is —Se-aryl, —SR, or —OR, in the presence of a peroxide, preferably in the presence of peroxide hydroxide. Corresponding oxidized selenium (—Se(=O)—aryl) or sulfur (—S(=O)—R) derivative is formed under these conditions giving rise to transposition in which the double bond between positions 4a and 5 (according to the TTX numbering) takes part and which after hydrolysis provides the compound of formula (XIV). The conditions for performing this type of transformations are known in the state of the art (see for example Scianowski, C. Tetrahedron 2009, 65, 10162-10174; Toyofuku, M. Org. Lett. 2008, 10, 3957-3960; Oshida, M. Chem. Pharm. Bull. 2008, 56, 404-406, for the case of selenium, or Braveman, S. Rearrangements Involving Sulfoxides The Chemistry of Sulphones and Sulphoxides, Chapter 14: John Wiley & Sons, 1988; p. 717-757, for the case of sulfur.

Therefore, another aspect of the invention is a method for synthesizing TTX which comprises transforming a compound of formula (XII) in a compound of formula (XIII) or of formula (XIV), according to the conditions described above. In a preferred embodiment, said compound of formula (XII) is obtained from a compound of formula (XI) according to the conditions described above. In another particular embodiment, said compound of formula (XI) is obtained from the compound of formula (X) according to the conditions described above.

Other Reactions

The compounds of the invention can comprise different hydroxyl groups, the configuration of which can be inverted by means of a Mitsunobu reaction. For example see (Mitsunobu, O.: Synthesis, 1, 1981)

The compounds of formula (II), (III), (VI), (VII), (IX), (Xo), (Xl), (XII), (XIII) or (XIV) can give different combinations for the groups R1 and R2, all of them can be obtained by means of the reaction sequence described in PCT/EP2005/005146 and PCT/EP2005/005149, the content of which is incorporated by reference. For example, see scheme 3.

Scheme 3

Wittig

CH2

1. Dihydroxylation

2. Protection

OH

—O—

Pr

—O—

OPr

R1 and R2 together form

a = O group

1. Ring opening

2. Protection

[0142] The presence of vicinal hydroxyl groups allows the simultaneous protection of two or more hydroxyls. This can be achieved by means of using acetics, such as acetics of isopropylidene, cyclohexylene, cyclopentenyl, arylmethylene, diphenylmethylene, 1,2-diactecals such as dispiroketals, cyclohexane-1,2-diactecals, butane-2,3-diactecals, silylenes, 1,1,3,3-tetraisopropylidisoxanylidenes or N,O-acetals. Additional examples of diol protecting groups can be found in reference books such as Greene and Wuts “Protective Groups in Organic Synthesis”, John Wiley & Sons, Inc., New York, 1999. Borolanes can also be formed on two vicinal hydroxyl groups, for example by using phenyl boronic acid.

[0143] Once the compounds of formula (VI), (VIII) or (IX) wherein X is —CN are obtained, it is easy to obtain the corresponding aldehyde by reduction with DIBAL, for example (see example 13).

[0144] Similarly, —CN (position 4 according to the TTX numbering) in the compounds of formula (XII) or (XIII) can be converted into different functional groups such as —COOR, —CONR1R2, —CHO, —CH2OH, —CH2N(R1R2), —Se-Aryl, —Se(=O)-aryl, said aryl being able to be optionally substituted, —S—R, —S(=O)R, —CH(OOR), —CH(NHR), —CH2CN and —CH2OR. The conditions for said conversions are known by the person skilled in the art. For example, aldehyde (—CH(=O)) can be obtained by reducing the nitrite group with DIBAL, as mentioned in the paragraph above. Alternatively, the —CH2OH group can be obtained by aldehyde reduction in the presence of a reducing agent, either from the aldehyde or directly from the nitrite. In addition, the (—COOH) acid can be obtained by oxidizing the nitrite, aldehyde or —CH2OH group, which can in turn be converted into different acid derivatives such as esters (—COOR), amides (—CONR1R2). The corresponding —CH2OH groups can also be converted into amines or thiol, or the aldehydes to be protected. The conditions for carrying out all these reductions are known by the person skilled in the art and are described in reference books such as chapter 19 of “Advanced Organic Chemistry: reactions, mechanisms and structures”, March, J., 5th edition, Wiley-interscience, for example.

[0145] A —Se-aryl or —SR group from the corresponding aryl can also be obtained by following the known methods. For example, reacting the corresponding hydroxyl with a compound of formula L—Se-aryl in the presence of a base. The group L is a leaving group, for example, nitrile or isothio-


**Naming and Numbering**

The cyclohexane type structures will be named in the examples shown below as 2,3-dihydroxy-1-aminocyclohexane derivatives and they will be numbered according to the numbering indicated below, regardless of the substituent moiety which the molecule has in any position.

![2,3-dihydroxy-1-aminocyclohexane](image)

#### EXAMPES

**[0147]** Abbreviations and acronyms (obtained from Guide for Authors; Abbreviations and Acronyms J. Org. Chem. 2008, 78, 10A)

<table>
<thead>
<tr>
<th>Ac</th>
<th>acetyl</th>
<th>acetyl</th>
<th>acetyl</th>
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<tr>
<td>Bn</td>
<td>benzyl</td>
<td>benzyl</td>
<td>benzyl</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
<td>butyl</td>
<td>butyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
<td>catalytic</td>
<td>catalytic</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
<td>doublet</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>d(t)</td>
<td>double of doublets</td>
<td>double of doublets</td>
<td>double of doublets</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
<td>N,N-dimethylformamide</td>
<td>N,N-dimethylformamide</td>
</tr>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
<td>dimethyl sulfoxide</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dtr</td>
<td>doublet of triplets</td>
<td>doublet of triplets</td>
<td>doublet of triplets</td>
</tr>
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<td>ethyl</td>
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<td>Hz</td>
<td>hertz</td>
<td>hertz</td>
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<tr>
<td>I.R.</td>
<td>infrared spectroscopy</td>
<td>infrared spectroscopy</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
<td>coupling constant</td>
<td>coupling constant</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrometry</td>
<td>low resolution mass spectrometry</td>
<td>low resolution mass spectrometry</td>
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<tr>
<td>m</td>
<td>multiplet</td>
<td>multiplet</td>
<td>multiplet</td>
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<tr>
<td>M</td>
<td>molarity</td>
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<td>molecular weight</td>
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<td>millimole</td>
<td>millimole</td>
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<td>m/z</td>
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<td>mass-to-charge ratio</td>
<td>mass-to-charge ratio</td>
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<td>m.p.</td>
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<td>melting point</td>
<td>melting point</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
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</tr>
<tr>
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<td>phenyl</td>
<td>phenyl</td>
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<td>pyridine</td>
<td>pyridine</td>
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<td>yield</td>
<td>yield</td>
<td>yield</td>
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<td>singlet</td>
<td>singlet</td>
<td>singlet</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated aqueous solution</td>
<td>saturated aqueous solution</td>
<td>saturated aqueous solution</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
<td>triplet</td>
<td>triplet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
<td>room temperature</td>
<td>room temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
<td>tetrabutylammonium fluoride</td>
<td>tetrabutylammonium fluoride</td>
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<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
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<td>tert-butyldimethylsilyl</td>
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<td>trifluoromethanesulfonate</td>
<td>trifluoromethanesulfonate</td>
<td>trifluoromethanesulfonate</td>
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<td>tetrahydrofuran</td>
<td>tetrahydrofuran</td>
<td>tetrahydrofuran</td>
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<td>TMS</td>
<td>trimethylsilyl</td>
<td>trimethylsilyl</td>
<td>trimethylsilyl</td>
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<td>p-toluene sulfonyl (tosyl)</td>
<td>p-toluene sulfonyl (tosyl)</td>
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<td>p-toluene sulfonic acid</td>
<td>p-toluene sulfonic acid</td>
<td>p-toluene sulfonic acid</td>
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</tbody>
</table>

**[0148]** The non-spiranic bicyclic structures synthesized will be named and numbered as indicated below, which does not coincide with the rules established by the IUPAC.

![9-oxabicyclo[3.2.2]nonane](image)

9-oxabicyclo[3.2.2]nonane 9-oxabicyclo[3.2.2]non-5-ene

![9-oxabicyclo[3.3.1]nonane](image)

9-oxabicyclo[3.3.1]non-5-ene 9-oxabicyclo[3.3.0]non-5-ene
Unless otherwise indicated, the chiral products synthesized are racemic (rac) and will be graphically depicted by means of the figure of one of their enantiomers.

