
METHODS OF PREPARING PHOSPHONAMIDATE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

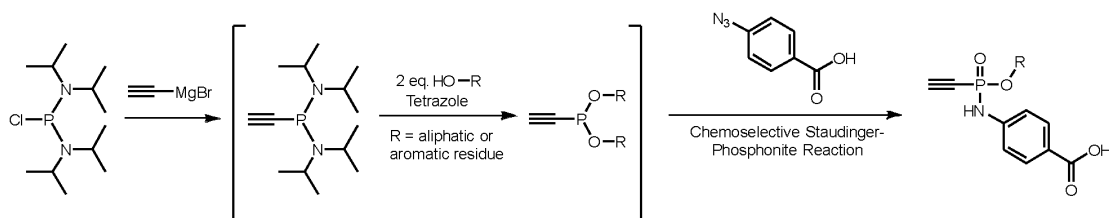
[001] The present application claims the benefit of priority of European Patent Application No. 23194788.8, filed September 1, 2023, the content of which is hereby incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

[002] The present invention relates to methods of preparing phosphonamidate compounds or salts or solvates thereof. The present invention also relates to phosphonamidate compounds or salts and solvates thereof. Also, the present invention relates to phosphonamidate compounds or salts or solvates thereof, obtainable or being obtained by the methods of the invention.

BACKGROUND

[003] Unsaturated phosphonamidates are important phosphorus(V) compounds, which can be used, for example, for the preparation of bioconjugates with proteins and antibodies, as well as for the preparation of biologically active agents such as antibody drug conjugates; see, for example, WO 2023/083900 A1 and WO 2023/083919 A1. So far, phosphonamidates have been synthesized involving a so-called Staudinger phosphonite reaction; see, for example, WO 2018/041985 A1; M.-A. Kasper, A. Stengl, P. Ochtrup, M. Gerlach, T. Stoschek, D. Schumacher, J. Helma, M. Penkert, E. Krause, H. Leonhardt, C.P.R. Hackenberger, *"Ethynylphosphonamidates for the Rapid and Cysteine-Selective Generation of Efficacious Antibody-Drug Conjugates"*, *Angew. Chem. Int. Ed.* 2019, vol. 58, pp. 11631-11636, <https://doi.org/10.1002/anie.201904193>; and M.-A. Kasper, M. Glanz, A. Stengl, M. Penkert, S. Klenk, T. Sauer, D. Schumacher, J. Helma, E. Krause, M.C. Cardoso, H. Leonhardt, C.P.R. Hackenberger, *"Cysteine-Selective Phosphonamidate Electrophiles for Modular Protein Bioconjugations"*, *Angew. Chem. Int. Ed.* 2019, vol. 58, pp. 11625-11630, <https://doi.org/10.1002/anie.201814715>. An illustrative example for the synthesis of phosphonamidates via the Staudinger route is depicted in the following scheme:



In any event, the Staudinger route towards phosphonamidates requires the use of an alcohol HO–R and an azide, i.e. a compound comprising an N₃ moiety.

[004] While the Staudinger reaction can deliver phosphonamidates within a reasonable number of steps, however, certain drawbacks remain. For example, as can be seen from the above scheme, according to the mechanism, two equivalents of the alcohol need to be employed as a starting material in the synthesis. In fact, even a larger excess of the alcohol of up to three equivalents is needed in the praxis to drive the reaction towards exceptable yields. However, only one equivalent of the alcohol is incorporated into the phosphonamidate product. The other equivalents of the alcohol do not contribute to the product, but may increase the amount of waste, and/or needs to be reisolated and/or recycled by additional steps. Also, when the alcohol HO–R is precious, e.g. when it is difficult to prepare or expensive, the loss of one equivalent of the alcohol during the synthesis needs to be taken into account. Further, as another example, azides are in general explosive compounds; see, for example Bräse S., Gil C., Knepper K., Zimmermann V., *Organic Azides: An Exploding Diversity of a Unique Class of Compounds*, *Angewandte Chemie International Edition* 2005, vol. 44, pp. 5188-5240, <https://doi.org/10.1002/anie.200400657>. Therefore, the use and handling of azides poses a substantial explosive hazard associated with the synthesis of phosphonamidates.

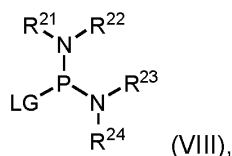
[005] Accordingly, there is a need for further synthetic routes towards phosphonamidates, in particular for synthetic routes to phosphonamidates which allow for efficient and safe implementation.

SUMMARY

[006] The technical problem is solved by the subject-matter as defined throughout the present specification, in particular in the appended claims.

[007] Accordingly, the present invention relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

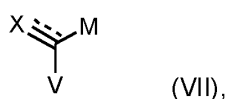
(i) reacting a compound of formula (VIII) or a salt or solvate thereof:



wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and
 LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when $\text{---} \text{---} \text{---}$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $\text{---} \text{---}$ is a double bond;

X is $R^3\text{---C}$ when $\text{---} \text{---} \text{---}$ is a triple bond; or

X is $R^4\text{---}\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when $\text{---} \text{---}$ is a double bond;

R^3 is selected from the group consisting of H, $\text{---Si(R}^{\text{Si}}\text{)}_3$ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

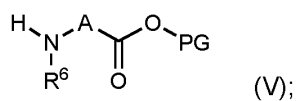
R^4 is H or (C₁-C₈)alkyl;

R^5 is H or (C₁-C₈)alkyl; and



M is a metal-containing group capable of transferring the group $\begin{array}{c} \text{X} \\ \text{---} \\ \text{C} \\ \text{---} \\ \text{V} \end{array}$ to the phosphorus atom to replace the leaving group LG;

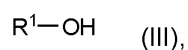
(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



wherein:

R^6 is H or (C₁-C₈)alkyl;
 A is a spacer; and
 PG is a protecting group;

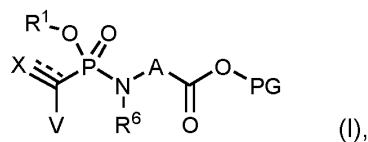
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
 and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

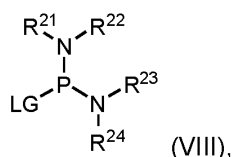
X is $R^4-\overset{\overset{R^5}{|}}{C}$ when is a double bond;

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

- R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
A is a spacer; and
PG is a protecting group.

[008] The present invention also relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

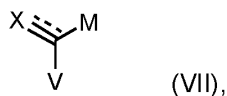
- (i) reacting a compound of formula (VIII) or a salt or solvate thereof:



wherein:

- R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted $(\text{C}_1\text{-C}_8)\text{alkyl}$; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and
LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is R⁴-C  when  is a double bond;

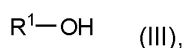
R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

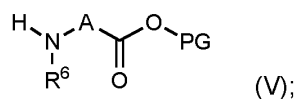
(ii) reacting the product obtained in step (i) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



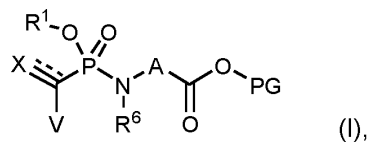
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

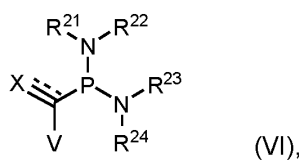
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[009] The present invention also relates to a method of preparing a compound of formula (I), comprising:

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when  is a double bond;

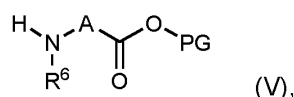
R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R²¹ and R²² may together form a ring; and/or optionally R²³ and R²⁴ may together form a ring; and/or optionally one of R²¹ and R²² may form a ring together with one of R²³ and R²⁴;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl; and

R⁵ is H or (C₁-C₈)alkyl

with a compound of formula (V) or a salt or solvate thereof:



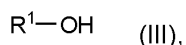
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group;

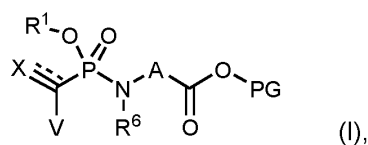
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is each, independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

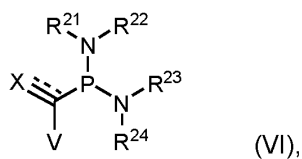
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[0010] The present invention also relates to a method of preparing a compound of formula (I), comprising:

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

$\text{---}\text{---}\text{---}$ is a triple bond; or

= is a double bond;

V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or

V is H or (C₁-C₈)alkyl when = is a double bond;

X is R³-C when $\text{---}\text{---}\text{---}$ is a triple bond; or

X is R⁴-C^{R⁵} when = is a double bond;

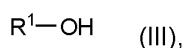
R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R²¹ and R²² may together form a ring; and/or optionally R²³ and R²⁴ may together form a ring; and/or optionally one of R²¹ and R²² may form a ring together with one of R²³ and R²⁴;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl; and

R⁵ is H or (C₁-C₈)alkyl

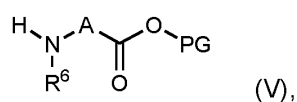
with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
and

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



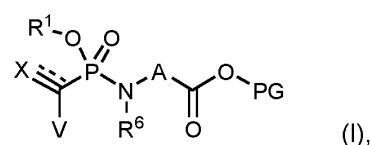
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³---C when $\equiv$ is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4\text{---C} \end{array}$ when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

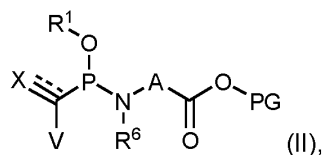
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[0011] The present invention also relates to a method of preparing a compound of formula (I), comprising:

reacting a compound of formula (II) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

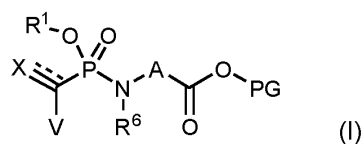
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is R⁴-C(R⁵) when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

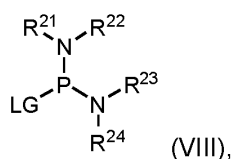
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[0012] The present invention also relates to a method of preparing a compound of formula (I*) or a salt or solvate thereof, comprising:

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

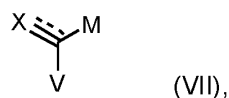


wherein:

R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R²¹ and R²² may together form a ring; and/or optionally R²³ and R²⁴ may together form a ring; and/or optionally one of R²¹ and R²² may form a ring together with one of R²³ and R²⁴; and

LG is a leaving group

with a compound of formula (VII):



wherein:

// is a triple bond; or

// is a double bond;

V is absent when // is a triple bond; or

V is H or (C₁-C₈)alkyl when // is a double bond;

X is R³-C when // is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when // is a double bond;

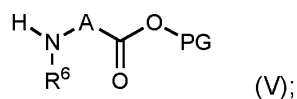
R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl; and

M is a metal-containing group capable of transferring the group $\begin{array}{c} \text{X} \\ \text{//} \\ \text{C} \\ \text{//} \\ \text{V} \end{array}$ to the phosphorus atom to replace the leaving group LG;

(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



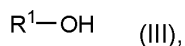
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group;

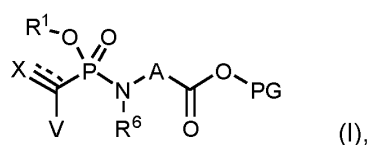
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $R^4-\overset{\overset{R^5}{|}}{C}$ when is a double bond;

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R^3 is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R^4 is H or (C₁-C₈)alkyl;

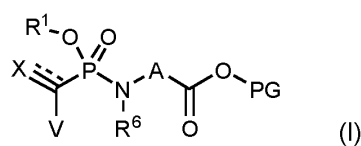
R^5 is H or (C₁-C₈)alkyl;

R^6 is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is R⁴-C(R⁵) when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

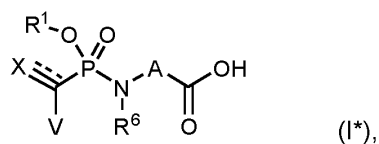
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



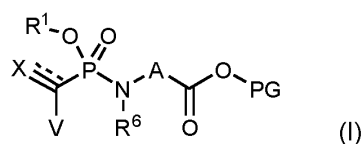
wherein:

$\equiv$ is a triple bond; or

-  is a double bond;
- V is absent when  is a triple bond; or
- V is H or (C₁-C₈)alkyl when  is a double bond;
- X is R³-C when  is a triple bond; or
- X is R⁴-C^{R⁵} when  is a double bond;
- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;
- R⁴ is H or (C₁-C₈)alkyl;
- R⁵ is H or (C₁-C₈)alkyl;
- R⁶ is H or (C₁-C₈)alkyl; and
- A is a spacer.

[0013] The present invention also relates to a method of preparing a compound of formula (I*) comprising:

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:

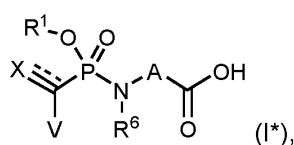


wherein:

-  is a triple bond; or
-  is a double bond;
- V is absent when  is a triple bond; or
- V is H or (C₁-C₈)alkyl when  is a double bond;
- X is R³-C when  is a triple bond; or
- X is R⁴-C^{R⁵} when  is a double bond;

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
 R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
A is a spacer; and
PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when is a double bond;

X is $\text{R}^3\text{-C}$ when is a triple bond; or

X is $\text{R}^4\text{-C}$ when is a double bond;

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

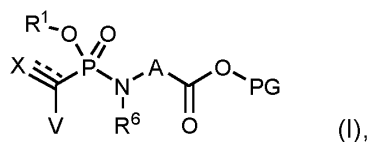
R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

A is a spacer.

[0014] The present invention also relates to a compound of formula (I*) or a salt or solvate thereof.

[0015] The present invention also relates to a compound of formula (I*) or a salt or solvate thereof, obtainable or being obtained by any one of the methods of the present invention.

[0016] The present invention also relates to a compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is R⁴-C(R⁵) when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[0017] The present invention also relates to a compound of formula (I), obtainable or being obtained by any one of the methods of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, respectively. The Figures show:

[0019] **Figure 1** shows an HPLC chromatogram of the compound P5(PEG24)-COOH synthesized according to **Example 2**.

[0020] **Figure 2** shows an HPLC chromatogram of the compound P5(PEG12)-COOH synthesized according to **Example 3**.

[0021] **Figure 3** shows an HPLC chromatogram of the compound P5(PEG12)-COOH synthesized according to **Comparative Example A** via the Staudinger route.

[0022] **Figure 4** shows a chromatogram of P5(PEG24)-COOtBu obtained by HPLC/UV analysis. P5(PEG24)-COOtBu was synthesized according to **Example 6**.

[0023] **Figure 5** shows a mass spectrum of P5(PEG24)-COOtBu synthesized according to **Example 6**.

[0024] **Figure 6** shows a ^1H NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

[0025] **Figure 7** shows a ^{31}P NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

[0026] **Figure 8** shows a ^{13}C NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

[0027] **Figure 9** shows an HPLC chromatogram of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

DETAILED DESCRIPTION

[0028] The present invention is described in detail in the following and is also illustrated by the appended examples and figures.