Materials and Methods

All the reactions were performed under argon atmosphere, except those indicated in each case. The reagents and solvents used come from the commercial manufacturers Aldrich, Fluka, Merck, Sigma, Acros, Lancaster, SDS or Schlarau, and were purified by common methods (see Armstrong, W. L.; Perrin, D. D. Purification of Laboratory Chemicals; Butterworth-Heinemann: Oxford, 1996) when necessary.

The solvents used were distilled and dried under argon atmosphere as indicated below: CH₃Cl, toluene, benzene, DMSO and DMF on CaH₂ (subsequently dry benzene and DMF market by Aldrich and Fluka, respectively, were used); THF (pre-drying with KOH) and Et₂O on Na/benzophenone; CH₃CN, EtOH and MeOH on molecular sieve of 4 Å in pore diameter (previously activated at 150°C). The CCls₄ marketed by Merck was used without distilling. The dioxide was degasified by passing an argon stream before being used.

The Et₃N, i-Pr₂EtN, i-Pr₂NH and pyridine were distilled under argon atmosphere on CaH₂, n-BuLi marketed by Aldrich was used as a 1.6 M solution in hexanes. 57-80% by weight m-CpBA marketed by Aldrich was used considering that its purity was 57%. NaH (60% in mineral oil) was washed twice with hexane under argon atmosphere immediately before being used. The Celite used was Celite-545 marketed by SDS.

DIBU-polimer bound marketed by Aldrich with reference 595128 was used.

The reaction products were purified by low-pressure column chromatography (flash chromatography), using 60 Merck silica gel (with a 230-400 mesh particle size) as stationary phase and previously distilled solvents as mobile phase. The eluent used is indicated in each case and the ratios of the mixture of solvents used are always volume/volume.

The reactions were monitored by thin layer chromatography (TLC), using 60 F₂₅₄ silica gel chromatography plates marketed by Merck. The plates were developed using iodine vapors, 2% solution of 2,4-dinitrophenylhydrazine in EtOH (with 0.04% by volume of 97% H₂SO₄), 10% solution of phosphonomolybdic acid in EtOH and UV light viewer (254 and 366 nm).

The (completely decoupled) ¹H and ¹³C nuclear magnetic resonance spectra were performed at room temperature in the solvent indicated in each case (CDCl₃, CD₂OD and DMSO-d₆) using the following apparatuses: Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz), Bruker Avance-300 (300 MHz) and Varian INOVA-400 (400 MHz). The chemical shift values are expressed in parts per million (δ, ppm), using as the internal reference the residue signal of the solvent: CDCl₃, 7.26 ppm (¹H-NMR) and 77.0 ppm (¹³C-NMR); CD₂OD, 3.31 ppm (¹H-NMR) and 49.0 ppm (¹³C-NMR).

The ¹H-NMR spectra are described indicating the number of protons and the apparent multiplicity of each signal. The coupling constants (J) are those apparent and are expressed in Hz. The following abbreviations have been used: s (singlet), d (doublet), t (triplet), c (quadruplet), q (quintuplet) and m (multiplet).

The assignment of NNE signals are provided in the double resonance and two-dimensional experiment techniques: DEPT (Distortionless Enhancement by Polarization Transfer), HMEC (Heteronuclear Multiple-Bond Connectivities), HSQC (Heteronuclear Single Quantum Correlation) and nOesy (nuclear Overhauser effect spectroscopy).

The melting points (M.P.) were measured in a Reichert brand Koehler microscope.

The infrared spectra (IR) were recorded in the Perkin-Elmer spectrophotometer models 681 and FT-IR Spectrum One, and the frequencies (ν) of the absorption maxima are expressed in cm⁻¹. The samples were analyzed as films between NaCl crystals or in KBr discs.

The low resolution mass spectra (LRMS) were recorded: (1) by direct injection of the sample in a Hewlett Packard 5973 MSD spectrophotometer using electron impact (EI) ionization technique with 70 eV ionization energy; or (2) in a Hewlett Packard LCMS1100 MSD spectrophotometer (an HPLC-coupled quadrupole analyzer) using electrospray chemical ionization technique (API-IS) in positive or negative modes, applying a capillary voltage of 4000 V, a drying temperature of 350°C and using a [1:1] H₂O/MEOH mixture with 1% AcOH as a carrier. The data obtained are expressed in mass units (m/z) and the values in parenthesis correspond to the relative intensities with respect to the base peak (100%). The molecular peak is specified as M⁺.

Example 1

Preparation of rac-(4R,5S,6S)-1-benzyl-8-bromo-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxy)-1,3-diy]-1-azaspiro[3.5]non-8-en-2,7-dione

A solution of Br₂ (64.9 mg, 0.40 mmol, 1.08 eq.) in CH₂Cl₂ (1 ml) was added in a solution of rac-(4R,5S,6S)-1-benzyl-8-bromo-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diy]-1-azaspiro[3.5]non-8-en-2,7-dione
loxane-1,3-diyl)-1-aZaspiro[3.5]non-8-ene-2,7-dione (200 mg, 0.376 mmol, 1.0 eq) in CH₂Cl₂ (1 ml) at 0° C. The resulting mixture was stirred at 0° C for 10 minutes. After that time, Et₂N (57.08 mg, 0.564 mmol, 1.5 eq) was added dropwise. The mixture was stirred at room temperature for 10 minutes. The solvent was then removed at reduced pressure. The residue was titrated with Et₂O, it was filtered through Celite and the solvent was removed at reduced pressure. The product, rac-(4R,5S,6S,8R,9S)-1-benzyloxy-8-bromo-9-cyano-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-aZaspiro[3.5]nonane-2,7-dione, was used in the following reaction without purifying (the yield has been considered quantitative).

Example 2 Preparation of rac-(4R,5S,6S,8R,9S)-1-benzyloxy-8-bromo-9-cyano-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-aZaspiro[3.5]nonane-2,7-dione

Example 3 Preparation of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-(benzoxymethyl) cyclohexane-6-carbonitrile

Example 2 Preparation of rac-(4R,5S,6S,8R,9S)-1-benzyloxy-8-bromo-9-cyano-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-aZaspiro[3.5]nonane-2,7-dione

Example 3 Preparation of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-(benzoxymethyl) cyclohexane-6-carbonitrile
ldisiloxane-1,3-diyl)-1-(benzylamino)cyclohexane-6-carbonitrile (866 mg, yield: 32%) being obtained as a white solid.

**[0173]** Pf: 103-104°C.

**[0174]** 1H-NMR (δ): 9.74 (1H, s); 7.36 (5H, m, Ar—H); 6.07 (1H, s); 4.77 (1H, d, J=11.7 Hz); 4.68 (1H, d, J=11.7 Hz); 4.49 (1H, m); 4.35 (1H, d, J=2.5, 11.8 Hz); 4.16 (1H, m); 4.15 (1H, m); 3.54 (1H, d, J=11.8 Hz); 3.50 (1H, d, J=18.5 Hz); 2.91 (1H, d, J=4.6 Hz); 2.87 (1H, d, J=18.5 Hz); 1.047 (28H, m).

**[0175]** 13C-NMR (δ): 199.3, 136.2, 128.8, 128.5, 128.3, 118.3, 76.7, 73.1, 72.5, 71.3, 66.1, 47.6, 43.7, 36.3, 17.6, 17.4, 17.4, 17.2, 17.1, 17.1, 17.0, 17.0, 13.9, 13.4, 13.0, 12.5.

**[0176]** LRMS (API-ES†): m/z 641 (M+H)+, 1304 (M+Na+H)+.

**[0177]** IR (KBr): ν 3523, 2946, 2867, 2246, 1720, 1464, 1388, 1248, 1102, 1014, 885, 754, 698 cm⁻¹.

**Example 4**

Preparation of rac-(4R,5S,6S,8R,9S)-1-benzyl-9-cyano-5,6,7-trihydroxy-5,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-azaspiro[3.5]nonan-2-one

**[0178]**

**[0179]** NaBH₄ (15.65 mg, 0.41 mmol, 1.1 eq.) was added in a solution of rac-(4R,5S,6S,8R,9S)-1-benzyl-9-cyano-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-azaspiro[3.5]nonane-2,7-dione (239 mg, 0.376 mmol, 1.0 eq.) in EtOH (10 ml) at 0°C. The mixture was stirred at 0°C for 30 minutes. After that time, H₂O (20 ml) was added at 0°C. The phases were separated, and the aqueous phase was extracted with AcOEt (3×10 ml). The organic phase was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt; 9:1), rac-(4R,5S,6S,9S)-1-benzyl-9-cyano-5,6,7-trihydroxy-5,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-azaspiro[3.5]nonan-2-one (44 mg, yield: 21%) being obtained as a white solid.

**[0180]** 1H-NMR (δ): 7.41 (5H, m, Ar—H); 5.04 (1H, d, J=12.0 Hz); 4.87 (1H, d, J=12.0 Hz); 4.46 (1H, m); 4.09 (1H, d, J=3.1 Hz); 3.90 (1H, d, J=3.1 Hz); 3.32 (1H, m); 3.10 (1H, d, J=14.1 Hz); 2.66 (1H, d, J=14.1 Hz); 1.69 (2H, m); 1.05 (28H, m).

**[0181]** LRMS (API-ES†): m/z 561 (M+H)+, 583 (M+Na)+, 1144 (2M+Na+H)+.

**Example 5**

Preparation of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-hydroxyethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzylamino)cyclohexane-6-carbonitrile

**[0182]**

**[0183]** NaBH₄ (26.0 mg, 0.687 mmol, 1.1 eq.) was added in a solution of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-hydroxyethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzylamino)cyclohexane-6-carbonitrile (0.4 g, 0.625 mmol, 1 eq.) in EtOH (16 ml) at 0°C. The resulting mixture was stirred at 0°C for 5 minutes. After that time, an aqueous solution of 0.1 M NaHPO₄ (8 ml) and AcOEt (10 ml) was added. The phases were separated, and the aqueous phase was extracted with AcOEt (3×10 ml). The organic phase was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 8:1), rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-hydroxyethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzylamino)cyclohexane-6-carbonitrile (330 mg, yield: 82%) being obtained as a colorless oil.

**[0184]** 1H-NMR (δ): 7.36 (5H, m, Ar—H); 5.93 (1H, s); 4.72 (2H, s, —OCH₂Ph); 4.46 (1H, d, J=2.4 Hz); 4.45 (1H, dd, J=2.7, 11.7 Hz); 4.33 (1H, m); 4.19 (1H, m); 3.89 (1H, m); 3.50 (1H, d, J=11.7 Hz); 3.15 (1H, d, J=5.6 Hz); 2.34 (1H, m); 2.26 (1H, m); 2.13 (1H, m); 1.06 (28H, m).
13C-NMR (δ): 135.8, 128.7, 128.6, 128.5, 118.6, 77.0, 73.6, 73.4, 71.3, 66.3, 58.1, 49.1, 37.9, 36.3, 17.4, 17.4, 17.3, 17.2, 17.1, 17.1, 14.1, 13.5, 13.2.

LRMS (API-IS²): m/z 643 (M+H)⁺, 644 (M+2H)⁺, 645 (M+3H)⁺, 665 (M+Na+H)⁺, 1308 (2M+Na+H)⁺.

IR (KBr): ν 3468, 3027, 2945, 2890, 2867, 2247, 1464, 1386, 1160, 1013, 885, 697 cm⁻¹.

Example 6
Preparation of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-tert-butyldimethylsilyloxyethyl)-2,3,4-trihydroxy-2,3-0-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzoyl氧amino)cyclohexane-6-carbonitrile

1H-NMR (δ): 7.36 (5H, m, Ar–H); 6.00 (1H, s); 4.67 (1H, d, J=15.0 Hz); 4.65 (1H, d, J=15.0 Hz); 4.43 (1H, s, broad); 4.37 (2H, m); 4.15 (1H, m); 3.92 (2H, m); 3.52 (1H, d, J=11.9 Hz); 3.21 (1H, d, J=5.6 Hz); 2.32 (1H, dt, J=7.4, 13.6 Hz); 2.04 (1H, dt, J=6.7, 7.4 Hz); 1.06 (28H, m); 0.86 (9H, s); 0.03 (6H, s).

Example 7
Reaction of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzoyl氧amino)cyclohexane-6-carbonitrile with DBU

[188]

A solution of THDMSCl (303 mg, 1.697 mmol, 3.3 eq.) in DMF (5 ml) was added in a solution of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzoyl氧amino)cyclohexane-6-carbonitrile (330 mg, 0.514 mmol, 1 eq.) and imidazole (115 mg, 1.697 mmol, 3.3 eq.) in DMF (12 ml) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. After that time, H₂O (15 ml) and AcOEt (15 ml) were added. The phases were separated, and the aqeous phase was extracted with AcOEt (4x7 ml). The organic phase was washed with a saturated aqueous solution of CuSO₄ (5 ml) and brine (4x7 ml), it was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 30:1), rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-tert-butyldimethylsilyloxyethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzoyl氧amino)cyclohexane-6-carbonitrile (264 mg, yld.: 68%) being obtained as a colorless oil.

[194] DBU (24 mg, 0.156 mmol, 1 eq.) was added in a solution of rac-(1R,2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-(benzoyl氧amino)cyclohexane-6-carbonitrile (100 mg, 0.156 mmol, 1 eq.) in CH₂Cl₂ (2 ml) at 0°C. The resulting mixture was stirred at room temperature for 3 hours. After that time, CH₂Cl₂ (10 ml) was added and the mixture was washed with a saturated aqueous solution of CuSO₄ (1×5 ml) and brine (1×5 ml), it was dried with anhy-
drous Na$_2$SO$_4$, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 8:1), rac-(2S,3S,5S,6R,8R)-1-(benzoxylamino)-5-bromo-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-9-oxabicyclo[3.2.2]nonane-6-carbonitrile (34 mg, yld.: 39%) was obtained as a colorless oil, and rac-(2S,3S,8R)-1-(benzoxylamino)-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile.

Example 8

**Method 1.**

![Chemical Structure](image)

rac-(2S,3S,5S,6R,8R)-1-(benzoxylamino)-5-bromo-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-9-oxabicyclo[3.2.2]nonane-6-carbonitrile. 

**Method 2.**

![Chemical Structure](image)

rac-(2S,3S,5S,6R,8R)-1-(benzoxylamino)-5-bromo-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile.
CH$_2$Cl$_2$ (11 ml) was added in a mixture of rac-(1R, 2S,3S,4R,5S,6R)-5-bromo-1-(2-oxoethyl)-2,3,4-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsilsloxane-1,3-diy)-1-(benzylamino)cyclohexane-6-carbonitrile (555 mg, 0.862 mmol, 1 eq.) and DBU-polymer bound (1.5 g, 1.724 mmol, 2.0 eq.) at 0°C. The resulting mixture was stirred at room temperature for 11 hours. After that time, the mixture was filtered in a Büchner with AcOEt and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 8:1), rac-(2S,3S,8R)-1-(benzylamino)-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diy)-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile (256 mg, yield: 53%) being obtained as a white solid.

Example 9
Preparation of rac-(2S,3S,5S,6R,8R)-1-(benzylamino)-5-bromo-2,3,8-trihydroxy-9-oxabicyclo[3.2.2]nonane-6-carbonitrile

3HF,Et$_3$N (517 mg, 3.209 mmol, 36 eq.) was added in a solution of rac-(2S,3S,8R)-1-(benzylamino)-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diy)-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile (50 mg, 0.089 mmol, 1 eq.) in MeOH (5 ml). The mixture was stirred at room temperature for 24 hours. After that time, an aqueous solution of Na$_2$HPO$_4$ (0.1M, 5 ml) and AcOEt (10 ml) was added. The phases were separated, and the aqueous phase was extracted with AcOEt (5×4 ml). The organic phase was dried with anhydrous Na$_2$SO$_4$, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 1:8), rac-(2S,3S,8R)-1-(benzylamino)-2,3,8-trihydroxy-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile (26 mg, yield: 93%) being obtained.

Example 10
Preparation of rac-(2S,3S,8R)-1-(benzylamino)-2,3,8-trihydroxy-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile

3HF,Et$_3$N (310 mg, 1.928 mmol, 36 eq.) was added in a solution of rac-(2S,3S,8R)-1-(benzylamino)-5-bromo-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diy)-9-oxabicyclo[3.2.2]non-6-carbonitrile (31 mg, 0.054 mmol, 1 eq.) in MeOH (3 ml). The mixture was stirred at room temperature for 24 hours. After that time, an aqueous solution of Na$_2$HPO$_4$ (0.1M, 3 ml) and AcOEt (6 ml) was added. The phases were separated, and the aqueous phase was extracted with AcOEt (3×5 ml). The organic phase was dried with anhydrous Na$_2$SO$_4$, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 1:8), rac-(2S,3S,8R)-1-(benzylamino)-5-bromo-2,3,8-trihydroxy-9-oxabicyclo[3.2.2]non-6-carbonitrile (8 mg, yield: 37%) being obtained.

$[0211]$ $^1$H-NMR (δ): 7.34 (S, 1H, $s_{broad}$); 5.94 (1H, $s_{broad}$); 5.56 (1H, m); 4.71 (2H, m); 4.63 (1H, m); 4.49 (1H, m); 4.21 (2H, m); 3.82 (1H, m); 3.53 (1H, m); 2.44 (1H, d, $J=11.9$ Hz); 3.24 (1H, m); 2.26 (1H, m); 2.04 (1H, m).