Definitions

[0029] Unless otherwise indicated, the term "alkyl" by itself or as part of another term in general refers to a substituted or unsubstituted straight chain or branched, saturated hydrocarbon having the indicated number of carbon atoms; e.g., "-(C₁-C₈)alkyl" or "-(C₁-C₁₀)alkyl" refer to an alkyl group having from 1 to 8 or 1 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkyl group may have from 1 to 8 carbon atoms. Representative straight chain -(C₁-C₈)alkyl groups include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl and -n-octyl; branched -(C₁-C₈)alkyl groups include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -*tert*-butyl, -isopentyl, and -2-methylbutyl. In some aspects, an alkyl group may be unsubstituted. Optionally, an alkyl group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0030] Unless otherwise indicated, the term "alkylene" by itself or as part of another term, in general refers to a substituted or unsubstituted branched or straight chain, saturated hydrocarbon radical of the stated number of carbon atoms, preferably 1-10 carbon atoms (-(C₁-C₁₀)alkylene-) or preferably 1 to 8 carbon atoms (-(C₁-C₈)alkylene-), and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. When the number of carbon atoms is not indicated, the alkylene group may have from 1 to 8 carbon atoms. Typical alkylene radicals include, but are not limited to: methylene (-CH₂-), 1,2-ethylene (-CH₂CH₂-), 1,3-n-propylene (-CH₂CH₂CH₂-), and 1,4-n-butylene (-CH₂CH₂CH₂CH₂-). In some aspects, an alkylene group may be unsubstituted. Optionally, an alkylene group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

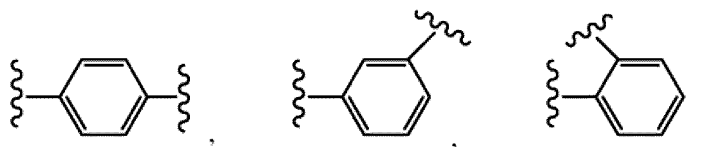
[0031] Unless otherwise indicated, the term "alkenyl" by itself or as part of another term in general refers to a substituted or unsubstituted straight chain or branched, unsaturated hydrocarbon having a double bond and the indicated number of carbon atoms; e.g., "-(C₂-C₈)alkenyl" or "-(C₂-C₁₀)alkenyl" refer to an alkenyl group having from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkenyl group may have from 2 to 8 carbon atoms. Representative -(C₂-C₈)alkenyl groups include, but are not limited to, -ethenyl, -1-propenyl, -2-propenyl, -1-butenyl, -2-butenyl, -isobutenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, and -2,3-dimethyl-2-butenyl. In some aspects, an alkenyl group may be unsubstituted. Optionally, an alkenyl group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0032] Unless otherwise indicated, the term "alkynyl" by itself or as part of another term in general refers to a substituted or unsubstituted straight chain or branched, unsaturated hydrocarbon having a triple bond and the indicated number of carbon atoms; e.g., "-(C₂-C₈)alkynyl" or "-(C₂-C₁₀)alkynyl"

refer to an alkynyl group having from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkynyl group may have from 2 to 8 carbon atoms. Representative $-(C_2-C_8)$ alkynyl groups include, but are not limited to, -acetylenyl, -1-propynyl, -2-propynyl, -1-butylnyl, -2-butylnyl, -1-pentylnyl, -2-pentylnyl and -3-methyl-1-butylnyl. In some aspects, an alkynyl group may be unsubstituted. Optionally, an alkynyl group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0033] Unless otherwise indicated, the term "aryl", by itself or as part of another term, in general means a substituted or unsubstituted monovalent carbocyclic aromatic hydrocarbon radical of 6 to 20 carbon atoms (preferably 6 to 14 carbon atoms, more preferably 6 to 10 carbon atoms, in very preferred embodiments 6 carbon atoms) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, and biphenyl. An exemplary aryl group is a phenyl group. In some aspects, an aryl group may be unsubstituted. Optionally, an aryl group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0034] Unless otherwise indicated, the term "arylene", by itself or as part of another term, in general is an aryl group as defined above wherein one of the hydrogen atoms of the aryl group is replaced with a bond (i.e., it is divalent) and can be in the para, meta, or ortho orientations as shown in the following structures, with phenylene as the exemplary group:



In selected embodiments, the arylene is an aryl group as defined above wherein two or more of the hydrogen atoms of the aryl group are replaced with a bond (i.e., the arylene can be trivalent). In some aspects, an arylene group may be unsubstituted. Optionally, an arylene group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0035] Unless otherwise indicated, the term "heterocycle" or "heterocyclic ring", by itself or as part of another term, in general refers to a monovalent substituted or unsubstituted aromatic or non-aromatic monocyclic or bicyclic ring system having the indicated number of carbon atoms (e.g., " (C_3-C_8) heterocycle" or " (C_3-C_{10}) heterocycle" refer to a heterocycle having from 3 to 8 or from 3 to 10 carbon atoms, respectively) and one to four heteroatom ring members independently selected from

N, O, P or S, and derived by removal of one hydrogen atom from a ring atom of a parent ring system. One or more N, C or S atoms in the heterocycle can be oxidized. The ring that includes the heteroatom can be aromatic or nonaromatic. Unless otherwise noted, the heterocycle is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Representative examples of a (C₃-C₈)heterocycle include, but are not limited to, pyrrolidinyl, azetidiny, piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, benzofuranyl, benzothiophene, indolyl, benzopyrazolyl, pyrrolyl, thiophenyl (thiophene), furanyl, thiazolyl, imidazolyl, pyrazolyl, pyrimidinyl, pyridinyl, pyrazinyl, pyridazinyl, isothiazolyl, and isoxazolyl. In some aspects, a heterocycle group may be unsubstituted. Optionally, a heterocycle group may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0036] Unless otherwise indicated, the term "heterocyclo" or "heterocyclic ring", by itself or as part of another term, in general refers to a heterocycle group as defined above and having the indicated number of carbon atoms (e.g., (C₃-C₈)heterocycle or (C₃-C₁₀)heterocycle) wherein one of the hydrogen atoms of the heterocycle group is replaced with a bond (i.e., it is divalent). In selected embodiments, the heterocyclo is a heterocycle group as defined above wherein two or more of the hydrogen atoms of the heterocycle group are replaced with a bond (i.e., the heterocyclo can be trivalent). In some aspects, a heterocyclo or heterocyclic ring may be unsubstituted. Optionally, a heterocyclo or heterocyclic ring may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0037] Unless otherwise indicated, the term "carbocycle" or "carbocyclic ring" by itself or as part of another term, in general refers to a monovalent, substituted or unsubstituted aromatic or non-aromatic monocyclic or bicyclic carbocyclic ring system having the indicated number of carbon atoms (e.g., "(C₃-C₈)carbocycle" or "(C₃-C₁₀)carbocycle" refer to a carbocycle having from 3 to 8 or from 3 to 10 carbon atoms, respectively) derived by the removal of one hydrogen atom from a ring atom of a parent ring system. As illustrative but non-limiting examples the carbocycle may be a 3-, 4-, 5-, 6-, 7- or 8-membered carbocycle. Representative (C₃-C₈)carbocycles include, but are not limited to, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, cycloheptyl, 1,3- cycloheptadienyl, 1,3,5-cycloheptatrienyl, cyclooctyl, and cyclooctadienyl. In some aspects, a carbocycle may be unsubstituted. Optionally, a carbocycle may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0038] Unless otherwise indicated, the term "carbocyclo" or "carbocyclic ring", by itself or as part of another term, in general refers to a carbocycle group as defined above having the indicated number of carbon atoms (e.g., "(C₃-C₈)carbocyclo" or "(C₃-C₁₀)carbocyclo" refer to a carbocyclo or carbocyclic ring having from 3 to 8 or from 3 to 10 carbon atoms, respectively), wherein another of

the hydrogen atoms of the carbocycle groups is replaced with a bond (i.e., it is divalent). In selected embodiments, the carbocyclo or carbocyclic ring is a carbocycle group as defined above, wherein two or more of the hydrogen atoms of the carbocycle group are replaced with a bond (i.e., the carbocyclo or carbocyclic ring can be trivalent). In some aspects, a carbocyclo or carbocyclic ring may be unsubstituted. Optionally, a heterocyclo or heterocyclic ring may be substituted, such as e.g. with one or more groups such as, e.g., described herein.

[0039] The term “halogen” or “halo”, unless defined otherwise, in general refers to elements of the 7th main group; preferably fluorine, chlorine, bromine and iodine; more preferably fluorine, chlorine and bromine; even more preferably, chlorine and bromine.

[0040] The term “substituted”, “optionally substituted”, “optionally may be substituted” or the like, unless otherwise indicated, in general means that one or more hydrogen atoms can be each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, -O⁻, -OR, -SR, -S⁻, -NR₂, -NR₃, =NR, -CX₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N₂, -N₃, -NRC(=O)R, -C(=O)R, -C(=O)NR₂, -SO₃⁻, -SO₃H, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NR, -S(=O)R, -OP(=O)(OR)₂, -P(=O)(OR)₂, -PO₄³⁻, -PO₃H₂, -C(=O)R, -C(=O)X, -C(=S)R, -CO₂R, -CO₂, -C(=S)OR, -C(=O)SR, -C(=S)SR, -C(=O)NR₂, -C(=S)NR₂, or -C(=NR)NR₂, where each X is independently a halogen: -F, -Cl, -Br, or -I; and each R is independently -H, -(C₁-C₂₀)alkyl (such as e.g. -(C₁-C₁₀)alkyl or -(C₁-C₈)alkyl), -(C₆-C₂₀)aryl, (such as e.g. -(C₆-C₁₀)aryl or, preferably, -C₆-aryl), -(C₃-C₁₄)heterocycle (such as e.g. -(C₃-C₁₀)heterocycle or -(C₃-C₈)heterocycle), a protecting group, or a prodrug moiety. Typical substituents also include (=O).

[0041] The term “aliphatic or aromatic residue”, as used herein, in general refers to an aliphatic substituent, such as e.g. but not limited to an alkyl residue, which, however, can be optionally substituted by further aliphatic and/or aromatic substituents. As non-limiting examples an aliphatic residue can be a nucleic acid, an enzyme, a co-enzyme, a nucleotide, an oligonucleotide, a monosaccharide, a polysaccharide, a polymer, a fluorophore, optionally substituted benzene, etc., as long as the direct link of such a molecule to the core structure (in case of R¹, e.g., the link to the oxygen atom bound to the phosphorus) is aliphatic. An aromatic residue is a substituent, wherein the direct link to the core structure is part of an aromatic system, e.g., an optionally substituted phenyl or triazolyl or pyridyl or nucleotide; as non-limiting example if the direct link of the nucleotide to the core structure is for example via a phenyl-residue. The term “aromatic residue”, as used herein, also includes a heteroaromatic residue.

[0042] The term “protecting group” or “protective group”, as used herein, in general refers to a moiety that is introduced into a molecule in order to protect a certain functional group and thus prevent a

reaction at this functional group under synthetic conditions to which the molecule is subjected in one or more subsequent steps. When the protection is no longer needed, such as e.g. after one or more reaction(s) have been carried out elsewhere at other functional groups in the molecule, the protecting group can be cleaved off. Cleavage of the protecting group, or also denoted as “deprotection”, results in the recovery of the original functional group, as present before the introduction of the protecting group to protect said functional group. As a merely illustrative example, it is referred to a protecting group for a carboxylic acid group --COOH . A protecting group, which may be, e.g., abbreviated as “PG”, is introduced to protect the carboxylic acid group resulting in the moiety --COOPG . After cleavage of the protecting group PG, i.e. after deprotection, and optionally aqueous workup and/or other purification methods, known to a person skilled in the art, the original carboxylic acid group --COOH is restored. As a mere precaution, in light of the foregoing general definition of a protecting group, it is noted that groups which serve to activate a functional group are not protecting groups within the meaning of the foregoing definition. For example, groups that are used to activate a carboxylic acid in order to increase the reactivity in a reaction to be carried out at the carboxy group, such as e.g. acid chlorides, anhydrides or active esters (such as, e.g., an N-hydroxysuccinimide (NHS) ester), are not protecting groups. Such activating groups are not used to protect the functional group and to prevent a reaction at this functional group, but to render, or provide or increase, the reactivity of the functional group. Further, the reaction carried out at the activated functional group typically does not recover the original functional group, but results in the formation of a new functional group, such as e.g. formation of an amide after activation of a carboxylic acid with, e.g., an NHS ester and subsequent reaction with an amine. For different functional groups, such as, e.g., amino, hydroxy, carbonyl, carboxy, carbonyl, phosphate groups and terminal alkynes, various possible protecting groups are known in the art, which differ in the conditions for their introduction and/or cleavage. Accordingly, suitable protecting groups are known and readily selected by a person skilled in the art.

[0043] The present disclosure also relates to a “pharmaceutically acceptable salt”. Any pharmaceutically acceptable salt can be used. In particular, the term “pharmaceutically acceptable salt” refers to a salt of a conjugate or compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts have low toxicity and may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include, but are not limited to: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic

acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, purely by way of example, sodium, potassium, calcium, magnesium, ammonium, trialkylammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of nontoxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. A counterion or anionic counterion can be used in a quaternary amine to maintain electronic neutrality. Exemplary counterions include halide ions (e.g., F^- , Cl^- , Br^- , I^-), NO_3^- , ClO_4^- , OH^- , $H_2PO_4^-$, HSO_4^- , sulfonate ions (e.g., methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, and the like), and carboxylate ions (e.g., acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

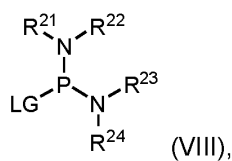
[0044] As used herein, the term "solvate" may refer to an aggregate that comprises one or more molecules of a conjugate or compound described herein with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the conjugates or compounds of the present disclosure may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compounds of the invention may be true solvates, while in other cases, the compounds of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

* * *

Method of Preparing a Compound of Formula (I)

[0045] The present invention relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

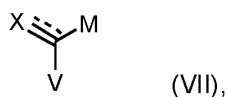
(i) reacting a compound of formula (VIII):



wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C_1 - C_8)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and
 LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C_1 - C_8)alkyl when is a double bond;

X is R^3-C when is a triple bond; or

X is $R^4-\overset{R^5}{\underset{|}{C}}$ when is a double bond;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and (C_1 - C_8)alkyl, wherein R^{Si} is, each independently, (C_1 - C_8)alkyl;

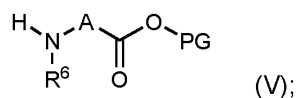
R^4 is H or (C_1 - C_8)alkyl;

R^5 is H or (C_1 - C_8)alkyl; and

M is a metal-containing group capable of transferring the group to the phosphorus atom to replace the leaving group LG;



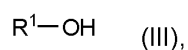
(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



wherein:

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 A is a spacer; and
 PG is a protecting group;

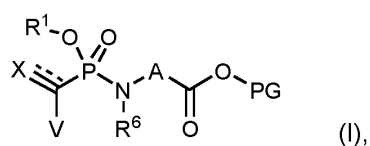
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
 and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

$\text{X} \equiv \text{C}$ is a triple bond; or

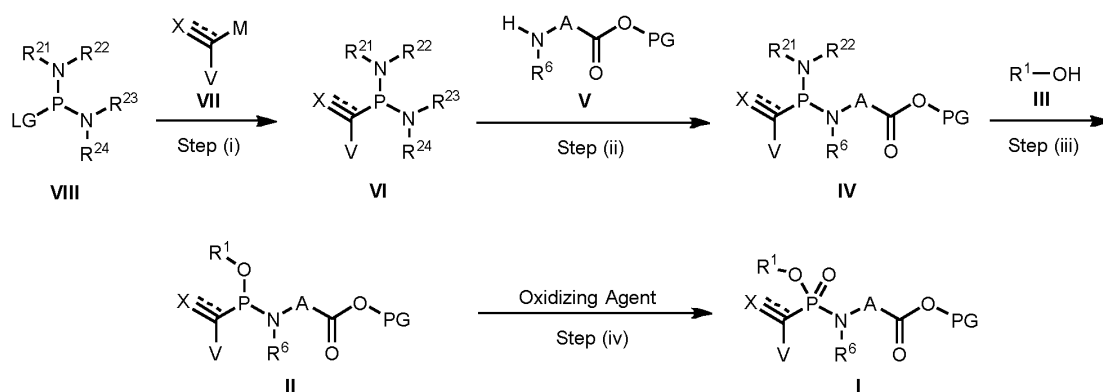
$\text{X} = \text{C}$ is a double bond;

V is absent when $\text{X} \equiv \text{C}$ is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when $\text{X} = \text{C}$ is a double bond;

- X is R^3-C when  is a triple bond; or
- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when  is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-Si(R^{Si})_3$ and (C_1-C_8) alkyl, wherein R^{Si} is, each independently, (C_1-C_8) alkyl;
- R^4 is H or (C_1-C_8) alkyl;
- R^5 is H or (C_1-C_8) alkyl;
- R^6 is H or (C_1-C_8) alkyl;
- A is a spacer; and
- PG is a protecting group.