$[0212]$ LRMS (API-MS$^*$): m/z 381 (M+H$_2$O)$^*$, 421 (M+Na)$^*$. 

$[0213]$
Example 11
Preparation of rac-(2S,3R,4S,8R)-1-(benzoxymino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile


[0218] p-TsOH (cat.) was added in a solution of rac-(2S, 3R,8R)-1-(benzoxymino)-2,3,8-trihydroxy-2,3-O-(1,1,3,3-tetramisopropyldisiloxane-1,3-diy1)-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile (102 mg, 0.182 mmol, 1 equiv.) in MeOH (7 mL) at room temperature. The resulting mixture was stirred at 55-60°C for 36 hours. After that time, Celite was added and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 1:2), rac-(2S,3R,4S,8R)-1-(benzoxymino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile (51 mg, yield: 84%) and rac-(2S,3R,4S,8R)-1-(benzoxymino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile (3 mg, yield: 5%) both being obtained as a colorless oil.

[0219] Method 2

[0220] p-TsOH (cat.) was added in a solution of rac-(2S, 3R,8R)-1-(benzoxymino)-2,3,8-trihydroxy-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile (82 mg, 0.257 mmol, 1 equiv.) in MeOH (55 mL) at room temperature. The resulting mixture was stirred at room temperature for 36 hours. After that time, Celite was added and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 1:2), rac-(2S,3R,4S,8R)-1-(benzoxymino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile (70 mg, yield: 82%) and rac-(2S,3R,4S,8R)-1-(benzoxymino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile (4 mg, yield: 5%) both being obtained as a colorless oil.

Example 12
Preparation of rac-(2S,3R,4S,8R)-1-(benzoxymino)-4-tert-butylidemethylsilyloxy-2-hydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile

[0231]
[0232] A solution of TBDMSCl (57.15 mg, 0.379 mmol, 3.0 eq.) in DMF (2 ml) was added in a solution of rac-(2S, 3R,4S,8R)-1-(benzoxylamino)-2,4-dihydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carboxitrole (42 mg, 0.126 mmol, 1 eq.) and imidazole (25.8 mg, 0.379 mmol, 3.0 eq.) in DMF (3 ml) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. After that time, H₂O (15 ml) and AcOEt (15 ml) were added. The phases were separated, and the aqueous phase was extracted with AcOEt (4×7 ml). The organic phase was washed with a saturated aqueous solution of CuSO₄ (2×15 ml) and brine (1×7 ml), it was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 4:1), rac-(2S,3R,4S,8R)-1-(benzoxylamino)-4-tert-butyldimethylsilyloxy-2-hydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carboxitrole (39 mg, yield: 70%) was obtained as a colorless oil.

[0233] 1H-NMR (δ): 7.31 (5H, m); 6.41 (1H, m); 6.39 (1H, s); 5.14 (1H, d, J=5.2 Hz); 4.73 (2H, s); 4.70 (1H, d, J=3.5 Hz); 4.36 (1H, m); 4.05 (1H, m); 3.35 (3H, s); 2.36 (1H, dd, J=5.4, 15.3 Hz); 1.97 (1H, d, J=13.5 Hz); 0.91 (9H, s); 0.11 (3H, s); 0.09 (3H, s).

[0234] 13C-NMR (δ): 147.2, 137.3, 128.8, 128.7, 128.3, 117.1, 116.6, 105.6, 79.3, 77.6, 71.9, 69.2, 67.1, 55.5, 41.4, 25.9, 18.3, 4.6, -4.7.

[0235] LRMS (API-IS⁰): m/z 415 (M-O-Me)⁺, 469 (M+Na)⁺.

[0236] IR (KBr): ν 3487, 3261, 2953, 2929, 2857, 2224, 1725, 1471, 1362, 1255, 1124, 1062, 1044, 895, 839 cm⁻¹.

Example 13
Preparation of rac-(2S,3R,4S,8R)-1-(benzoxylamino)-4-tert-butyldimethylsilyloxy-2-hydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carboxaldehyde

[0237] DIBAL (21.3 mg, 0.148 mmol, 2.0 eq.) was added in a solution of rac-(2S,3R,4S,8R)-1-(benzoxylamino)-4-tert-butyldimethylsilyloxy-2-hydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carboxaldehyde (33 mg, 0.074 mmol, 1 eq.) in THF (2 ml) at 0°C. The resulting mixture was stirred at 0°C for 2 hours. After that time, AcOEt (2 ml) was added at 0°C, and the mixture was stirred at 0°C for 5 minutes. Saturated NaCl (8 ml) was then added. The phases were separated, and the aqueous phase was extracted with AcOEt (3×5 ml). The organic phase was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 3:1), rac-(2S,3R,4S,8R)-1-(benzoxylamino)-4-tert-butyldimethylsilyloxy-2-hydroxy-8-methoxy-9-oxabicyclo[3.3.1]non-5-ene-6-carboxaldehyde (8 mg, yield: 32%) being obtained, and the starting product (8 mg) was recovered.

[0239] 1H-NMR (δ): 9.44 (1H, s); 7.34-7.20 (5H, m); 6.51 (1H, d, J=1.6, 3.3 Hz); 6.44 (1H, s); 5.18 (1H, d, J=5.4 Hz); 4.65 (1H, d, J=11.1 Hz); 4.63 (1H, d, J=3.4 Hz); 4.52 (1H, d, J=11.1 Hz); 4.51 (1H, m); 4.09 (1H, m); 3.40 (3H, s); 2.32 (1H, m); 2.27 (1H, d, J=14.1 Hz); 2.16 (1H, dd, J=5.4, 14.1 Hz); 0.92 (9H, s); 0.13 (3H, s); 0.12 (3H, s).

[0240] LRMS (API-IS⁰): m/z 415 (M-O-Me)⁺, 450 (M+H)⁺, 473 (M+H+Na)⁺, 880 (2M-H₂O)⁺.

Example 14
Preparation of rac-(2S,3R,4S,8R)-1-(benzoxylamino)-8-(benzoyloxy)(methyl)amino)-2,3,8-trihydroxy-2,3,6-(1,1,3,3-tetraisopropylidiloxilane-1,3-diy1)-9-oxabicyclo[3.2.2]non-5-ene-6-carboxitrole

[0241] N-methyl-O-benzoylhydroxylamine hydrochloride (46.8 mg, 0.249 mmol, 2 eq.) was added in a solution of rac-(2S,3R,4S,8R)-1-(benzoxylamino)-2,3,8-trihydroxy-2,3,6-(1,1,3,3-tetraisopropylidiloxilane-1,3-diy1)-9-oxabicyclo[3.2.2]non-5-ene-6-carboxitrole (70 mg, 0.124 mmol, 1 eq.) in DMSO (1.5 ml). The mixture was stirred at room temperature for 48 hours. After that time, AcOEt (10 ml) was added, it was washed with brine (2×5 ml). The organic phase was dried with anhydrous Na₂SO₄, it was filtered and the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 9:1), rac-(2S,3R,4S,8R)-1-(benzoxylamino)-8-(benzoxy)(methyl)amino)-2,3,8-trihydroxy-2,3,6-(1,1,3,3-tetraisopropylidiloxilane-1,3-diy1)-9-oxabicyclo[3.2.2]non-5-ene-6-carboxitrole (41 mg, yield: 47%) being obtained as a white solid.

[0243] 1H-NMR (δ): 8.01 (2H, m); 7.57 (1H, m); 7.42 (2H, m); 7.27 (5H, m); 6.64 (1H, s); 5.50 (1H, dd, J=1.7, 3.4 Hz); 5.06 (1H, m); 4.72 (1H, m); 4.64 (2H, m); 4.49 (1H, m); 2.88 (1H, s); 2.50 (1H, dd, J=7.8, 14.2 Hz); 1.96 (1H, dd, J=2.4, 14.2 Hz); 1.01 (28H, m).

[0244] 13C-NMR (δ): 164.8, 148.1, 137.2, 133.4, 129.6, 128.8, 128.5, 127.9, 112.9, 114.9, 96.5, 97.4, 79.4, 77.2, 74.7, 72.2, 67.3, 41.7, 38.4, 17.5, 17.4, 17.2, 17.1, 17.0, 14.0, 13.6, 13.0, 12.6.

[0245] LRMS (API-IS⁰): m/z 694 (M+H)⁺, 695 (M+2H)⁺, 716 (M+Na)⁺.