[0046] Without wishing to be bound by any theory, it is assumed that the method of preparing a compound of formula (I) may proceed according to the following proposed reaction scheme:

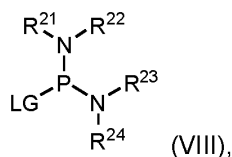


Accordingly, in step (i), a compound (VII) (as an illustrative example, compound (VII) may be, for example, a Grignard compound) may react with a compound of formula (VIII) in a substitution reaction at the phosphorus to give intermediate (VI), thereby releasing the leaving group LG. In step (ii), intermediate (VI) may be reacted with a compound of formula (V) to give intermediate (IV), thereby releasing $HNR^{21}R^{22}$ (or $HNR^{23}R^{24}$). In step (iii), intermediate (IV) may be reacted with an alcohol of formula (III) to give intermediate (II), thereby releasing $HNR^{23}R^{24}$ (or $HNR^{21}R^{22}$, when in step (ii) $HNR^{23}R^{24}$ is released). Intermediate (II), wherein the phosphorus is in the oxidation state III, may then be oxidized in step (iv), using an oxidizing agent to give a phosphonamidate of formula (I), wherein the phosphorus is in the oxidation state V. In preferred embodiments, as described herein further below, the method may be carried out as a one-pot process. However, it may be also possible to isolate one or more intermediate(s). As also described herein, the order of introducing the

compound of formula (V) and the alcohol of formula (III) may be reversed, i.e. it is possible to introduce the alcohol of formula (III) in step (ii), and then the compound of formula (V) in step (iii).

[0047] It has turned out that the order of the substitution reactions at the phosphorus atom can be exchanged, i.e. the product obtained in step (i) by reacting a compound of formula (VIII) with a compound of formula (VII) can be reacted with a compound of formula (III) in step (ii), and then the product obtained in step (ii) can be reacted with a compound of formula (V) in step (iii). Accordingly, the present invention also relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

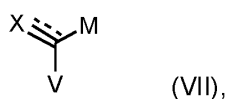
(i) reacting a compound of formula (VIII):



wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted ($\text{C}_1\text{-C}_8$)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and
 LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or ($\text{C}_1\text{-C}_8$)alkyl when is a double bond;

X is R^3-C when  is a triple bond; or

X is $R^4-\overset{R^5}{\underset{|}{C}}$ when  is a double bond;

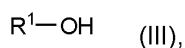
R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1-\text{C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1-\text{C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1-\text{C}_8)\text{alkyl}$;

R^5 is H or $(\text{C}_1-\text{C}_8)\text{alkyl}$; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

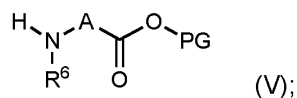
(ii) reacting the product obtained in step (i) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



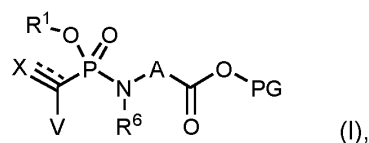
wherein:

R^6 is H or $(\text{C}_1-\text{C}_8)\text{alkyl}$;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4-\text{C} \end{array}$ when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

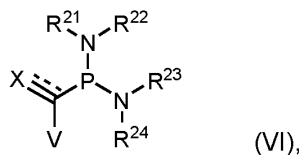
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

[0048] Compounds of formula (VI) have turned out to be quite stable and can thus be isolated and stored. It is thus also possible to use compounds of formula (VI) as starting material in the processes of preparing a compound of formula (I). Accordingly, the present invention also relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(ii) reacting a compound of formula (VI):



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is R⁴-C(R⁵) when  is a double bond;

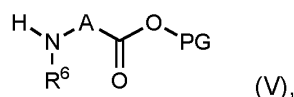
R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R²¹ and R²² may together form a ring; and/or optionally R²³ and R²⁴ may together form a ring; and/or optionally one of R²¹ and R²² may form a ring together with one of R²³ and R²⁴;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl; and

R⁵ is H or (C₁-C₈)alkyl

with a compound of formula (V) or a salt or solvate thereof:



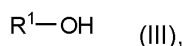
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group;

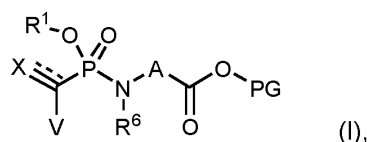
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is each, independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

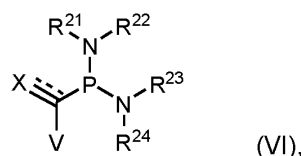
A is a spacer; and

PG is a protecting group. For the ease of comparing the foregoing method with the method comprising steps (i) to (iv), the numbering of the steps has been maintained, i.e., the foregoing method comprises steps (ii) to (iv).

[0049] When a compound of formula (VI) is used as starting material in step (ii), it is also possible to exchange the order of the substitution reactions at the phosphorus atom, i.e. in step (ii) a compound of formula (VI) can be reacted with a compound of formula (III), and then the product

obtained in step (ii) can be reacted with a compound of formula (V) in step (iii). Accordingly, the present invention also relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is R⁴-C(R⁵) when $=$ is a double bond;

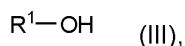
R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R²¹ and R²² may together form a ring; and/or optionally R²³ and R²⁴ may together form a ring; and/or optionally one of R²¹ and R²² may form a ring together with one of R²³ and R²⁴;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl; and

R⁵ is H or (C₁-C₈)alkyl

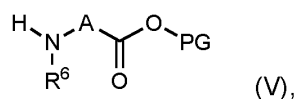
with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
and

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



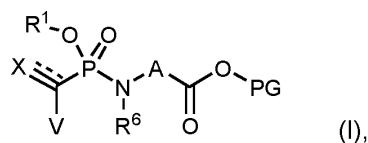
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4 - \text{C} \end{array}$ when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

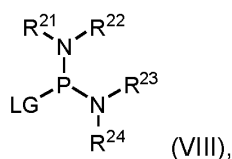
- R⁴ is H or (C₁-C₈)alkyl;
R⁵ is H or (C₁-C₈)alkyl;
R⁶ is H or (C₁-C₈)alkyl;
A is a spacer; and
PG is a protecting group.

[0050] As an initial advantage, the methods of the present invention allow for the preparation of phosphoramidates without a need to use azides; see also below **Examples 1, 2, 3, 4, 5, 6 and 7**. Accordingly, by using the methods of the present invention, the synthesis of phosphoramidates can be carried out avoiding the explosive hazard associated with the preparation, use and storage of azides. Further, it has been found that the methods of preparing phosphoramidates described herein allow for using a substantially equimolar amount, or about only one molar equivalent, of the alcohol of formula (III) based on a starting material of, for example, formula (VIII) or formula (VI); see also **Examples 1, 2, 3, 4, 5 and 6**. For comparison, the Staudinger route requires at least two equivalents of alcohol for preparing phosphoramidates; see also **Comparative Examples A and B**. This may be explained by the above reaction scheme showing the reaction sequence with possible intermediates; see, for example, step (iii) in the above reaction scheme, where one molar equivalent of the alcohol (III) and one molar equivalent of intermediate (IV) can react with each other to give intermediate (II). Therefore, in comparison to the Staudinger route, the methods of the present invention allow for reducing the amount of the alcohol needed for the preparation of phosphoramidates. Consequently, the methods of the present invention also allow for a decrease of the amount of waste, and/or the decrease of additional efforts to reisolate, recycle and/or dispose of excess alcohol. In particular, this is even more advantageous when the alcohol is precious, e.g. when the alcohol is difficult to prepare or expensive. As a further advantage, the inventors could show that the methods of the present invention allow for increasing the yields of the prepared phosphoramidates when compared to the Staudinger route; see **Example 3** and **Comparative Example A**, as well as **Example 4** and **Comparative Example B**. In addition, the methods of the present invention allow for preparing phosphoramidates with significantly shorter reaction times compared to the Staudinger route; see the combined total reaction times of **Examples 1** (the general procedure of **Example 1** is applied to **Examples 2 and 3**), **4, 5, 6 and 7** in comparison to **Comparative Examples A and B**. As a particular advantage with regard to potential industrial applications, it has been found that the methods of the present invention are well scalable and can be used for large scale syntheses of phosphoramidates in an excellent manner; see **Examples 6 and 7**. All in all, the methods of the present invention allow for a safe and efficient implementation of a phosphoramidate synthesis.

[0051] The present invention, as described herein, relates to various methods of preparing a compound of formula (I) which, inter alia, differ with regard to the starting materials, e.g., a compound of formula (VIII) or a compound of formula (VI), and the order of the substitution reactions of steps (ii) and (iii). In preferred embodiments, the present invention relates to a method of preparing a compound of formula (I) comprising step (i), wherein a compound of formula (VIII) is used as starting material, step (ii) is reacting the product obtained in step (i) with a compound of formula (V), step (iii) is reacting the product obtained in step (ii) with a compound of formula (III), and step (iv) is reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I). The inventors have found that a method of preparing a compound of formula (I) using such starting material and order of steps (i) to (iv) results in particularly good yields and purity of the products, and excellent scalability of the process. In particular, good results are obtained with such preferred method when the group R^1 is a polyethylene glycol unit, as described herein.

[0052] In any one of the methods described herein, which comprise step (i), it is possible to replace step (i) by a step (i*), wherein step (i*) is:

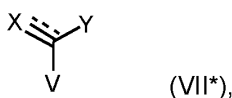
(i*) reacting a compound of formula (VIII):



wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C_1 - C_8)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and LG is a leaving group

with a compound of formula (VII*):



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is R⁴-C^{R⁵} when  is a double bond; and

Y is a halogen; preferably Y is selected from the group consisting of chlorine (Cl), bromine (Br) and iodine (I); and

the reaction is carried out as an electrochemical reaction. The leaving group LG may be any leaving group as described herein; preferably, LG may be selected from the group consisting of chlorine (Cl), bromine (Br) and iodine (I). Without wishing to be bound by any theory, it is assumed that in step (i*) an intermediate (VI), as described herein, may be formed by the electrochemical reaction through a mechanism involving radicals. The electrochemical reaction can be carried out, for example, as known in the art by using an electrode (such as e.g. a metal electrode), which is immersed into a solution comprising a compound of formula (VIII) and a compound of formula (VII*).

[0053] The present disclosure also relates to a salt. The salt is not particularly limited. In general, any salt can be used which is compatible with the applied reactants and reaction conditions. A person skilled in that art will readily selected suitable salts. In some embodiments, the salt is a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable salts are known in the art, and can be readily selected by a person skilled in the art. As illustrative examples, pharmaceutically acceptable salts, which can be used in embodiments of the invention, are also described herein.

[0054] The groups R²¹, R²², R²³ and R²⁴ are, each independently, H or optionally substituted (C₁-C₈)alkyl. Preferably, R²¹, R²², R²³ and R²⁴ are, each independently, optionally substituted (C₁-C₈)alkyl. More preferably, R²¹, R²², R²³ and R²⁴ are, each independently, optionally substituted (C₁-C₆)alkyl, still more preferably optionally substituted (C₁-C₄)alkyl, even more preferably optionally substituted (C₁-C₃)alkyl. The groups R²¹, R²², R²³ and R²⁴ may be same or different. In particular, all substituents on the nitrogen atoms in a compound of formula (VIII) may be, e.g. methyl, ethyl or propyl, e.g. n-propyl or iso-propyl. In some embodiments, R²¹, R²², R²³ and R²⁴ are each n-propyl or iso-propyl. Preferably, R²¹, R²², R²³ and R²⁴ are each iso-propyl. In some embodiments, R²¹, R²², R²³ and R²⁴ are each methyl. In some embodiments, R²¹, R²², R²³ and R²⁴ are each ethyl.

[0055] Optionally, groups R^{21} and R^{22} , in particular when being, each independently, optionally substituted (C₁-C₈)alkyl, preferably optionally substituted (C₁-C₆)alkyl, more preferably optionally substituted (C₁-C₄)alkyl, still more preferably optionally substituted (C₁-C₃)alkyl, may together form a ring; and/or optionally R^{23} and R^{24} , in particular when being, each independently, optionally substituted (C₁-C₈)alkyl, preferably optionally substituted (C₁-C₆)alkyl, more preferably optionally substituted (C₁-C₄)alkyl, still more preferably optionally substituted (C₁-C₃)alkyl, may together form a ring; and/or optionally, in particular when being, each independently, optionally substituted (C₁-C₈)alkyl, preferably optionally substituted (C₁-C₆)alkyl, more preferably optionally substituted (C₁-C₄)alkyl, still more preferably optionally substituted (C₁-C₃)alkyl, one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} , in particular when being, each independently, optionally substituted (C₁-C₈)alkyl, preferably optionally substituted (C₁-C₆)alkyl, more preferably optionally substituted (C₁-C₄)alkyl, still more preferably optionally substituted (C₁-C₃)alkyl. Preferably, in any one of these embodiments, the ring may be a three- to eight-membered ring, more preferably a four- to seven-membered ring, still more preferably a five- or six-membered ring.

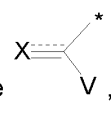
[0056] The leaving group LG is not particularly limited. The term “leaving group”, as used herein, in general denotes a moiety, e.g. an atom or a group of atoms, which is capable to detach from the main or residual part of a substrate during a reaction or elementary step of a reaction. In particular, a leaving group can be replaced by another moiety, e.g. an atom or a group of atoms, during a substitution reaction such as e.g. a nucleophilic substitution. With regard to the present invention, any leaving group which is capable to undergo a substitution reaction at the phosphorus atom, in particular a nucleophilic substitution, can be used. Suitable leaving groups are known to a person skilled in the art and may include, as illustrative examples, halogen, tosylate, mesylate or substituted phenols; see, e.g., Y. Huang et al., “Asymmetric Synthesis of P-Stereogenic Diarylphosphinites by Palladium-Catalyzed Enantioselective Addition of Diarylphosphines to Benzoquinones”, *Journal of the American Chemical Society*, 2014, vol. 136, pp. 4865–4868, DOI: dx.doi.org/10.1021/ja501007t, and S.H. Jun, “Preparation of Phosphine-Amido Hafnium and Zirconium Complexes for Olefin Polymerization”, *Organometallics* 2013, vol. 32, pp. 7357–7365, DOI: dx.doi.org/10.1021/om400899g). In some embodiments, the leaving group LG is selected from the group consisting of halogen and optionally substituted phenoxy. In some embodiments, the leaving group LG is a halogen (e.g., fluorine (F), chlorine (Cl), bromine (Br) or iodine (I)). In some embodiments, the leaving group is selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I). Preferably, the leaving group LG is chlorine (Cl). In some embodiments the leaving group LG is optionally substituted phenoxy.

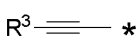
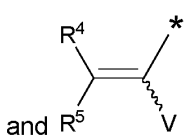
[0057] Preferably,  is a triple bond; V is absent; X is R^3-C ; and R^3 is selected from the group consisting of H (hydrogen), $-Si(R^{Si})_3$ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-

C₈)alkyl. When R³ is (C₁-C₈)alkyl, R³ may be preferably (C₁-C₆)alkyl, more preferably (C₁-C₄)alkyl, still more preferably (C₁-C₂)alkyl. More preferably,  is a triple bond; V is absent; X is R³-C; and R³ is H or -Si(R^{Si})₃, wherein R^{Si} is, each independently, (C₁-C₈)alkyl. Still more preferably,  is a triple bond; V is absent; X is R³-C; and R³ is H. Alternatively,  may be a triple bond; V is absent; X is R³-C; and R³ is -Si(R^{Si})₃. The group R^{Si}, whenever present, may be, each independently, (C₁-C₈)alkyl, preferably (C₁-C₆)alkyl, more preferably (C₁-C₄)alkyl, still more preferably (C₁-C₃)alkyl. R^{Si} may be same or different. In some embodiments, each R^{Si} is methyl or ethyl. Preferably, each R^{Si} is methyl. Accordingly, in some embodiments, R³ is -Si(CH₃)₃. It is noted that, when R³ is -Si(R^{Si})₃, in particular -Si(CH₃)₃, as known in the art, R³ can be converted into H (hydrogen) by reacting the silyl group with a suitable reagent, in particular fluoride, such as e.g. tetra-n-butylammonium fluoride (TBAF), or acid.