[0246] IR (KBr): ν 3218, 2945, 2867, 2225, 1747, 1464, 1365, 1257, 1156, 1062, 1010, 886, 755, 707 cm⁻¹.
Example 15
Preparation of rac-(2S,3S,8R)-1-(benzylxoyamino)-2,3-dihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-7-phenylselenyl-8-methoxy-9-oxabicyclo[3.2.2]non-5-ene-6-carbonitrile

[0247]

DBU (25.11 mg, 0.162 mmol, 1 eq.) was added in a solution of rac-(2S,3S,5S,6R,8R)-1-(benzylxoyamino)-5-bromo-2,3-dihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-7-phenylselenyl-8-morpholin-9-oxabicyclo[3.2.2]nonane-6-carbonitrile (122 mg, 0.155 mmol, 1 eq.). CH₂Cl₂ (6 ml) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. After that time, the solvent was removed at reduced pressure. The product was purified by means of column chromatography (hexane/AcOEt, 8:1), rac-(2S,3S,8R)-1-(benzylxoyamino)-2,3-dihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-7-phenylselenyl-8-morpholin-9-oxabicyclo[3.2.2]nonane-6-carbonitrile (82 mg, yld.: 65%) being obtained as an oil.

[0249] p-TsOH (cat.) was added in a solution of rac-(2S,3S,8R)-1-(benzylxoyamino)-2,3-dihydroxy-2,3-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-7-phenylselenyl-8-methoxy-9-oxabicyclo[3.2.2]nonane-5-ene-6-carbonitrile (42 mg, yld.: 37%) being obtained as a brown oil.

[0251] 1H-NMR (δ): 7.54 (1H, m); 5.70 (1H, d, J=7.2 Hz); 5.60 (1H, d, J=6.9 Hz); 5.18 (1H, d, J=7.3 Hz); 5.10 (1H, d, J=2.5 Hz); 5.03 (2H, m); 4.95 (2H, m); 4.70 (1H, m); 4.57 (1H, m); 4.51 (1H, m); 4.46 (1H, m); 4.37 (1H, m); 4.06 (1H, m); 3.98 (1H, m); 3.67 (3H, s); 3.63 (3H, s); 3.56 (3H, s); 3.51 (3H, s); 3.54 (1H, m); 2.35 (1H, m); 1.07 (28H, m).

[0252] 1RMS (API-MS⁺): m/z 729 (M+H)⁺, 731 (M+H)⁺, 732 (M+2H)⁺, 733 (M+3H)⁺, 753 (M+4Na)⁺.

Example 16
Preparation of rac-(4R,5S,6S)-1-benzylxoy-9-cyano-5,6-dihydroxy-5,6-O-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-1-azispiro[3.5]nonane-8-ene-2,7-dione (2)

[0253]
Example 17
Preparation of rac-(4R,5S,6S)-1-benzzyloxy-9-cyano-5,6-dihydroxy-7-methylidene-5,6-O-(1,3,3-tetramisopropyldisiloxane-1,3-diy1)-azaspiro(3.5)non-8-en-2-one (3)

[0254]  Et₂AlCN (413 mg, 3.71 mmol) was added in a solution of 1 (1.65 g, 3.09 mmol) in 32 ml of THF at 0°C. The resulting solution was heated to 80°C for 3 hours. After that time the mixture was cooled to 0°C and NBS (827 mg, 4.64 mmol) was added. The resulting solution was stirred at room temperature for 15 minutes. After that time, the solvent was removed at reduced pressure. The residue was titrated with Et₃O, it was filtered in sieve plate no. 3 through Celite® with Et₃O and the solvent was removed at reduced pressure. The residue was dissolved in 39 ml of CH₂Cl₂, Et₃N (351 mg, 3.47 mmol) was added to the solution at 0°C. The solution was stirred at room temperature for 15 minutes. After that time, Celite® was added to the reaction and the solvent was removed at reduced pressure. The product 2 was isolated after column chromatography separation (hexane/ChCl₂, 10:1), being obtained as a yellow solid.

[0255] P.F.: 115-118°C C.

[0256] 'H-NMR: δ 7.37 (5H, m); 6.19 (1H, s); 5.09 (1H, part A syst. AB, J=11.7 Hz); 4.92 (1H, part B syst. AB, J=11.7 Hz); 4.89 (1H, d, J=2.3 Hz); 4.50 (1H, d, J=2.3 Hz); 3.14 (1H, part A syst. AB, J=14.8 Hz); 3.05 (1H, part B syst. AB, J=14.8 Hz); 1.06 (22H, m); 0.94 (3H, d, J=3.5 Hz); 0.90 (3H, d, J=2.0 Hz).

[0257] 13C-NMR: δ 192.0, 164.3, 138.1, 134.7, 129.7, 129.5, 129.1, 127.6, 114.4, 79.9, 77.2, 74.8, 65.2, 42.6, 17.4, 17.3, 17.2, 17.0, 16.8, 16.6, 14.0, 13.5, 13.3, 12.4.

[0258] LRMS (API-IS+): m/z 589 (M+H)+, 611 (M+Na)+, 1200 (2M+Na)+.

[0259] IR (KBr): ν 3436, 2946, 2890, 2868, 2075, 1799, 1697, 1462, 1372, 1262, 1160, 1105, 1053, 1009, 994, 968, 932, 886, 841, 790, 753, 699 cm⁻¹.


[0261] n-BuLi (93 mg, 1.45 mmol) was added dropwise in a suspension of triphenylphosphonium bromide (499 mg, 1.40 mmol) in 20 ml of THF at −78°C. The suspension was stirred at −78°C for 15 minutes. After that time, 2 (622 mg, 1.12 mmol) dissolved in 15 ml of THF was added dropwise at −78°C. The suspension was stirred at −78°C for 1 hour and then at 0°C for 18 hours. After that time, the solvent was removed at reduced pressure. The residue was titrated with Et₂O (the process is repeated 3 times). Celite® was added to the reaction crude and the solvent was removed at reduced pressure. The product 3 was filtered on 60 Merck silica with Et₂O a brown solid being obtained (when product 3 was isolated after column chromatography separation (hexane/ChCl₂, 20:1) it was obtained as a white solid). The reaction crude was used in the dihydroxylation reaction of the exocyclic double bond.

[0262] 'H-NMR: δ 7.36 (5H, m); 6.74 (1H, s); 5.63 (1H, s); 5.50 (1H, m); 5.07 (1H, part A syst. AB, J=11.4 Hz); 4.94 (1H, part B syst. AB, J=11.4 Hz); 4.86 (1H, d, J=2.6, 1.4 Hz); 4.36 (1H, d, J=2.6 Hz); 3.22 (1H, part A syst. AB, J=14.3 Hz); 2.83 (1H, part B syst. AB, J=14.3 Hz); 1.07 (28H, m).


[0265] LRMS (API-IS+): m/z 513 (M−Pr+H)+, 555 (M+H)+, 577 (M+Na)+, 1131 (2M+Na)+.

[0266] IR (film): ν 3436, 3033, 2945, 2890, 2868, 2220, 1787, 1770, 1629, 1464, 1385, 1250, 1156, 1060, 1013, 967, 912, 886, 843, 792, 747, 679 cm⁻¹.
Example 18
Preparation of rac-(4R,5S,6S,7R)-1-benzylxoy-9,10-cyano-5,6,7-trihydroxy-7-(hydroxymethyl)-5,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-azaspiro[3.5]non-8-en-2-one (4)

NMO (290 mg, 2.47 mmol) and dissolved OsO<sub>4</sub> (0.85 ml, 2.5% by weight in 'BuOH, 0.07 mmol) were added in a solution of 3 (624 mg, 1.125 mmol) in 16 ml of acetone and 3.2 ml of H<sub>2</sub>O at room temperature. The solution was stirred at room temperature for 17 hours. After that, Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (10%, 3.4 ml) was added at room temperature and was stirred for 5 minutes. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (7x15 ml). The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, they were filtered and the solvent was removed at reduced pressure. Celite<sup>®</sup> and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 4 was filtered on 60 Merck silica (hexane/AcOEt, 1:1) a brown oil being obtained (when product 4 was isolated after column chromatography separation (hexane/AcOEt, 3:1) it was obtained as a white solid). The reaction crude was used in the protection reaction of the generated diol.

P. f.: 128-131° C.

Example 19
Preparation of rac-(4R,5S,6S,7R)-1-benzylxoy-9,10-cyano-5,6,7-trihydroxy-7-(hydroxymethyl)-5,6-O-(propane-2,2-diyl)-5,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-azaspiro[3.5]non-8-en-2-one (5)

[0273] IR (KBr): v 3438, 2947, 2869, 2231, 1778, 1633, 1466, 1389, 1369, 1249, 1214, 1153, 1094, 1006, 971, 929, 885, 840, 790, 745, 697 cm<sup>-1</sup>.

[0274] HRMS (ESI<sup>+</sup>): calculated for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> (M+NH<sub>4</sub>)<sup>+</sup> 606.3031; 606.3040 found (Δm=2.41).

[0275] 2,2-dimethoxypropane (310 mg, 2.98 mmol) and a catalytic amount of p-toluenesulfonic acid were added in a solution of 4 (585 mg, 0.99 mmol) in 40 ml of acetone at 0° C. The solution was stirred at room temperature for 18 hours. After that, Celite<sup>®</sup> was added to the reaction crude and the solvent was removed at reduced pressure. The product 5 was isolated after column chromatography separation (hexane/AcOEt, 6:1), being obtained as a white solid.

P. f.: 159-162° C.

[0276] 1H-NMR: δ 7.45 (2H, m); 7.37 (3H, m); 6.38 (1H, d, J=1.4 Hz); 5.11 (1H, part A syst. AB, J=12.1 Hz); 4.96 (1H, part B syst. AB, J=12.1 Hz); 4.65 (1H, d, J=2.4 Hz); 4.31 (1H, dd, J=2.4, 1.4 Hz); 3.68 (1H, part A syst. AB, J=10.9 Hz); 3.63 (1H, part B syst. AB, J=10.9 Hz); 3.24 (1H, part A syst. AB, J=14.2 Hz); 2.65 (1H, part B syst. AB, J=14.2 Hz); 2.26 (1H, s<sub>broad</sub>, OH); 2.04 (1H, s<sub>broad</sub>, OH); 1.05 (28H, m).

[0277] 13C-NMR: δ 164.6, 144.5, 135.3, 128.8, 128.6, 5, 117.9, 115.2, 111.5, 79.3, 79.0, 74.8, 70.6, 68.5, 64.3, 40.4, 26.9, 26.4, 17.7, 17.6, 17.5, 17.1, 17.0, 16.9, 14.4, 14.0, 13.3, 13.2.

[0278] LRMS (API-IS<sup>+</sup>): m/z 571 (M=H<sub>2</sub>O+H)<sup>+</sup>, 589 (M+H)<sup>+</sup>, 611 (M+Na)<sup>+</sup>, 1199 (2M+Na)<sup>+</sup>.

[0279] IR (KBr): v 3436, 3063, 2947, 2869, 2225, 1785, 1641, 1466, 1373, 1259, 1219, 1182, 1151, 1125, 1097, 1064, 999, 946, 926, 886, 845, 798, 759, 745, 697, 663, 607, 517 cm<sup>-1</sup>.

[0280] LRMS (API-IS<sup>+</sup>): calculated for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> (M+H)<sup>+</sup> 629.3078; 629.3000 found (Δm=1.66).
Example 20
Preparation of rac-(1R,2S,3S,4R)-1-(benzylamino)-2,3,4-trihydroxy-4-(hydroxymethyl)-4,7-O-(propane-2,2-diyl)-2,3-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)-1-(2-oxoethyl)cyclohex-5-ene-6-carbonitrile (6)

[0283] \[ \text{DIBAL-H (318 mg, 2.20 mmol) was added in a solution of 5 (462 mg, 0.74 mmol) in 26 ml of THF at 0°C. The solution was stirred at 0°C for 1 hour. After that time, 26 ml of AcOEt was added at 0°C and it was stirred at 0°C for 5 minutes. Saturated NaCl (15 ml) was then added at 0°C. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (6×15 ml). The combined organic extracts were dried with anhydrous Na$_2$SO$_4$; they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. The product 6 was isolated after column chromatography separation (hexane/AcOEt, 10:1), being obtained as a colorless oil.} \]

[0284] \[ \text{H-NMR: δ 9.82 (1H, t, J=2.5 Hz); 7.33 (5H, m); 6.59 (1H, s); 5.84 (1H, s$_{max}$, NH); 4.84 (1H, part A syst. AB, J=11.9 Hz); 4.79 (1H, part B syst. AB, J=11.9 Hz); 4.75 (1H, d, J=2.9 Hz); 4.53 (1H, d, J=2.9 Hz); 4.36 (1H, part A syst. AB, J=9.4 Hz); 3.85 (1H, part B syst. AB, J=9.4 Hz); 2.84 (1H, dd, J=16.8, 2.5 Hz); 2.74 (1H, dd, J=16.8, 2.5 Hz); 1.47 (3H, s); 1.43 (3H, s); 1.07 (28H, m).} \]

Example 21
Preparation of rac-(1R,2S,3S,4R,8R)-1-(benzylamino)-2,4,8-trihydroxy-4-(hydroxymethyl)-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)-9-oxabicyclo[3.3.1]non-5-ene-6-carbonitrile (7)

[0289] \[ \text{DBU poly-bound toluene, reflux} \]
[0290] 27 ml of toluene was added in a mixture of 6 (469 mg, 0.74 mmol) and bound DBU (969 mg 1.15 mmol/g load, 1.12 mmol) at room temperature. The suspension was heated to 120°C for 18 hours. After that time, the suspension was filtered in Buchner funnel under vacuum. The solid was washed alternatively with CH₂Cl₂ and MeOH. Then the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 7 was isolated after column chromatography separation (hexane/AcOEt, 20:1), being obtained as a colorless oil.

[0291] ¹H-NMR: δ 7.34 (5H, m); 6.55 (1H, s); 5.61 (1H, d, J=5.0 Hz); 5.51 (1H, s, CH₂CN); 4.82 (1H, part A syst. AB, J=2.9 Hz); 4.81 (1H, part B syst. AB, J=2.9 Hz); 4.72 (2H, s); 4.53 (1H, part A syst. AB, J=9.3 Hz); 3.69 (1H, part B syst. AB, J=9.4 Hz); 2.38 (1H, dd, J=14.4, 5.0 Hz); 1.84 (1H, dd, J=14.4, 0.7 Hz); 1.50 (3H, s); 1.44 (3H, s); 1.07 (28H, m).

[0292] ¹³C-NMR: δ 150.5, 136.9, 128.8, 128.4, 128.0, 116.5, 114.6, 109.9, 96.8, 81.2, 80.4, 77.0, 70.7, 69.1, 68.1, 45.2, 27.5, 26.0, 17.8, 17.7, 17.5, 17.3, 17.2, 17.1, 17.0, 16.9, 14.2, 13.7, 13.2, 12.7.

[0293] LRMS (API-ESI⁺): m/z 631 (M+H)+, 653 (M+Na)+.

[0294] IR (film): ν 3249, 2946, 2868, 2225, 1630, 1497, 1464, 1382, 1370, 1320, 1306, 1287, 1254, 1215, 1142, 1105, 1080, 1050, 992, 961, 887, 866, 833, 756, 698 cm⁻¹.

[0295] HRMS (ESI⁺): calculated for C₆H₅N₂O₇Si₂ (M+H)+ 631.3235; 631.3229 found (Δm=1.39).

Example 22
Preparation of rac-(1R,2S,3S,4R,8R)-1-(benzylloxymino)-2,4,8-trihydroxy-4-(hydroxymethyl)-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxacycliclo[3.3.1]non-5-ene-6-carbaldehyde (8)

[0296] DIBAL-H
THF, 0°C → r.t.

[0297] DIBAL-H (169 mg, 1.17 mmol) was added in a solution of 7 (185 mg, 0.29 mmol) in 15 ml of THF at 0°C. The solution was stirred at 0°C for 2 hours and at room temperature for 2 hours. After that time 15 ml of AcOEt was added at 0°C and it was stirred at 0°C for 5 minutes. Saturated H₂SO₄ (8 ml) was then added. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (5×10 ml). The combined organic extracts were dried with anhydrous Na₂SO₄. They were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 8 was isolated after column chromatography separation (hexane/AcOEt, 15:1), being obtained as a colorless oil.

[0298] ¹H-NMR: δ 9.36 (1H, s); 7.21 (5H, m); 6.58 (1H, s); 6.15 (1H, s, NH); 7.48 (1H, d, J=5.0 Hz); 4.78 (1H, part A syst. AB, J=2.5 Hz); 4.73 (1H, part B syst. AB, J=2.8 Hz); 4.65 (1H, part A syst. AB, J=12.1 Hz); 4.56 (1H, part A syst. AB, J=9.3 Hz); 4.53 (1H, part B syst. AB, J=12.1 Hz); 3.67 (1H, part B syst. AB, J=9.3 Hz); 2.21 (1H, dd, J=14.2, 5.0 Hz); 2.00 (1H, d, J=14.2 Hz); 1.47 (3H, s); 1.42 (3H, s); 1.03 (28H, m).

Example 23
Preparation of rac-(1R,2S,3S,4R,8R)-1-(benzylloxymino)-2,4,8-trihydroxy-4,6-bis-(hydroxymethyl)-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxacycliclo[3.3.1]non-5-ene (9)

[0300] LRMS (API-ESI⁺): m/z 634 (M+H)+, 656 (M+Na)+.