[0058] In some embodiments,  is a double bond; V is H or (C₁-C₈)alkyl; X is ; and R⁴ and R⁵ are, each independently, H or (C₁-C₈)alkyl. Preferably, R⁴ and R⁵ are, each independently, H or (C₁-C₆)alkyl, more preferably H or (C₁-C₄)alkyl, still more preferably H or (C₁-C₂)alkyl. Preferably, R⁴ and R⁵ are the same; even more preferably, R⁴, R⁵ and V are the same. More preferably, R⁴ and R⁵ are both H. Preferably, V is H or (C₁-C₆)alkyl, more preferably H or (C₁-C₄)alkyl, still more preferably H or (C₁-C₂)alkyl. Even more preferably, V is H. In preferred embodiments, R⁴, R⁵ and V are each H.

[0059] With regard to the representation  used herein, it is noted that, as commonly known to a

person skilled in the art, each carbon atom is tetravalent. Accordingly, a structure , wherein X and V are as defined herein and the asterisk (*) indicates attachment to the phosphorus, includes

the structures  and , wherein R³, R⁴, R⁵ and V are as defined herein. A wavy bond indicates that the configuration of the double bond may be E or Z. It is also possible that the compound is present as a mixture of the E and Z isomers.

[0060] The group M, as described herein for a compound of formula (VII), is a metal-containing



group capable of transferring the group  to the phosphorus atom of a compound of formula (VIII) to replace the leaving group LG. Organometallic compounds of formula (VII), which are capable to perform such replacement by a substitution reaction at phosphorus, are generally known in the art and readily selected by a person skilled in the art. A person skilled in the art is also capable to readily prepare such compounds, if needed or desired; as a mere example, it is referred to a Grignard compound, which can be readily prepared by reacting a suitable halide precursor, in particular a suitable chloro, bromo or iodo compound, with magnesium to give a compound of formula (VII). As illustrative examples, compounds of formula (VII) may be selected from the group consisting lithium compounds wherein M is Li; Grignard compounds wherein M is MgY with Y being a halogen preferably selected from Cl, Br and I; zinc compounds wherein M may be ZnY with Y being a halogen preferably selected from Cl, Br and I; and cuprates wherein M may be CuY with Y being a halogen preferably selected from Cl, Br and I; see, e.g., T.A. Betley et al., "The Strong-Field Tripodal Phosphine Donor, $[PhB(CH_2^iPr_2)_3]^-$ Provides Access to Electronically and Coordinatively Unsaturated Transition Metal Complexes", *Inorganic Chemistry*, vol. 42, no. 17, 2003, pp. 5074-5084, DOI: 10.1021/ic0343096 (lithium compounds); A.C. Vetter et al., "Long sought synthesis of quaternary phosphonium salts from phosphine oxides: inverse reactivity approach", *Chemical Communications*, 2018, vol. 54, pp. 5843-5846, DOI: 10.1039/c8cc02173b (Grignard compounds); F. Langer et al., "A New Efficient Preparation of Polyfunctional Phosphines Using Zinc Organometallics", *Tetrahedron Letters*, vol. 36, no. 26, pp. 4591-4594, DOI: 10.1016/0040-4039(95)00813-r (zinc compounds); and B.H. Lipshutz et al., "Organocopper Reagents: Substitution, Conjugate Addition, Carbo/Metallocupration, and other Reactions", *Organic Reactions*, 1992, vol. 41, edited by Leo A. Paquette et al., pp. 135-631, DOI: 10.1002/0471264180.or041.02 (copper compounds). In preferred embodiments, the group M is Li (lithium). More preferably, the group M is MgY, wherein Y is halogen; preferably Y is Cl, Br or I; more preferably Y is Br.

[0061] The group R^6 bound to the nitrogen atom of, for example, compounds of formula (V), formula (I) or formula (I*), is H (hydrogen) or (C_1-C_8) alkyl. When R^6 is (C_1-C_8) alkyl, R^6 is preferably (C_1-C_6) alkyl, more preferably (C_1-C_4) alkyl, still more preferably (C_1-C_2) alkyl. In some preferred embodiments, R^6 is H (hydrogen).

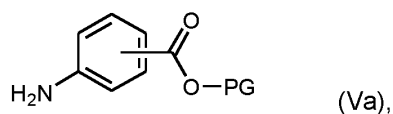
[0062] The group A is a spacer. In a compound of, for example, formula (V), formula (I) or formula (I*), the spacer serves to connect a nitrogen atom with a carboxylic acid or protected carboxylic acid group, in particular with the carbonyl carbon atom of the carboxylic acid or protected carboxylic acid group. The spacer A may be any chemical group or moiety which is capable to connect a nitrogen atom with a carboxylic acid or ester group, in particular with the carbonyl carbon atom of the

carboxylic acid or ester group. The spacer A may be any spacer known to a person skilled in the art, for example, a straight or branched hydrocarbon-based moiety. The spacer A can also comprise cyclic moieties, such as e.g., but not limited to, aromatic moieties. If the spacer A is a hydrocarbon-based moiety, the main chain of the spacer A may comprise only carbon atoms but can also contain heteroatoms such as oxygen (O), nitrogen (N) or sulfur (S) atoms, and/or can contain carbonyl groups (C=O). The spacer A may comprise or may be, for example, a (C₁-C₂₀) carbon atom chain. In typical embodiments of hydrocarbon-based spacers A, the spacing moiety comprises between 1 to about 150, 1 to about 100, 1 to about 75, 1 to about 50, or 1 to about 40, or 1 to about 30, or 1 to about 20, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19 main chain atoms. A person skilled in the art knows to select suitable spacers A.

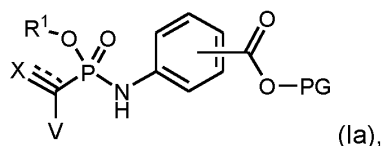
[0063] In some embodiments, the spacer A is selected from the group consisting of optionally substituted -(C₆-C₁₀)arylene-, optionally substituted -(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)carbocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₆-C₁₀)arylene-, optionally substituted -(C₆-C₁₀)arylene-(C₁-C₁₀)alkylene-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)carbocyclo-, optionally substituted -(C₃-C₈)carbocyclo-(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)heterocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)heterocyclo- and optionally substituted -(C₃-C₈)heterocyclo-(C₁-C₁₀)alkylene-. Preferably, the spacer A is selected from the group consisting of optionally substituted -(C₆-C₁₀)arylene-, optionally substituted -(C₁-C₁₀)alkylene- and optionally substituted -(C₃-C₈)carbocyclo-. In more preferred embodiments, the spacer A is optionally substituted -phenylene-.

[0064] The moiety PG is a protecting group. In particular, PG is a protecting group suitable for protection of a carboxylic acid moiety. For example, in embodiments of the invention, a carboxylic acid moiety can be protected in form of a carboxylic acid ester. Protecting groups suitable for protection of carboxylic acid moieties are known and readily selected by a person skilled in the art. Illustrative examples, which may be used in embodiments of the present invention, include optionally substituted (C₁-C₈)alkyl, such as, e.g., (C₁-C₈)alkyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl, allyl or benzyl. Preferably, PG is (C₁-C₈)alkyl, more preferably (C₁-C₆)alkyl, still more preferably (C₁-C₄)alkyl. PG may be methyl, ethyl, propyl or butyl. In some preferred embodiments, PG is tert-butyl. By removing the protecting group PG, in other words by deprotection, PG is replaced by hydrogen so that a carboxylic acid moiety (COOH) is formed. Suitable methods for introducing and removing carboxylic acid protecting groups are known to a person skilled in the art. For example, acidic or basic conditions can be used to cleave a carboxylic acid ester to obtain a free carboxylic acid moiety.

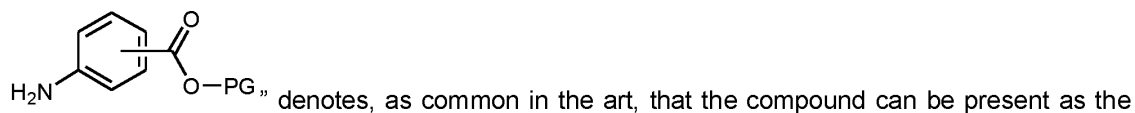
[0065] Preferably, in any one of the methods described herein, the compound of formula (V) is a compound of formula (Va):



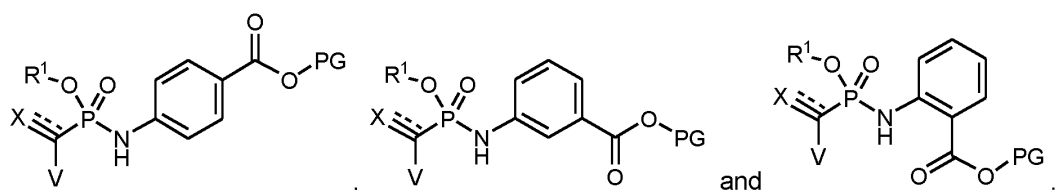
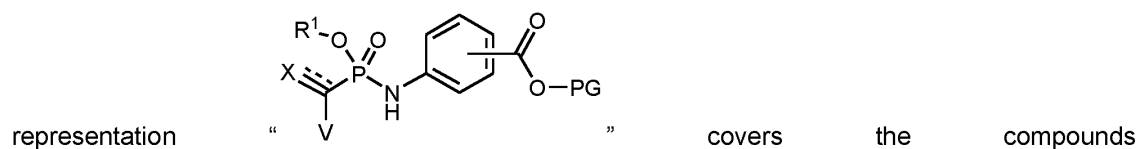
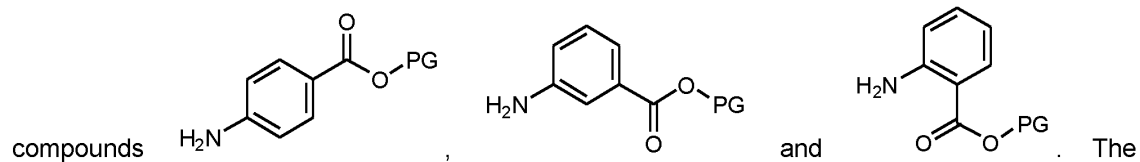
wherein PG is as defined herein. Accordingly, and also preferably, the compound of formula (I) is a compound of formula (Ia):



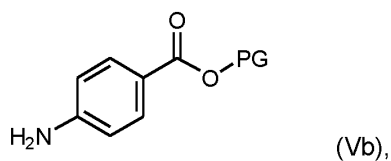
wherein , X, V, R¹ and PG are as defined herein. It is noted that the representation “



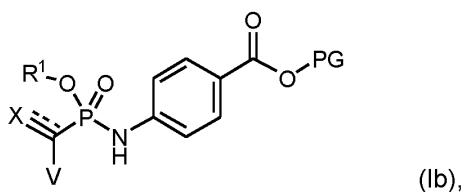
ortho, meta or para isomer. Accordingly, the representation “H₂N--COO-PG” covers the



[0066] More preferably, in any one of the methods described herein, the compound of formula (V) is a compound of formula (Vb):



wherein PG is as defined herein. Accordingly, and also more preferably, the compound of formula (I) is a compound of formula (Ib):



wherein , X, V, R¹ and PG are as defined herein.

[0067] R¹ is an optionally substituted aliphatic residue or optionally substituted aromatic residue.

[0068] In some embodiments, R¹ may represent optionally substituted (C₁-C₈)alkyl.

[0069] R¹ may represent (C₁-C₈)alkyl optionally substituted with at least one of F, Cl, Br, I, -NO₂, -N((C₁-C₈)alkyl)H, -NH₂, -N₃, -N((C₁-C₈)alkyl)₂, =O, (C₃-C₈)cycloalkyl, -S-S-((C₁-C₈)alkyl), (C₂-C₈)alkenyl or (C₂-C₈)alkynyl.

[0070] R¹ may represent optionally substituted phenyl.

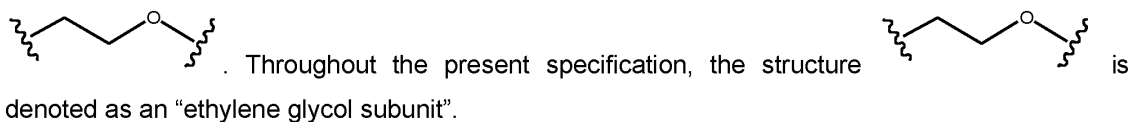
[0071] R¹ may represent phenyl optionally independently substituted with at least one of (C₁-C₈)alkyl, F, Cl, I, Br, -NO₂, -N((C₁-C₈)alkyl)H, -NH₂ or -N((C₁-C₈)alkyl)₂.

[0072] R¹ may represent an optionally substituted 5- or 6-membered heteroaromatic ring such as e.g. pyridyl.

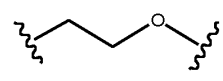
[0073] R¹ may represent (C₁-C₈)alkyl, (C₁-C₈)alkyl substituted with -S-S-(C₁-C₈)alkyl, (C₁-C₈)alkyl substituted with optionally substituted phenyl; or phenyl; or phenyl substituted with -NO₂.

[0074] In some preferred embodiments, R¹ is (C₁-C₈)alkyl. More preferably, R¹ is methyl, ethyl, propyl or butyl. Still more preferably, R¹ is methyl or ethyl. Even more preferably, R¹ is ethyl.

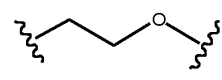
[0075] In particularly preferred embodiments, R¹ is a polyethylene glycol unit. In some embodiments, R¹ is a polyethylene glycol unit comprising of from 1 to 100, preferably of from 2 to 50, more preferably of from 3 to 45, still more preferably of from 4 to 40, still more preferably of from 6 to 35, even more preferably of from 8 to 30 ethylene glycol subunits each having the structure:

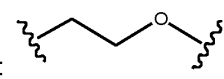


[0076] Preferably, R¹ is a polyethylene glycol unit comprising of from 16 to 30, more preferably of from 20 to 28, still more preferably 22, 23, 24, 25 or 26, even more preferably 23, 24 or 25 ethylene

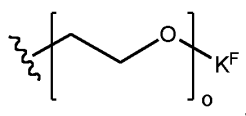
glycol subunits each having the structure:  . In preferred embodiments, R¹ is a

polyethylene glycol unit comprising 24 or about 24 ethylene glycol subunits each having the

structure:  . It is also possible that R¹ is a polyethylene glycol unit comprising 12

or about 12 ethylene glycol subunits each having the structure:  .

[0077] More preferably, R¹ is a polyethylene glycol unit having the structure:



wherein:



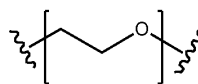
indicates the position of the O attached to the phosphorus;

K^F is H (hydrogen) or a capping group as described herein; preferably K^F is selected from the group consisting of -H (hydrogen), a protecting group, -PO₃H, -(C₁-C₁₀)alkyl, -(C₁-C₁₀)alkyl-SO₃H, -(C₂-C₁₀)alkyl-CO₂H, -(C₂-C₁₀)alkyl-OH, -(C₂-C₁₀)alkyl-NH₂, -(C₂-C₁₀)alkyl-NH(C₁-C₃)alkyl and -(C₂-C₁₀)alkyl-N((C₁-C₃)alkyl)₂; and

o is an integer ranging from 1 to 100.

[0078] In some preferred embodiments, K^F is H (hydrogen).