[0302] HRMS (ESI⁺): calculated for C₆H₅N₂O₈Si₂ (M+H)+ 634.3231; 634.3246 found (Δm=0.04).

Example 24
Preparation of rac-(1R,2S,3S,4R,8R)-1-(benzylloxymino)-2,4,8-trihydroxy-4,6-bis-(hydroxymethyl)-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxacycliclo[3.3.1]non-5-ene (9)
Example 24
Preparation of rac-(1R,2S,3S,4R,8R)-1-(benzylloxycarbonyl)-6-[(phenylselenyl)methyl]-2,4,8-trihydroxy-4-(hydroxymethyl)-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxabicyclo non-5-ene (10)

[0304] Method A
NaBH₄ (0.75 mmol) was added in a suspension of 8 (141 mg, 0.22 mmol) in 3.3 ml of MeOH at 0°C. The solution was stirred at 0°C for 45 minutes. After that time, Na₂HPO₄ (0.1 M, 11 ml) was added at 0°C. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (6×4 ml). The combined organic extracts were dried with anhydrous Na₂SO₄, they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 9 was isolated after column chromatography separation (hexane/ AcOEt, 4:1), being obtained as a white solid.

[0306] Method B
BH₃(CH₃)₂S (29 mg, 0.39 mmol) was added in a solution of 8 (49 mg, 0.08 mmol) in 2 ml of THF at 0°C. The solution was stirred at 0°C for 15 minutes. After that time, H₂O₂ (33%, 1 ml) and saturated NaHCO₃ (1 ml) were added at 0°C and it was stirred at 0°C for 5 minutes. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (4×2 ml). The combined organic extracts were dried with anhydrous Na₂SO₄, they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 9 was isolated after column chromatography separation (hexane/ AcOEt, 4:1), being obtained as a white solid.

[0308] ¹H-NMR: 8 7.31 (5H, m); 5.75 (1H, t, J=1.1 Hz); 5.59 (1H, s, NCH₂), NH); 5.57 (1H, d, J=5.1 Hz); 4.84 (1H, d, J=3.0 Hz); 4.72 (1H, d, J=3.0 Hz); 4.71 (1H, part A syst. AB, J=13.1 Hz); 4.67 (1H, part B syst. AB, J=13.1 Hz); 4.50 (1H, part A syst. AB, J=8.9 Hz); 4.25 (1H, d, J=13.2 Hz); 4.07 (1H, d, J=13.2 Hz); 3.60 (1H, part B syst. AB, J=8.9 Hz); 2.73 (1H, s, NCH₂), OH); 2.36 (1H, d, J=14.1 Hz); 1.88 (1H, d, J=14.1 Hz); 1.48 (3H, s); 1.44 (3H, s); 1.09 (20H, m); 1.00 (8H, m).

[0309] ¹³C-NMR: 8 137.3, 134.9, 134.2, 128.7, 128.6, 128.5, 109.1, 96.8, 82.8, 80.7, 76.8, 71.9, 69.8, 69.2, 63.9, 43.8, 27.8, 26.5, 18.1, 18.0, 17.8, 17.6, 17.5, 17.4, 17.1, 14.5, 14.0, 13.5, 12.9.

[0310] LRMS (API-IS*): m/z 636 (M+H)+, 658 (M+Na)+.

[0311] IR (film): ν 3415, 3060, 2957, 2846, 2868, 1651, 1547, 1464, 1368, 1253, 1213, 1121, 1090, 1048, 992, 885, 834, 747, 698 cm⁻¹.

[0312] HRMS (ESI*): calculated for C₅₃H₅₂NO₃Si₂ (M+H)+ 636.3388; 636.3375 found (Δ=+1.01).

[0314] N-(phenylselenyl)phthalimide (38 mg, 0.13 mmol) and n-Bu₃P (27 mg, 0.15 mmol) were added in a solution of 9 (61 mg, 0.10 mmol) in 1 ml of CH₂Cl₂ at ~78°C. The suspension was stirred at 0°C for 2 hours and at room temperature for 2 hours. N-(phenylselenyl)phthalimide (74 mg, 0.25 mmol) and n-Bu₃P (54 mg, 0.26 mmol) were then added at 0°C. The suspension was stirred at room temperature for 1 hour. After that time, the suspension is filtered in sieve plate no. 3 under vacuum with CH₂Cl₂ and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 10 was isolated after column chromatography separation (hexane/AcOEt, 20:1), being obtained as a white solid.

[0315] ¹H-NMR: 8 7.50 (2H, m); 7.31 (8H, m); 5.56 (1H, s); 5.52 (1H, d, J=5.2 Hz); 5.42 (1H, s, NCH₂), NH); 4.76 (1H, part A syst. AB, J=2.9 Hz); 4.67 (1H, part B syst. AB, J=2.9 Hz); 4.66 (1H, part A syst. AB, J=12.0 Hz); 4.60 (1H, part B syst. AB, J=12.0 Hz); 4.44 (1H, part A syst. AB, J=8.9 Hz); 3.54 (1H, part A syst. AB, J=12.2 Hz); 3.48 (1H, part B syst. AB, J=12.2 Hz); 3.44 (1H, part B syst. AB, J=8.9 Hz); 2.62 (1H, d, J=14.0 Hz); 1.72 (1H, d, J=14.0 Hz); 1.41 (3H, s); 1.36 (3H, s); 1.05 (28H, m).

[0316] LRMS (API-IS*): m/z 776 (M+H)+, 798 (M+Na)+, 1576 (2M+Na+M+H)+.
Example 25
Preparation of rac-(1S,2S,3S,4R,8R)-1-(benzylamino)-2,4,8-trihydroxy-4-(hydroxymethyl)-6-[(2-nitrophenyl)selenyl][methyl]-4,10-O-(propane-2,2-diyl)-2,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxabicyclo[3.3.1]non-5-ene (11)

![Chemical Structure Image 1]

[0317]

Example 26
Preparation of rac-(1R,2S,3S,4R,5R,8R)-2,4,5,8-tetrahydroxy-4,6-(hydroxymethyl)-6-methylidene-1-nitro-4,10-O-(propane-2,2-diyl)-2,8-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-9-oxabicyclo[3.3.1]nonane (12)

![Chemical Structure Image 2]

[0321] Method A

[0318] 2-nitrophenyl selenocyanate (36 mg, 0.16 mmol) and n-Bu₃P (32 mg, 0.16 mmol) were added in a solution of 9 (84 mg, 0.13 mmol) in 1 ml of THF at room temperature. The solution was stirred at room temperature for 4 hours. 2-nitrophenyl selenocyanate (72 mg, 0.32 mmol) and n-Bu₃P (64 mg, 0.32 mmol) were then added at room temperature. The suspension was stirred at room temperature for 30 minutes. After that time, the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 11 was isolated after column chromatography separation (hexane/AcOEt, 10:1), being obtained as a yellow oil.

[0319] 'H-NMR: 8.8.31 (1H, d, J=8.5 Hz); 7.47 (3H, m); 7.31 (5H, m); 5.93 (1H, s); 5.60 (1H, d, J=5.2 Hz); 5.44 (1H, s, NH); 4.82 (1H, part A syst AB, J=3.01 Hz); 4.76 (1H, part B syst AB, J=3.0 Hz); 4.70 (2H, s); 4.52 (1H, part A syst AB, J=9.2 Hz); 3.63 (1H, part B syst AB, J=9.2 Hz); 3.48 (2H, s); 2.50 (1H, dd, J=14.2, 5.2 Hz); 1.74 (1H, d, J=14.2 Hz); 1.44 (6H, s); 1.08 (28H, m).

[0320] LRMS (APPI-MS+): m/z 821 (M+H)+, 843 (M+Na)+.

[0322] Pyridine (12 mg, 0.16 mmol) and H₂O₂ (18 mg, 0.54 mmol) were added in a solution of 10 (60 mg, 0.08 mmol) in 1.5 ml of CH₂Cl₂ at room temperature. The mixture was stirred at room temperature for 40 minutes. After that time, Na₂HPO₄ (0.1 M, 2 ml) was added at room temperature. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (4x2 ml). The combined organic extracts were dried with anhydrous Na₂SO₄, they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 12 was isolated after column chromatography separation (hexane/ AcOEt, 7:1), being obtained as a colorless oil.
Pyridine (14 mg, 0.18 mmol) and H₂O₂ (21 mg, 0.63 mmol) were added in a solution of 11 (74 mg, 0.09 mmol) in 1.5 ml of CH₂Cl₂ at room temperature. The mixture was stirred at room temperature for 40 minutes. After that time, Na₂HPO₄ (0.1 M, 2 ml) was added at room temperature. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (4x2 ml). The combined organic extracts were dried with anhydrous Na₂SO₄, they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 12 was isolated after column chromatography separation (hexane/ AcOEt, 7:1), being obtained as a colorless oil.