[0079] In some preferred embodiments, K^F is a protecting group. In particular, when K^F is a protecting group, K^F is a protecting group suitable for protection of a hydroxy group. Protecting groups suitable for protection of hydroxy groups are known and readily selected by a person skilled in the art. Illustrative examples, which may be used in embodiments of the present invention, include tert-butyl, trityl, acetyl and a silyl protecting group. The silyl protecting group may be selected from the group consisting of trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS) and triisopropyl (TIPS). By removing the protecting group, in other words by deprotection, K^F is replaced by hydrogen so that a hydroxy moiety (OH) is formed. Suitable methods for introducing and removing hydroxy protecting groups are known to a person skilled in the art. For example, acidic or basic conditions can be used to cleave ethers or esters to obtain a free hydroxy moiety. Fluoride, such as e.g. tetra-n-butylammonium fluoride (TBAF), can be used to remove silyl protecting groups to obtain a free hydroxy moiety.



[0080] The integer o denotes the number of repeating units in the polyethylene glycol unit. The integer o may range from 1 to 100. Preferably, o ranges from 2 to 50. More preferably, o ranges from 3 to 45. Still more preferably, o ranges from 4 to 40. Still more preferably, o ranges from 6 to 35. Even more preferably, o ranges from 8 to 30. Even more preferably, o ranges from 16 to 30. Even more preferably, o ranges from 20 to 28. Even more preferably, o is 22, 23, 24, 25 or 26. Even more preferably, o is 23, 24 or 25. In even more preferred embodiments, o is 24 or about 24. In some preferred embodiments, o ranges from 8 to 16. More preferably, o is 10, 11, 12, 13 or 14. Still more preferably, o is 11, 12 or 13. Even more preferably, o is 12 or about 12.

[0081] In general, in the polyethylene glycol unit, polydisperse polyethylene glycols, monodisperse polyethylene glycols, and discrete polyethylene glycols can be used. Polydisperse polyethylene glycols are a heterogeneous mixture of sizes and molecular weights, whereas monodisperse polyethylene glycols are typically purified from heterogeneous mixtures and therefore provide a single chain length and molecular weight. Preferred polyethylene glycol units are discrete polyethylene glycols, i.e. compounds that are synthesized in step-wise fashion and not via a polymerization process. Discrete polyethylene glycols provide a single molecule with defined and specified chain length.

[0082] The polyethylene glycol unit provided herein comprises one or multiple polyethylene glycol chains. The polyethylene glycol chains can be linked together, for example, in a linear, branched or star shaped configuration. Optionally, at least one of the polyethylene glycol chains may be derivatized at one end for covalent attachment to the oxygen atom bound to the phosphorus.

[0083] The polyethylene glycol unit will be attached to the oxygen atom which is bound to the phosphorus. The other terminus (or termini) of the polyethylene glycol unit will be free and untethered and may take the form of a hydrogen, methoxy, carboxylic acid, alcohol or other suitable functional group, such as e.g. any capping group as described herein. The methoxy, carboxylic acid, alcohol or other suitable functional group acts as a cap for the terminal polyethylene glycol subunit of the polyethylene glycol unit. By untethered, it is meant that the polyethylene glycol unit will not be attached at that untethered site to another moiety. For those embodiments wherein the polyethylene glycol unit comprises more than one polyethylene glycol chain, the multiple polyethylene glycol chains may be the same or different chemical moieties (e.g., polyethylene glycols of different molecular weight or number of subunits). The multiple polyethylene glycol chains are attached to the oxygen atom bound to the phosphorus at a single attachment site. The skilled artisan will understand that the polyethylene glycol unit in addition to comprising repeating polyethylene glycol subunits may also contain non-polyethylene glycol material (e.g., to facilitate coupling of multiple polyethylene glycol chains to each other or to facilitate coupling to the oxygen atom bound to the phosphorus). Non-polyethylene glycol material refers to the atoms in the polyethylene glycol unit that are not part of the repeating $-\text{CH}_2\text{CH}_2\text{O}-$ subunits. In embodiments provided herein, the polyethylene glycol unit can comprise two monomeric polyethylene glycol chains linked to each other via non-polyethylene glycol elements. In other embodiments provided herein, the polyethylene glycol unit can comprise two linear polyethylene glycol chains attached to a central core that is attached to the oxygen atom bound to the phosphorus (i.e., the polyethylene glycol unit is branched).

[0084] There are a number of polyethylene glycol attachment methods available to those skilled in the art, [see, e.g., EP 0 401 384 (coupling PEG to G-CSF); U.S. Pat. No. 5,757,078 (PEGylation of EPO peptides); U.S. Pat. No. 5,672,662 (polyethylene glycol and related polymers mono substituted with propionic or butanoic acids and functional derivatives thereof for biotechnical applications); U.S. Pat. No. 6,077,939 (PEGylation of an N- terminal .alpha.-carbon of a peptide); and Veronese (2001) Biomaterials 22:405-417 (review article on peptide and protein PEGylation)].

[0085] In preferred embodiments, the polyethylene glycol unit is directly attached to the oxygen atom bound to the phosphorus. In these embodiments, the polyethylene glycol unit does not comprise a functional group for attachment to the oxygen atom bound to the phosphorous, i.e. the oxygen atom is directly bound to a carbon atom of the polyethylene glycol unit, preferably to a CH_2 of the polyethylene glycol unit.

[0086] In one group of embodiments, the polyethylene glycol unit comprises at least 1 ethylene glycol subunit, preferably at least 2 ethylene glycol subunits, more preferably at least 3 ethylene glycol subunits, still more preferably at least 4 ethylene glycol subunits, still more preferably at least

6 ethylene glycol subunits, even more preferably at least 8 ethylene glycol subunits. In some such embodiments, the polyethylene glycol unit comprises no more than about 100 ethylene glycol subunits, preferably no more than about 50 ethylene glycol units, more preferably no more than about 45 ethylene glycol subunits, more preferably no more than about 40 ethylene glycol subunits, more preferably no more than about 35 ethylene glycol subunits, even more preferably no more than about 30 ethylene glycol subunits.

[0087] In one group of embodiments, the polyethylene glycol unit comprises one or more linear polyethylene glycol chains each having at least 1 ethyleneglycol subunit, preferably at least 2 ethylene glycol subunits, more preferably at least 3 ethylene glycol subunits, still more preferably at least 4 ethylene glycol subunits, still more preferably at least 6 ethylene glycol subunits, even more preferably at least 8 ethylene glycol subunits. In preferred embodiments, the polyethylene glycol unit comprises a combined total of at least 1 ethylene glycol subunit, preferably at least 2 ethylene glycol subunits, more preferably at least 3, still more preferably at least 4, still more preferably at least 6, or even more preferably at least 8 ethylene glycol subunits. In some such embodiments, the polyethylene glycol unit comprises no more than a combined total of about 100 ethylene glycol subunits, preferably no more than a combined total of about 50 ethylene glycol subunits, more preferably no more than a combined total of about 45 ethylene glycol subunits, still more preferably no more than a combined total of about 40 ethylene glycol subunits, still more preferably no more than a combined total of about 35 ethylene glycol subunits, even more preferably no more than a combined total of about 30 ethylene glycol subunits.

[0088] In another group of embodiments, the polyethylene glycol unit comprises a combined total of from 1 to 100, preferably of from 2 to 50, more preferably of from 3 to 45, still more preferably of from 4 to 40, still more preferably of from 6 to 35, even more preferably of from 8 to 30 ethylene glycol subunits. In any one of these embodiments, the ethylene glycol subunit may be any ethylene glycol subunit as described herein.

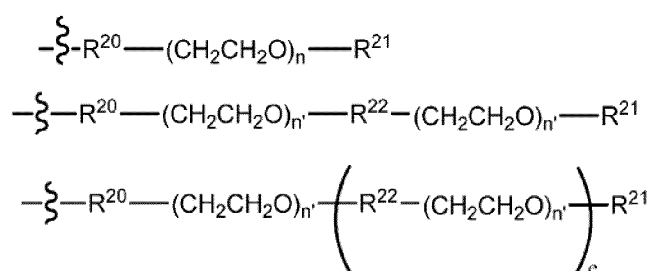
[0089] In another group of embodiments, the polyethylene glycol unit comprises one or more linear polyethylene glycol chains having a combined total of from 1 to 100, preferably 2 to 50, more preferably 3 to 45, still more preferably 4 to 40, still more preferably 6 to 35, even more preferably 8 to 30 ethylene glycol subunits.

[0090] In another group of embodiments, the polyethylene glycol unit is a linear single polyethylene glycol chain having at least 1 ethylene glycol subunit, preferably at least 2 ethylene glycol subunits, more preferably at least 3 ethylene glycol subunits, still more preferably at least 6 ethylene glycol

subunits, even more preferably at least 8 ethylene glycol subunits. Optionally, in any one of these embodiments the linear single polyalkylene glycol chain may be derivatized.

[0091] In another group of embodiments, the polyethylene glycol unit is a linear single polyethylene glycol chain having from 1 to 100, preferably 2 to 50, more preferably 3 to 45, more preferably 4 to 40, more preferably 6 to 35, more preferably 8 to 30 ethylene glycol subunits. Optionally, in any one of these embodiments the linear single polyethylene glycol chain may be derivatized.

[0092] Exemplary linear polyethylene glycol units that can be used as R¹, in any one of the embodiments provided herein, are as follows:



wherein the wavy line indicates the site of attachment to the oxygen atom bound to the phosphorus;

R²⁰ is a PEG attachment unit; preferably, R²⁰ is absent;

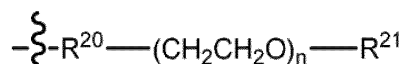
R²¹ is a PEG capping unit (herein, R²¹ is also denoted as "K^F");

R²² is a PEG coupling unit (i.e. for coupling multiple PEG subunit chains together);

n is independently selected from 1 to 100, preferably from 2 to 50, more preferably from 3 to 45, more preferably from 4 to 40, still more preferably from 6 to 35, even more preferably from 8 to 30; e is 2 to 5;

each n' is independently selected from 1 to 100, preferably from 2 to 50, more preferably from 3 to 45, more preferably from 4 to 40, still more preferably from 6 to 35, even more preferably from 8 to 30. In preferred embodiments, there are at least 1, preferably at least 2, more preferably at least 3, more preferably at least 4, more preferably at least 6, even more preferably at least 8 ethylene glycol subunits in the polyethylene glycol unit. In some embodiments, there are no more than 100, preferably no more than 50, more preferably no more than 45, more preferably no more than 40, more preferably no more than 35, even more preferably no more than 30 ethylene glycol subunits in the polyethylene glycol unit. When R²⁰ is absent, a (CH₂CH₂O) subunit is directly bound to the oxygen atom, which is attached to the phosphorus.

[0093] Preferably, the linear polyethylene glycol unit is



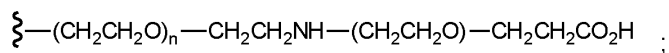
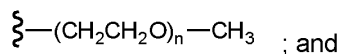
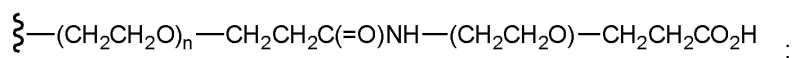
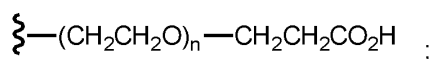
wherein the wavy line indicates the site of attachment to the oxygen atom bound to the phosphorus; R^{20} , R^{21} (also denoted herein as “ K^F ”) and n are as defined herein; more preferably R^{20} is absent. In preferred embodiments, n is 12 or about 12. In preferred embodiments, n is 24 or about 24. Preferably, R^{21} is H or a protecting group.

[0094] The polyethylene glycol attachment unit R^{20} , when present, is part of the polyethylene glycol unit and acts to link the polyethylene glycol unit to the oxygen atom bound to the phosphorus. In this regard, the oxygen atom bound to the phosphorus forms a bond with the polyethylene glycol unit. In exemplary embodiments, the PEG attachment unit R^{20} , when present, is selected from the group consisting of $^*-(C_1-C_{10})alkyl-^{\#}$, $^*-arylene-^{\#}$, $^*-(C_1-C_{10})alkyl-O-^{\#}$, $^*-(C_1-C_{10})alkyl-C(O)-^{\#}$, $^*-(C_1-C_{10})alkyl-C(O)O-^{\#}$, $^*-(C_1-C_{10})alkyl-NH-^{\#}$, $^*-(C_1-C_{10})alkyl-S-^{\#}$, $^*-(C_1-C_{10})alkyl-C(O)-NH-^{\#}$, $^*-(C_1-C_{10})alkyl-NH-C(O)-^{\#}$, and $^*-CH_2-CH_2SO_2-(C_1-C_{10})alkyl-^{\#}$; wherein * denotes the attachment point to the oxygen bound to the phosphorus, and $^{\#}$ denotes the attachment point to the ethylene glycol unit.

[0095] The PEG coupling unit R^{22} , when present, is part of the polyethylene glycol unit and is non-PEG material that acts to connect two or more chains of repeating $-CH_2CH_2O-$ subunits. In exemplary embodiments, the PEG coupling unit R^{22} , when present, is independently selected from the group consisting of $^*-(C_1-C_{10})alkyl-C(O)-NH-^{\#}$, $^*-(C_1-C_{10})alkyl-NH-C(O)-^{\#}$, $^*-(C_2-C_{10})alkyl-NH-^{\#}$, $^*-(C_2-C_{10})alkyl-O-^{\#}$, $^*-(C_1-C_{10})alkyl-S-^{\#}$, or $^*-(C_2-C_{10})alkyl-NH-^{\#}$; wherein * denotes the attachment point to an oxygen atom of an ethylene glycol subunit, and $^{\#}$ denotes the attachment point to a carbon atom of another ethylene glycol subunit.

[0096] The group R^{21} , also denoted herein as “ K^F ”, in exemplary embodiments is H (hydrogen), or may be a capping group, as described herein; preferably, R^{21} is independently selected from the group consisting of $-H$, a protecting group, $-PO_3H$, $-(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl-SO_3H$, $-(C_2-C_{10})alkyl-CO_2H$, $-(C_2-C_{10})alkyl-OH$, $-(C_2-C_{10})alkyl-NH_2$, $-(C_2-C_{10})alkyl-NH(C_1-C_3)alkyl$ and $-(C_2-C_{10})alkyl-N((C_1-C_3)alkyl)_2$. In some embodiments R^{21} may be $-(C_1-C_{10})alkyl$, in particular methyl. More preferably, R^{21} is H or a protecting group. Even more preferably, R^{21} is H. In some preferred embodiments, R^{21} is a protecting group. The protecting group may be as described herein when K^F is a protecting group.

[0097] Illustrative linear polyethylene glycol units, which can be used as R^1 in any one of the embodiments provided herein, are as follows.

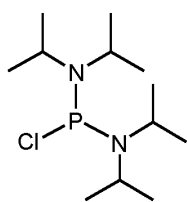


wherein the wavy line indicates the site of attachment to the oxygen atom which is bound to the phosphorus; and each n is from 1 to 100, preferably from 2 to 50, more preferably from 3 to 45, still more preferably from 4 to 40, still more preferably from 6 to 35, even more preferably from 8 to 30. In some embodiments, n is about 12. In some embodiments, n is about 24.

[0098] In some embodiments, the polyethylene glycol unit is from about 300 daltons to about 5 kilodaltons; from about 300 daltons, to about 4 kilodaltons; from about 300 daltons, to about 3 kilodaltons; from about 300 daltons, to about 2 kilodaltons; or from about 300 daltons, to about 1 kilodalton. In some such aspects, the polyethylene glycol unit may have at least 6 ethylene glycol subunits or at least 8 ethylene glycol subunits. In some such aspects, the polyethylene glycol unit may have at least 6 ethylene glycol subunits or at least 8 ethylene glycol subunits but no more than 100 ethylene glycol subunits, preferably no more than 50 ethylene glycol subunits. In some embodiments, the polyethylene glycol unit is a polyethylene glycol unit being from about 300 daltons to about 5 kilodaltons; from about 300 daltons to about 4 kilodaltons; from about 300 daltons to about 3 kilodaltons; from about 300 daltons to about 2 kilodaltons; or from about 300 daltons to about 1 kilodalton. In some such aspects, the polyethylene glycol unit may have at least 6 ethylene glycol subunits or at least 8 ethylene glycol subunits. In some aspects, the polyethylene glycol unit has at least 6 ethylene glycol subunits or at least 8 ethylene glycol subunits but no more than 100 ethylene glycol subunits, preferably no more than 50 ethylene glycol subunits.

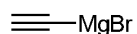
[0099] It will be appreciated that when referring to ethylene glycol subunits, depending on context, the number of subunits can represent an average number, e.g., when referring to a population of conjugates or intermediate compounds, and using polydisperse polyethylene glycols.

[00100] In some preferred embodiments of any one of the methods described herein, the compound of formula (VIII) is a compound of formula (VIIIc):



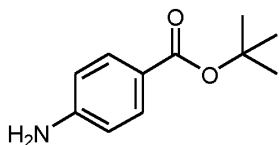
(VIIIc),

the compound of formula (VII) is a compound of formula (VIIc):



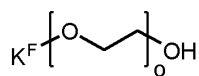
(VIIc),

the compound of formula (V) is a compound of formula (Vc):



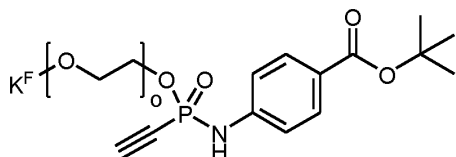
(Vc),

the compound of formula (III) is a compound of formula (IIIc):



(IIIc), and

the compound of formula (I) is a compound of formula (Ic):

(Ic). In any one of these embodiments, K^F and o are as

defined herein. Preferably, K^F is H. In some also preferred embodiments, K^F is a protecting group. Preferably, in addition or alternatively, the integer o is 24 or 12. More preferably, o is 24.

[00101] Preferably, as an advantage of the methods described herein, compounds of formula (V) and/or compounds of formula (III) can be used in a substantially equimolar amount based on the amount of the compound of formula (VIII) or the amount of the compound of formula (VI). The term “substantially equimolar amount”, as used herein, may in general refer to a molar ratio of from 0.5 : 1.5 to 1.5 : 0.5.

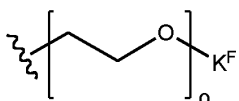
[00102] In some preferred embodiments, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in a substantially equimolar amount based on the amount of the compound of formula (VIII). Accordingly, preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). More preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Still more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Still more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Even more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (V) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VIII). In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with a compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V).

[00103] In some preferred embodiments, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (V) is used in a substantially equimolar amount based on the amount of the compound of formula (VI). Accordingly, preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). More preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Still more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (V) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Still more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the

methods described herein, the compound of formula (V) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Even more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (V) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VI). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V).

[00104] In some preferred embodiments, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in a substantially equimolar amount based on the amount of the compound of formula (VIII). Accordingly, preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). More preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Still more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Still more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII). Even more preferably, when a compound of formula (VIII) is used as starting material in step (i) of any one of the methods described herein, the compound of formula (III) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VIII). In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V). The inventors have found that the methods of preparing phosphoramidates of formula (I) described herein allow for using the alcohol of formula (III) in a substantially equimolar amount based on a starting material of formula (VIII), when compared to the Staudinger route which requires at least two equivalents of an alcohol for preparing

phosphonamidates. Therefore, as an advantage in comparison to the Staudinger route, the methods of the present invention allow for reducing the amount of the alcohol of formula (III) needed for the preparation of compounds of formula (I). Consequently, the methods of the present invention also allow for a decrease of the amount of waste, and/or the decrease of additional efforts to reisolate, recycle and/or dispose of excess alcohol. In particular, using the alcohol in a substantially equimolar amount is advantageous when precious alcohols are used as compound of formula (III). Precious alcohols, which can be used in embodiments of the present invention, include, for example,

polyethylene glycols, such as, for example where R^1 is , wherein , K^F and o are as defined herein, for example, wherein K^F is H and o is an integer ranging from 1 to 100.

[00105] In some preferred embodiments, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in a substantially equimolar amount based on the amount of the compound of formula (VI). Accordingly, preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). More preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Still more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Still more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI). Even more preferably, when a compound of formula (VI) is used as starting material in step (ii) of any one of the methods described herein, the compound of formula (III) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VI). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V). Again, it is noted that the methods of preparing phosphonamidates of formula (I) described herein allow for using the alcohol of formula (III) in a substantially equimolar amount based on a starting material of formula (VI), when compared to the

Staudinger route which requires at least two equivalents of an alcohol for preparing phosphoramidates. Accordingly, the amount of the alcohol of formula (III) needed for the preparation of compounds of formula (I) and thus the amount of waste, and/or the additional efforts to reisolate, recycle and/or dispose off excess alcohol, can be decreased; again, in particular, using the alcohol in a substantially equimolar amount is advantageous when precious alcohols are used as compound of formula (III) such as, for example, polyethylene glycols.

[00106] Preferably, step (ii) and/or step (iii) of any one of the methods described herein is carried out in presence of an activator. Such activator is capable to facilitate substitution reactions at the phosphorus atom. Suitable activators are known and will be readily selected by a person skilled in the art. In particular, activators used in oligonucleotide synthesis using the phosphoramidite approach can be used in the methods described herein; see, e.g., X. Wei, *"Coupling activators for the oligonucleotide synthesis via phosphoramidite approach"*, Tetrahedron, vol. 69 (2013), pp. 3615-3637, DOI: 10.1016/j.tet.2013.03.001. Suitable activators may include, e.g., 1H-tetrazole, 5-ethylthio-1H-tetrazole (ETT), 5-benzylthio-1H-tetrazole (BTT) and 4,5-dicyanoimidazole (DCI).

[00107] Preferably, in any one of the methods described herein, step (ii) is carried out in the presence of an activator. More preferably, the activator is selected from the group consisting of 1H-tetrazole, 5-ethylthio-1H-tetrazole (ETT), 5-benzylthio-1H-tetrazole (BTT) and 4,5-dicyanoimidazole (DCI). Still more preferably, the activator is 1H-tetrazole. In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with a compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V).

[00108] Preferably, in any one of the methods described herein, step (iii) is carried out in the presence of an activator. More preferably, the activator is selected from the group consisting of 1H-tetrazole, 5-ethylthio-1H-tetrazole (ETT), 5-benzylthio-1H-tetrazole (BTT) and 4,5-dicyanoimidazole (DCI). More preferably, the activator is 1H-tetrazole. In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with a

compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V).

[00109] In step (iv) of any one of the methods described herein an oxidizing agent is used to provide a compound of formula (I). Any oxidizing agent which is capable to convert a phosphorus(III) compound into a phosphorus(V) compound may be used. Suitable oxidizing agents are known and readily selected by a person skilled in the art; see, for example, WO 2019/170710 A2. The oxidizing agent may be selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA), a urea-hydrogen peroxide adduct, (camphorsulfonyl)oxaziridine (CSO), iodine, tert-butylhydroperoxide (tBuOOH) and air. Preferably, the oxidizing agent is selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA) and a urea-hydrogen peroxide adduct. More preferably, the oxidizing agent is hydrogen peroxide. See, e.g., **Example 4**, where good results are demonstrated by using hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA) or a urea-hydrogen peroxide adduct as oxidizing agent.

[00110] The solvents used in the methods described herein are not particularly limited. Solvents for carrying out the steps of the methods described herein, such as e.g. substitution reactions and oxidation reactions at the phosphorus, including the use of organometallic reagents, are known, and a person skilled in the art knows to select suitable solvents. Step (i) of any one of the methods described herein may be carried out in a solvent selected from the group consisting of tetrahydrofuran (THF), diethylether, methyltetrahydrofuran, benzene, toluene, xylene, methyl-tert-butyl ether (MTBE), diisopropylether, dioxane and any combination thereof. These solvents are inert towards organometallic reagents, such as e.g. Grignard compounds or organolithium compounds. Preferably, step (i) is carried out in tetrahydrofuran (THF) or diethylether. More preferably, step (i) is carried out in tetrahydrofuran (THF). Step (ii) of any one of the methods described herein may be carried out in a solvent selected from the group consisting of acetonitrile, acetone, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof. These solvents are polar-aprotic solvents which facilitate substitution reactions at the phosphorus atom, in particular nucleophilic substitutions. Solvent(s) used in step (i) may be also present in step (ii), for example, when the method is carried out as a one-pot process. Preferably, step (ii) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether. Step (iii) of any one of the methods described herein may be carried out in a solvent selected from the group consisting of acetonitrile,

acetone, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof. These solvents are polar-aprotic solvents which facilitate substitution reactions at the phosphorus atom, in particular nucleophilic substitutions. Solvent(s) used in step (i) and/or solvent(s) used in step (ii) may be also present in step (iii), for example, when the method is carried out as a one-pot process. Preferably, step (iii) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether. Step (iv) of any one of the methods described herein may be carried out in a solvent selected from the group consisting of acetonitrile, acetone, water, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof. Solvent(s) used in step (i), solvent(s) used in step (ii) and/or solvent(s) used in step (iii) may be also present in step (iv), for example, when the method is carried out as a one-pot process. Preferably, step (iv) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether, optionally further in combination with water. In particular, water may be used when the oxidizing agent is hydrogen peroxide. In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with a compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V).

[00111] The methods described herein can be carried out at large scale, e.g. a compound of formula (I) can be produced at a scale of several 100 grams, e.g. at a 600 gram scale. Preferably, in particular for large scale application, in any one of the methods described herein step (i) is carried out in tetrahydrofuran (THF). Preferably, in particular for large scale application, in any one of the methods described herein step (ii) is carried out in a solvent selected from the group consisting of tetrahydrofuran (THF), acetonitrile and a combination thereof. More preferably, in particular for large scale application, in any one of the methods described herein step (ii) is carried out in tetrahydrofuran (THF), optionally in combination with acetonitrile. Preferably, in particular for large scale application, in any one of the methods described herein step (iii) is carried out in a solvent selected from the group consisting of tetrahydrofuran (THF), acetonitrile and a combination thereof. More preferably, in particular for large scale application, in any one of the methods described herein step (iii) is carried out in tetrahydrofuran (THF), optionally in combination with acetonitrile. Preferably, in particular for large scale application, in any one of the methods described herein step (iv) is carried out in a solvent

selected from the group consisting of tetrahydrofuran (THF), acetonitrile and a combination thereof. More preferably, in particular for large scale application, in any one of the methods described herein step (iv) is carried out in tetrahydrofuran (THF), optionally in combination with acetonitrile and/or water. In any one of these embodiments, step (ii) may be reacting the product obtained in step (i) with the compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the product obtained in step (i) with a compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with the compound of formula (V). In any one of these embodiments, step (ii) may be reacting the compound of formula (VI) with a compound of formula (V), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (III). It is also possible that in any one of these embodiments step (ii) may be reacting the compound of formula (VI) with the compound of formula (III), and step (iii) may be reacting the product obtained in step (ii) with a compound of formula (V).

[00112] The temperature(s) for carrying out the methods described herein are not particularly limited. A person skilled in the art knows to select suitable temperature(s) for carrying out the steps of the methods described herein. For example, in any one of the methods described herein step (i), which uses organometallic reagents, may be carried out at a temperature of from -80°C to $+60^{\circ}\text{C}$. In particular, in any one of the methods described herein step (i) may be carried out at a temperature of from -20 to $+60^{\circ}\text{C}$. Preferably, in any one of the methods described herein, step (i) is carried out at a temperature of from -10 to $+40^{\circ}\text{C}$. More preferably, in any one of the methods described herein, step (i) is carried out at a temperature of from -5 to $+35^{\circ}\text{C}$. In any one of the methods described herein step (i) may be carried out at a temperature of from -20 to $+60^{\circ}\text{C}$. Preferably, in any one of the methods described herein, step (i) is carried out at a temperature of from -10 to $+40^{\circ}\text{C}$. More preferably, in any one of the methods described herein, step (i) is carried out at a temperature of from -5 to $+35^{\circ}\text{C}$. In any one of the methods described herein step (ii) may be carried out at a temperature of from 0 to $+60^{\circ}\text{C}$. Preferably, in any one of the methods described herein, step (ii) is carried out at a temperature of from $+5$ to $+40^{\circ}\text{C}$. More preferably, in any one of the methods described herein, step (ii) is carried out at a temperature of from $+10$ to $+35^{\circ}\text{C}$. In any one of the methods described herein step (iii) may be carried out at a temperature of from 0 to $+60^{\circ}\text{C}$. Preferably, in any one of the methods described herein, step (iii) is carried out at a temperature of from $+5$ to $+40^{\circ}\text{C}$. More preferably, in any one of the methods described herein, step (iii) is carried out at a temperature of from $+10$ to $+35^{\circ}\text{C}$. In any one of the methods described herein step (iv) may be carried out at a temperature of from 0 to $+60^{\circ}\text{C}$. Preferably, in any one of the methods described herein, step (iv) is carried out at a temperature of from $+5$ to $+40^{\circ}\text{C}$. More preferably, in any one of the methods described herein, step (iv) is carried out at a temperature of from $+10$ to $+35^{\circ}\text{C}$. Suitable reaction times are also readily selected or determined by a person skilled in the art.

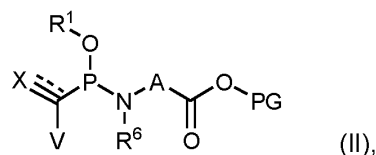
Methods for monitoring the progress of the reaction(s), such as e.g. chromatographic or spectroscopic methods, are known in the art.

[00113] Preferably, any one of the methods of preparing a compound of formula (I) described herein can be carried out as a one-pot process. In particular, any method of preparing a compound of formula (I) comprising steps (i) to (iv), wherein a compound of formula (VIII) is used as starting material, as described herein, can be carried out as a one-pot process. It is also possible to carry out any method of preparing a compound of formula (I) comprising steps (ii) to (iv), wherein a compound of formula (VI) is used as starting material, as described herein, as a one-pot process. The term "one-pot process", as used herein, in general refers to a method of preparing a compound of formula (I), wherein all steps (i) to (iv) or, depending on the respective method, all steps (ii) to (iv) are carried out without work-up, isolation and/or purification of intermediates. The term "one-pot process" thus includes, for example, that reactants are added to the reaction mixture, different temperatures are adjusted as needed, and/or also that the reaction mixture is subjected to filtration, as long as the reaction mixture is not subjected to work-up, isolation and/or purification of intermediates between the steps. In this regard, the term "one-pot process" also includes that the solvent is removed and/or exchanged, as long as non-volatile intermediates, reactants and/or impurities remain together in the reaction mixture, i.e. the mixture is not subjected to work-up, isolation and/or purification of intermediates between the steps. Accordingly, during a one pot process, the solvent may be removed, e.g. by evaporation in vacuo. It is also possible that another solvent may be added after removal of the solvent, as long as the reaction mixture is not subjected to work-up, isolation and/or purification. In particular, the reaction mixture comprising intermediates, reactants and/or impurities may remain in the reaction vessel when the solvent is removed and/or exchanged. All steps (i) to (iv) may be carried out, for example, in the same reaction vessel. When any one of the methods further comprises a step (v) to provide a compound of formula (I*), as described herein, it is possible to also include step (v) into the one-pot process. Accordingly, in some embodiments, any method of preparing a compound of formula (I*) comprising steps (i) to (v), wherein a compound of formula (VIII) is used as starting material, as described herein, can be carried out as a one-pot process. In some embodiments, any method of preparing a compound of formula (I*) comprising steps (ii) to (v), wherein a compound of formula (VI) is used as starting material, as described herein, can be carried out as a one-pot process. However, in contrast to a one-pot process, it is also possible to conduct any one of the methods described herein, comprising steps (i) to (iv), or steps (ii) to (iv), or steps (i) to (v), or steps (ii) to (v), as a sequence of one or more separate stage(s), wherein the reaction mixture is subjected to work-up, isolation and/or purification of intermediate(s) at least between two of the steps.