H-NMR δ 5.85 (1H, s); 5.75 (1H, s); 5.53 (1H, dd, J=5.2, 1.9 Hz); 5.36 (1H, d, J=3.8 Hz); 4.99 (1H, d, J=3.8 Hz); 4.24 (1H, s); 4.17 (1H, part A syst. AB, J=9.6 Hz); 3.51 (1H, part B syst. AB, J=9.6 Hz); 3.20 (1H, dd, J=14.1, 5.2 Hz); 2.36 (1H, dd, J=14.1, 1.9 Hz); 1.48 (3H, s); 1.42 (3H, s); 1.05 (28H, m).

LRMS (API-IL*: m/z 513 (M–NO₃)⁺, 560 (M+H)⁺, 582 (M+Na)⁺ 1141 (2M+Na)⁺).

Et₃N(HF)₃ (404 mg, 2.51 mmol) was added in a suspension of 10 (54 mg, 0.07 mmol) in 4 ml of MeOH at room temperature. The mixture was stirred at room temperature for 16 hours. After that time Et₃N(HF)₃ (404 mg, 2.51 mmol) was added at room temperature. The mixture was stirred at room temperature for 3 days. Na₂HPO₄ (0.1 M, 4 ml) was then added at room temperature. The phases were separated in an extraction funnel. The aqueous phase was extracted with AcOEt (5x4 ml). The combined organic extracts were dried with anhydrous Na₂SO₄, they were filtered and the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. After column chromatography separation (hexane/AcOEt, 1:3) a transparent oil was obtained. Et₃N(HF)₃ (224 mg, 1.39 mmol) was added in a solution of this oil (50 mg, 0.04 mmol) in 2 ml of MeOH at room temperature. The mixture was stirred at room temperature for 18 hours. After that time, the solvent was removed at reduced pressure. Celite® and AcOEt were added to the reaction crude and the solvent was removed at reduced pressure. Product 13 was isolated after column chromatography separation (hexane/ AcOEt, 1:3), being obtained as a white solid.
[0329] $^1$H-NMR: δ 7.51 (2H, m); 7.31 (5H, m); 7.21 (3H, m); 5.70 (1H, t, J=1.2 Hz); 5.36 (1H, d, J=3.3 Hz); 4.70 (2H, s); 4.55 (1H, s, group); 4.54 (1H, d, J=3.5 Hz); 4.11 (1H, d, J=11.7 Hz); 3.59 (1H, dd, J=3.5, 1.2 Hz); 3.06 (1H, dd, J=11.7, 1.2 Hz); 2.47, d, J=12.2 Hz); 1.89 (1H, dd, J=12.2, 3.3 Hz).

[0330] LRMS (API-ES$^+$): m/z 476 (M$^-$H$_2$O+H)$^+$, 498 (M$^-$H$_2$O+Na)$^+$, 973 (2M$^-$H$_2$O+Na)$^+$.

1-56 (canceled)

57. A compound selected from the group consisting of the compounds of formula (II), (IIa), (III), (IIia), (IIib), (IV), (V), (VI), (VII), (VIII), (IXa), (XII), (XIII) and (XIV), stereoisomers, salts or solvates thereof.

(IIa)

(II)

(III)

(IIia)

(IIib)

(IV)

(V)

(VI)

(VII)

(VIII)

(Xa)
wherein
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl and NReR₂F, wherein Re and R₂F are each independently selected from the group consisting of H, OH, OPPr, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxyl, substituted or unsubstituted amino and halogen; and
Pr is a hydroxy protecting group;
Z is —COOH or —CHR₆R₇, wherein R₆ is hydrogen, and R₇ is OH or OPPr; or R₆ and R₇ together form —O—
Y is selected from the group consisting of —OR₈, —SR₈, Se-aryl, —N(R₉)₂, —NHR₉, and —NHR¹₀, wherein R₉ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted alkylalkyl and substituted or unsubstituted heterocyclyl; and
R₁₀ is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl, —O—alkyl, —O—aryl, —O—aryalkyl, —O—(C═O)—alkyl, —O—(C═O)—aryl and —O—(C═O)—aryalkyl.
X is —C(O)— or —CN;
X₁ is selected from the group consisting of —CN, —CHO, —CH₂OH, —Se-aryl, said aryl being optionally substituted; and
each R₁₆ is independently —OH or —OPPr.
58. A compound selected from the group consisting of the compounds of formula (IX) and (XI), stereoisomers, salts or solvates thereof.
R_2 is hydrogen, OH, or OPr; or
R_1 and R_2 together form a group selected from the group consisting of —O—alkyldiene and CH_2—O—Pr—O—;
R_8 and R_10 are each independently selected from the group consisting of hydrogen, OH, OPr and —O—Pr—O— group;
W is selected from the group consisting of —H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl and substituted or unsubstituted alkynyl;
Ra and Rb are each independently selected from the group consisting of H, OH, OPr, Se-aryl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino and halogen; and
Pr is a hydroxyl protecting group;
X is —C(=O)— or —CN—;
Z is —COOH or —CHR_5 R_6, wherein R_5 is hydrogen, and R_6 is OH or OPr; or R_5 and R_6 together form —O—;
Y is selected from the group consisting of —OR_6 —SR_7 —Se-aryl, —N(R_7)_2 —(CONH) —NH—R_7, wherein R_7 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl and substituted or unsubstituted heterocyclyl, and
R_9 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino and halogen.
59. The compound according to claim 57, wherein W is CReRD_4-aryl, wherein Ra and Rb are each independently selected from the group consisting of H, OH, OPr, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino and halogen.
60. The compound according to claim 58, wherein W is CReRD_4-aryl, wherein Ra and Rb are each independently selected from the group consisting of H, OH, OPr, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino and halogen.
61. The compound according to claim 60, wherein Ra is hydrogen and Rb is hydrogen.
62. The compound according to claim 60, wherein Ra and Rb are hydrogen.
63. The compound according to claim 60, wherein Ra is hydrogen and Rb is selected from the group consisting of halogen, preferably bromine, OH, OPr and Se-aryl.
64. The compound according to claim 60, wherein Ra and Rb are hydrogen.
65. The compound according to claim 59, wherein Re is other than hydrogen and Rd is hydrogen.
66. The compound according to claim 59, wherein Re and Rd are both hydrogen.
67. The compound according to claim 59, wherein Ra is hydrogen and Rb is selected from the group consisting of halogen, preferably bromine, OH, OPr and Se-aryl.
68. The compound according to claim 59, wherein Ra and Rb are both hydrogen.
69. The compound according to claim 57, wherein R_9 and R_10 together form a group of formula —O—Si(R_11 R_12)—O—Si(R_13 R_14)—O—, wherein R_11 and R_12 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl, and
70. The compound according to claim 58, wherein R_9 and R_10 together form a group of formula —O—Si(R_11 R_12)—O—Si(R_13 R_14)—O—, wherein R_11 and R_12 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heterocyclyl, and
71. The compound according to claim 57, wherein W is CReRD_4-aryl, wherein Ra and Rd are each independently selected from the group consisting of H, OH, OPr, or Halogen, and wherein R_9 and R_10 together form a group of formula —O—Si(R_11 R_12)—O—Si(R_13 R_14)—O—, wherein R_11 and R_12 are independently selected from the group consisting of substituted or unsubstituted alkyl.
72. The compound according to claim 58, wherein R_9 and R_10 together form a group of formula —O—Si(R_11 R_12)—O—Si(R_13 R_14)—O—, wherein R_11 and R_12 are independently selected from the group consisting of substituted or unsubstituted alkyl.
73. The compound of claim 72 wherein Pr is —{(R_15) X (R_16)}_, wherein R_15 and R_16 are independently substituted or unsubstituted alkyl.
74. A process for the synthesis of TTX and TTX analogs comprising at least on step that comprises the preparation of a compound of formula (XI), stereoisomers, salts or solvates thereof, by reacting in the presence of a hydrate, preferably DibalH, a compound of formula (X), stereoisomers, salts or solvates thereof

\[ \text{[Diagram]} \]

wherein R_1, R_2, R_9, R_10, R_a, R_b and W are as defined in claim 1.
75. The process of claim 74, wherein said compound of formula (XI), stereoisomers, salts or solvates thereof, reacts with a base to form compound of formula (XII), stereoisomers, salts or solvates thereof, as defined in claim 1.
76. A process for the synthesis of TTX and TTX analogs comprising at least one step that comprises the preparation of a compound of formula (IX), stereoisomers, salts or solvates thereof, by reacting in the presence of an acid, a compound of formula (V) as defined in claim 1.

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