[00114] Preferably, in any one of the methods described herein, in particular steps (i) to (iv), are carried out under an inert gas atmosphere. More preferably, any one of the methods described herein, in particular steps (i) to (iv), are carried out under nitrogen or argon. Using an inert gas atmosphere, which keeps away air and moisture from the reaction mixture(s), may result in increased yields, purity and quality of the obtained products.

[00115] An important step of the methods described herein is the oxidation of step (iv) to give a compound of formula (I). Accordingly, the present invention also relates to a method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

reacting a compound of formula (II) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4-\text{C} \end{array}$ when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

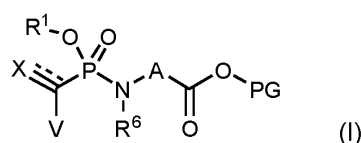
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

with an oxidizing agent to give a compound of formula (I) or salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is R⁴-C(R⁵) when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

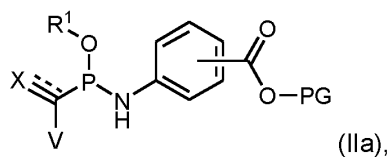
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

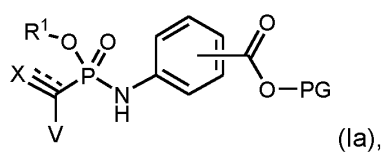
A is a spacer; and

PG is a protecting group. Any variable such as, for example, $\equiv$, $=$, X, V, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A, PG and the oxidizing agent may be as defined herein. The method may be further defined as described herein with regard to step (iv) of any one of the methods described herein. Optionally, a compound of formula (II) may be prepared according to any method comprising steps (i), (ii) and (iii), as described herein. Optionally, a compound of formula (II) may be also prepared according to any method comprising steps (ii) and (iii), as described herein.

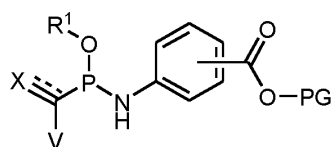
[00116] Preferably, the compound of formula (II) is a compound of formula (IIa):



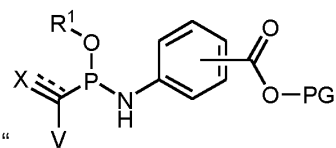
wherein , X, V, R¹ and PG are as defined herein. Accordingly, and also preferably, the compound of formula (I) is a compound of formula (Ia):



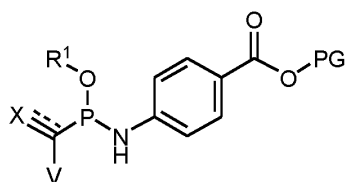
wherein , X, V, R¹ and PG are as defined herein. It is noted that the representation “



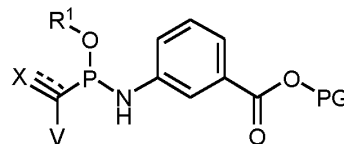
“ denotes, as common in the art, that the compound can be present as



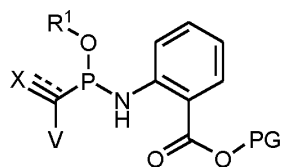
the ortho, meta or para isomer. Accordingly, the representation “



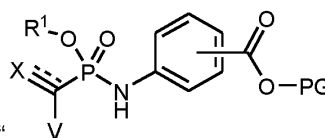
covers the compounds



and



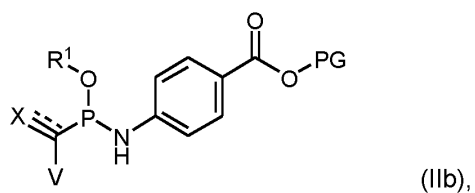
. The representation “



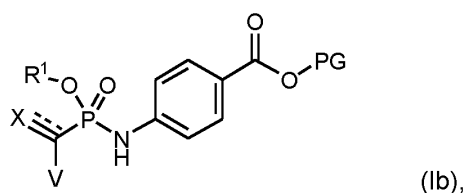
” has been already

explained herein above.

[00117] More preferably, in any one of the methods described herein, the compound of formula (II) is a compound of formula (IIb):

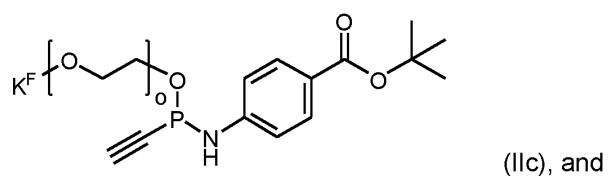


wherein , X, V, R¹ and PG are as defined herein. Accordingly, also more preferably, the compound of formula (I) is a compound of formula (Ib):

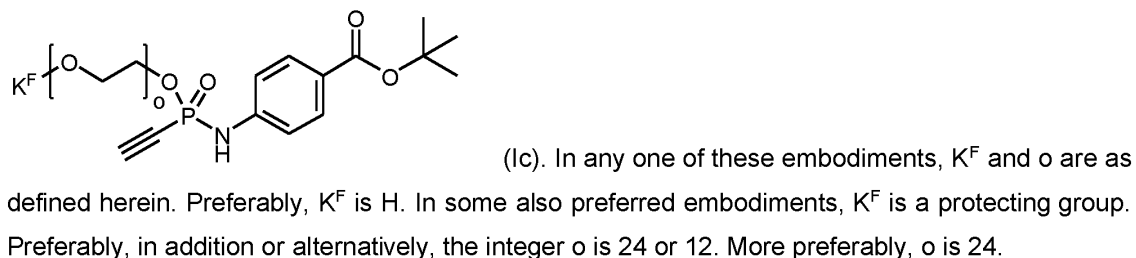


wherein , X, V, R¹ and PG are as defined herein.

[00118] In some preferred embodiments, the compound of formula (II) is a compound of formula (IIc):



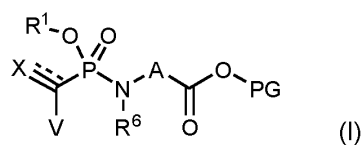
the compound of formula (I) is a compound of formula (Ic):



Method of Preparing a Compound of Formula (I*)

[00119] In some embodiments, any method described herein of preparing a compound of formula (I) may further comprise a step (v) of removing a protecting group PG to prepare a compound of formula (I*), comprising:

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

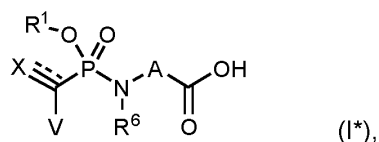
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is R⁴-C(^{R⁵}) when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

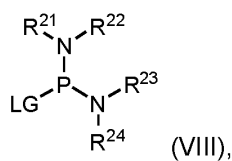
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl; and

A is a spacer. Any variable such as, for example, , X, V, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A and PG may be as defined herein. In any one of these embodiments, step (v) may be as described herein. For example, step (v) may be as described herein further below.

[00120] Optionally, a compound of formula (I) may be prepared according to any one of the methods of preparing a compound of formula (I) described herein. Step (v) may then be carried out using a compound of formula (I) as starting material. Thus, in some embodiments, the present invention also relates to a method of preparing a compound of formula (I*) comprising steps (i), (ii), (iii), (iv) and (v). In these embodiments, a compound of formula (VIII) is used as starting material in step (i). In some embodiments, the present invention also relates to a method of preparing a compound of formula (I*) comprising steps (ii), (iii), (iv) and (v). In these embodiments, a compound of formula (VI) is used as starting material in step (ii). In any one of these embodiments, steps (i), (ii), (iii), (iv) and/or (v) may be as described herein. In some preferred embodiments, the present invention relates to a method of preparing a compound of formula (I*) or a salt or solvate thereof, comprising:

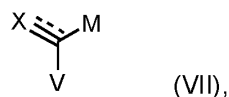
(i) reacting a compound of formula (VIII) or a salt or solvate thereof:



wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and
 LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $R^4-\overset{R^5}{\underset{|}{C}}$ when is a double bond;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

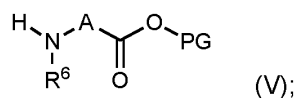
R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl; and

M is a metal-containing group capable of transferring the group to the phosphorus atom to replace the leaving group LG;



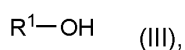
(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



wherein:

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 A is a spacer; and
 PG is a protecting group;

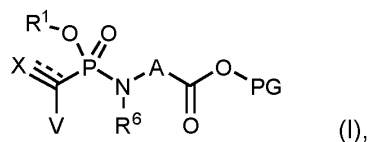
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



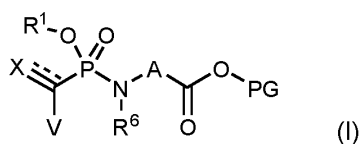
is a double bond;

V is absent when is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when is a double bond;

- X is R^3-C when $\equiv$ is a triple bond; or
- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when $=$ is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(C_1-C_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(C_1-C_8)\text{alkyl}$;
- R^4 is H or $(C_1-C_8)\text{alkyl}$;
- R^5 is H or $(C_1-C_8)\text{alkyl}$;
- R^6 is H or $(C_1-C_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group; and

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:

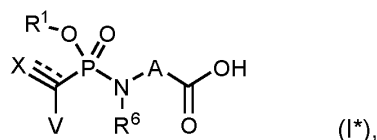


wherein:

- $\equiv$ is a triple bond; or
- $=$ is a double bond;
- V is absent when $\equiv$ is a triple bond; or
- V is H or $(C_1-C_8)\text{alkyl}$ when $=$ is a double bond;
- X is R^3-C when $\equiv$ is a triple bond; or
- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when $=$ is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(C_1-C_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(C_1-C_8)\text{alkyl}$;
- R^4 is H or $(C_1-C_8)\text{alkyl}$;
- R^5 is H or $(C_1-C_8)\text{alkyl}$;
- R^6 is H or $(C_1-C_8)\text{alkyl}$;

A is a spacer; and
PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is R⁴-C^{R⁵} when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

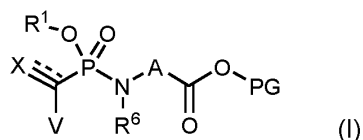
R⁶ is H or (C₁-C₈)alkyl; and

A is a spacer. In these embodiments, any variable such as, for example, R²¹, R²², R²³, R²⁴, , X, V, M, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A and PG, may be as defined herein. In these embodiments, steps (i), (ii), (iii), (iv) and/or (v) may be as described herein. For example, step (v) may be as described herein further below.

[00121] The removal of the protecting group PG, however, is also an important reaction per se in order to provide a free carboxylic acid group in compound (I*), which can then be used for further reaction or functionalization. The inventors have also found that compounds of formula (I) have excellent stability and can thus be well isolated and stored. Accordingly, the present invention

also relates to a method of preparing a compound of formula (I*) or a salt or solvate thereof, comprising:

(v) removing a protecting group PG from a compound of formula (I):



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is R⁴-C^{R⁵} when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

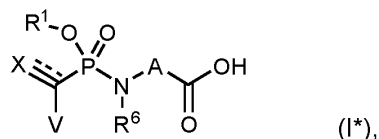
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl; and

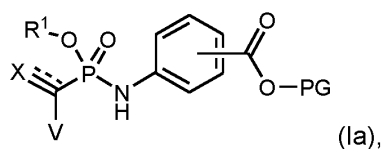
A is a spacer. Any variable such as, for example, , X, V, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A and PG may be as defined herein. Regarding the method of removing a protecting group from a compound of formula (I) to give a compound of formula (I*), it is, however, not required to prepare the compound of formula (I) using the methods of the present invention. Although the methods of the present invention allow for advantageous preparations of compounds of formula (I), the method of removing a protecting group PG from a compound of formula (I) to give a compound of formula (I*) is not limited to include any preparation of a compound of formula (I).

[00122] The moiety PG is a protecting group. In particular, PG is a protecting group suitable for protection of a carboxylic acid moiety. Protecting groups suitable for protection of carboxylic acid moieties are known and readily selected by a person skilled in the art. Illustrative examples, which may be used in embodiments of the present invention, include optionally substituted (C₁-C₈)alkyl, such as, e.g., (C₁-C₈)alkyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl, allyl or benzyl. Preferably, PG is (C₁-C₈)alkyl, more preferably (C₁-C₆)alkyl, still more preferably (C₁-C₄)alkyl. PG may be methyl, ethyl, propyl or butyl. In some preferred embodiments, PG is tert-butyl. By removing the protecting group PG, in other words by deprotection, PG is replaced by hydrogen so that a carboxylic acid moiety (COOH) is formed. Suitable methods for introducing and removing carboxylic acid protecting groups are known to a person skilled in the art. For example, acidic or basic conditions can be used to cleave a carboxylic acid ester to obtain a free carboxylic acid moiety. In some preferred embodiments, the protecting group PG is tert-butyl, and PG is removed with an acid. More

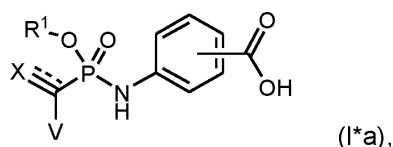
preferably, the protecting group is tert-butyl, and PG is removed with trifluoroacetic acid (TFA). When the tert-butyl protecting group is removed with trifluoroacetic acid, the reaction can be carried out under neat conditions, i.e. no further solvent is used in addition to the trifluoroacetic acid. Suitable reaction conditions are readily determined by a person skilled in the art. For example, removal of the tert-butyl protecting group with trifluoroacetic acid (TFA) may be carried out at a temperature of from -20 to $+60$ °C, preferably of from -10 to $+30$ °C.

[00123] Preferably, the protecting group PG is removed under an inert gas atmosphere. More preferably, the protecting group is removed under nitrogen or argon. Using an inert gas atmosphere, which keeps away air and moisture from the reaction mixture, may result in increased yields, purity and quality of the obtained products.

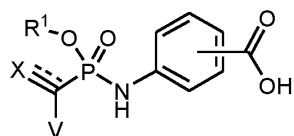
[00124] Preferably, the compound of formula (I) is a compound of formula (Ia):



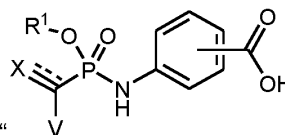
wherein , X, V, R¹ and PG are as defined herein. Accordingly, and also preferably, the compound of formula (I*) is a compound of formula (I*a):



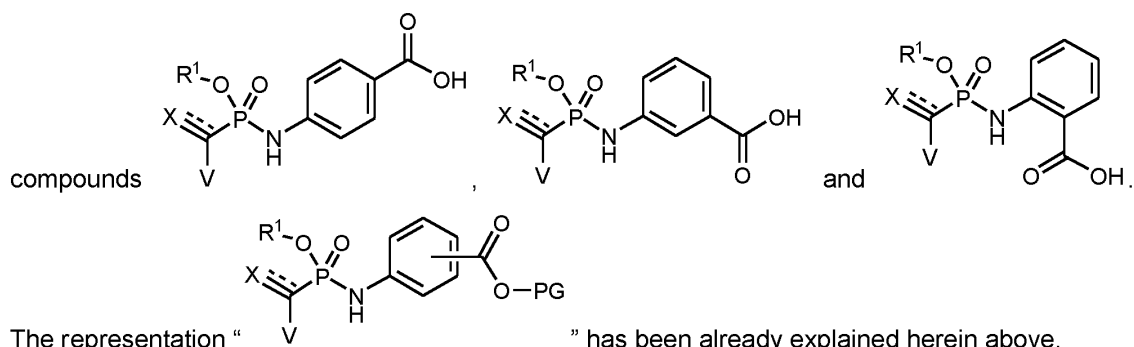
wherein , X, V, R¹ and PG are as defined herein. It is noted that the representation “



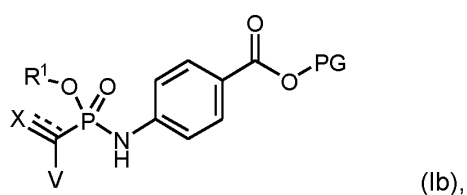
“ denotes, as common in the art, that the compound can be present as the



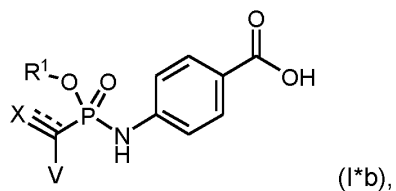
ortho, meta or para isomer. Accordingly, the representation “



[00125] More preferably, the compound of formula (I) is a compound of formula (Ib):

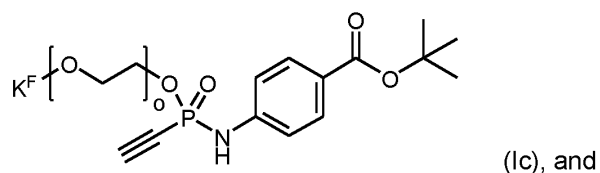


wherein , X, V, R¹ and PG are as defined herein. Accordingly, and even more preferably, the compound of formula (I*) is a compound of formula (I*b):

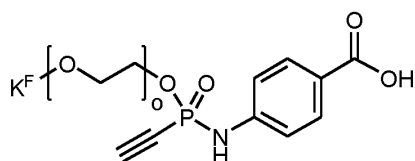


wherein , X, V, R¹ and PG are as defined herein.

[00126] In some preferred embodiments, the compound of formula (I) is a compound of formula (Ic):

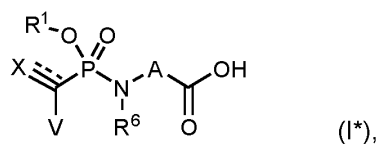


the compound of formula (I*) is a compound of formula (I*c):



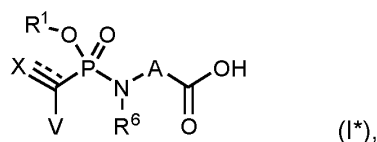
(I*c). In any one of these embodiments, K^F and o are as defined herein. Preferably, K^F is H. In some also preferred embodiments, K^F is a protecting group. Preferably, in addition or alternatively, the integer o is 24 or 12. More preferably, o is 24.

[00127] The present invention also relates to a compound of formula (I*) or a salt or solvate thereof:



wherein , X, V, R^1 , R^6 and A are as defined herein. It has turned out that compounds of formula (I*) have an excellent stability and can thus be well isolated and stored.

[00128] The present invention also relates to a compound of formula (I*) or a salt or solvate thereof:

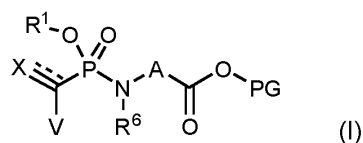


obtainable or being obtained by any one of the methods of the present invention,

wherein , X, V, R^1 , R^6 and A are as defined herein.

Compound of Formula (I)

[00129] The inventors have found that compounds of formula (I) have excellent stability and can thus be well isolated and stored. Accordingly, the present invention also relates to a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is R⁴-C^{R⁵} when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

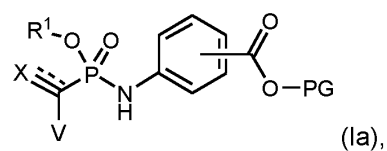
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

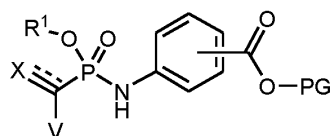
A is a spacer; and

PG is a protecting group. Any variable such as, for example, , X, V, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A, PG may be as defined herein. Optionally, a compound of formula (I) may be prepared according to any one of the methods of preparing a compound of formula (I) described herein.

[00130] Preferably, the compound of formula (I) is a compound of formula (Ia):

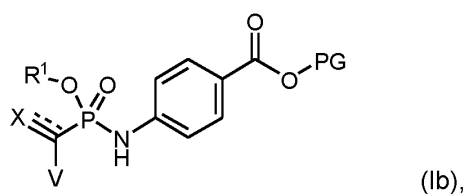


wherein , X, V, R¹ and PG are as defined herein. The representation “



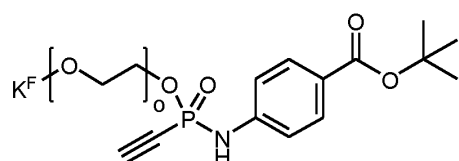
” has been already explained herein above.

[00131] More preferably, the compound of formula (I) is a compound of formula (Ib):



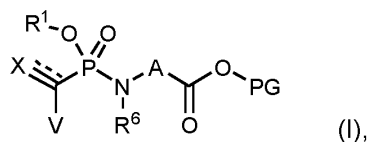
wherein , X, V, R¹ and PG are as defined herein.

[00132] In some preferred embodiments, the compound of formula (I) is a compound of formula (Ic):



(Ic). In any one of these embodiments, K^F and o are as defined herein. Preferably, K^F is H. In some also preferred embodiments, K^F is a protecting group. Preferably, in addition or alternatively, the integer o is 24 or 12. More preferably, o is 24.

[00133] The present invention also relates to a compound of formula (I) or a salt or solvate thereof:



obtainable or being obtained by any one of the methods of the present invention,

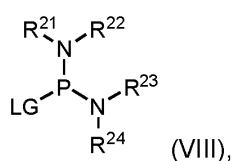
wherein , X, V, R¹, R⁶, A and PG are as defined herein.

Items of the Invention

[00134] The present invention is also characterized by the following items:

1. A method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

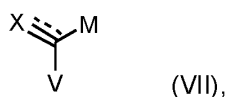


wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted ($\text{C}_1\text{-C}_8$)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and

LG is a leaving group

with a compound of formula (VII):



wherein:

$\text{---}\text{---}\text{---}$ is a triple bond; or

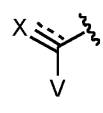
= is a double bond;

V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or

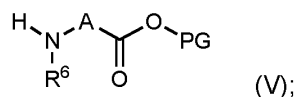
V is H or ($\text{C}_1\text{-C}_8$)alkyl when = is a double bond;

X is $\text{R}^3\text{-C}$ when $\text{---}\text{---}\text{---}$ is a triple bond; or

- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when  is a double bond;
- R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

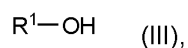
(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



wherein:

- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group;

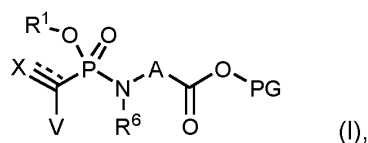
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is $\begin{matrix} \text{R}^5 \\ | \\ \text{R}^4\text{-C} \end{matrix}$ when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

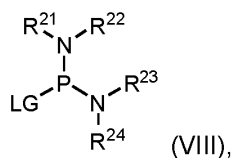
R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.

2. A method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

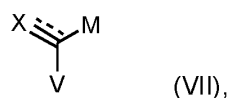


wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C_1 - C_8)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and

LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or (C_1 - C_8)alkyl when is a double bond;

X is R^3 -C when is a triple bond; or

X is $\begin{array}{c} R^5 \\ | \\ R^4\text{---}C \end{array}$ when is a double bond;

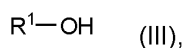
R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and (C_1 - C_8)alkyl, wherein R^{Si} is, each independently, (C_1 - C_8)alkyl;

R^4 is H or (C_1 - C_8)alkyl;

R^5 is H or (C_1 - C_8)alkyl; and

M is a metal-containing group capable of transferring the group to the phosphorus atom to replace the leaving group LG;

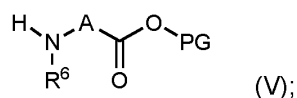
(ii) reacting the product obtained in step (i) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



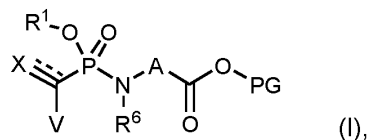
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

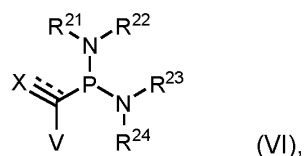
X is R³-C when $\equiv$ is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4 - \text{C} \end{array}$ when $=$ is a double bond;

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
 R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
 R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
A is a spacer; and
PG is a protecting group.

3. A method of preparing a compound of formula (I), comprising:

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when is a double bond;

X is $\text{R}^3\text{-C}$ when is a triple bond; or

X is $\text{R}^4\text{-C}$ when is a double bond;

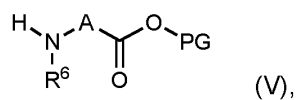
R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted $(\text{C}_1\text{-C}_8)\text{alkyl}$; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

R⁵ is H or (C₁-C₈)alkyl

with a compound of formula (V) or a salt or solvate thereof:



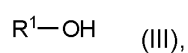
wherein:

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group;

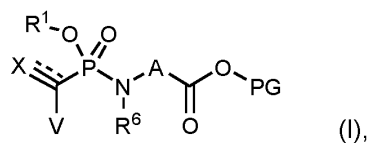
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or

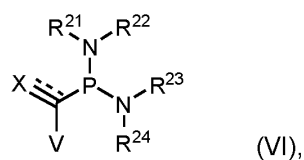


is a double bond;

- V is absent when $\equiv$ is a triple bond; or
- V is H or (C₁-C₈)alkyl when $=$ is a double bond;
- X is R³-C when $\equiv$ is a triple bond; or
- X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4-\text{C} \end{array}$ when $=$ is a double bond;
- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is each, independently, (C₁-C₈)alkyl;
- R⁴ is H or (C₁-C₈)alkyl;
- R⁵ is H or (C₁-C₈)alkyl;
- R⁶ is H or (C₁-C₈)alkyl;
- A is a spacer; and
- PG is a protecting group.

4. A method of preparing a compound of formula (I), comprising:

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4-\text{C} \end{array}$ when $=$ is a double bond;

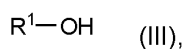
R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R^4 is H or (C₁-C₈)alkyl; and

R^5 is H or (C₁-C₈)alkyl

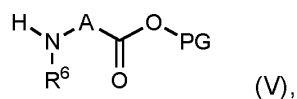
with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



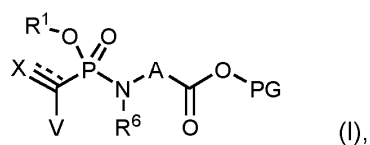
wherein:

R^6 is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

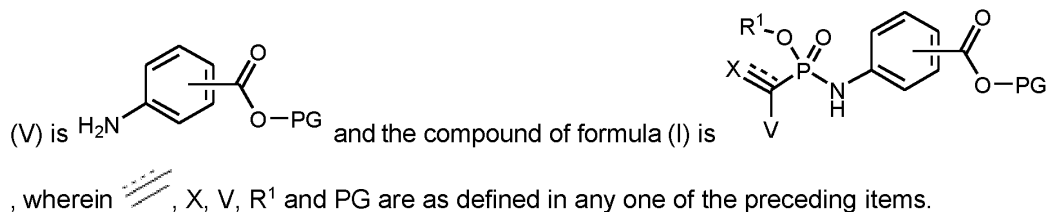
A is a spacer; and

PG is a protecting group.

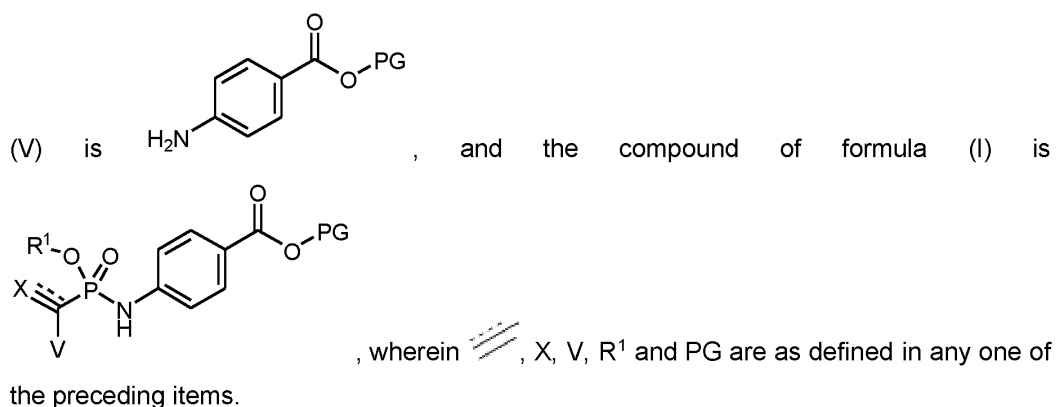
5. The method according to any one of the preceding items, wherein R²¹, R²², R²³ and R²⁴ are each iso-propyl.
6. The method according to any one of items 1 to 4, wherein R²¹, R²², R²³ and R²⁴ are each methyl; or wherein R²¹, R²², R²³ and R²⁴ are each ethyl.
7. The method according to any one of items 1, 2, 5 and 6, wherein the leaving group LG is selected from the group consisting of halogen (e.g., F, Cl, Br or I) and optionally substituted phenoxy; preferably wherein the leaving group LG is Cl.
8. The method according to any one of the preceding items, wherein  is a triple bond; V is absent; X is R³-C; and R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl; preferably R³ is H or -Si(R^{Si})₃, wherein R^{Si} is, each independently, (C₁-C₈)alkyl; more preferably R³ is H.

9. The method according to any one of items 1 to 7, wherein  is a double bond; V is H or (C₁-C₈)alkyl, preferably V is H; X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$; R⁴ is H or (C₁-C₈)alkyl, preferably R⁴ is H and R⁵ is H or (C₁-C₈)alkyl, preferably R⁵ is H.
10. The method according to any one of the preceding items, wherein M is MgY, wherein Y is halogen, preferably wherein Y is Br.
11. The method according to any one of items 1 to 9, wherein M is Li.
12. The method according to any one of the preceding items, wherein R⁶ is H.
13. The method according to any one of the preceding items, wherein the spacer A is selected from the group consisting of optionally substituted -(C₆-C₁₀)arylene-, optionally substituted -(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)carbocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₆-C₁₀)arylene-, optionally substituted -(C₆-C₁₀)arylene-(C₁-C₁₀)alkylene-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)carbocyclo-, optionally substituted -(C₃-C₈)carbocyclo-(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)heterocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)heterocyclo- and optionally substituted -(C₃-C₈)heterocyclo-(C₁-C₁₀)alkylene-;
- preferably wherein the spacer A is selected from the group consisting of optionally substituted -(C₆-C₁₀)arylene-, optionally substituted -(C₁-C₁₀)alkylene- and optionally substituted -(C₃-C₈)carbocyclo-;
- more preferably wherein the spacer A is optionally substituted -phenylene-.
14. The method according to any one of the preceding items, wherein PG is optionally substituted (C₁-C₈)alkyl, preferably wherein PG is selected from the group consisting of (C₁-C₈)alkyl, 9-fluorenylmethyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl, allyl and benzyl, more preferably wherein PG is (C₁-C₈)alkyl, still more preferably wherein PG is tert-butyl.

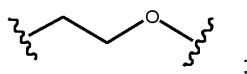
15. The method according to any one of the preceding items, wherein the compound of formula



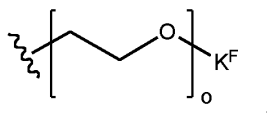
16. The method according to any one of the preceding items, wherein the compound of formula



17. The method according to any one of the preceding items, wherein R¹ is (C₁-C₈)alkyl, preferably methyl, ethyl propyl or butyl, more preferably methyl or ethyl, still more preferably ethyl.
18. The method according to any one of items 1 to 16, wherein R¹ is a polyethylene glycol unit.
19. The method according to item 18, wherein the polyethylene glycol unit comprises 1 to 100 subunits having the structure:



20. The method according to item 18 or 19, wherein R¹ is:



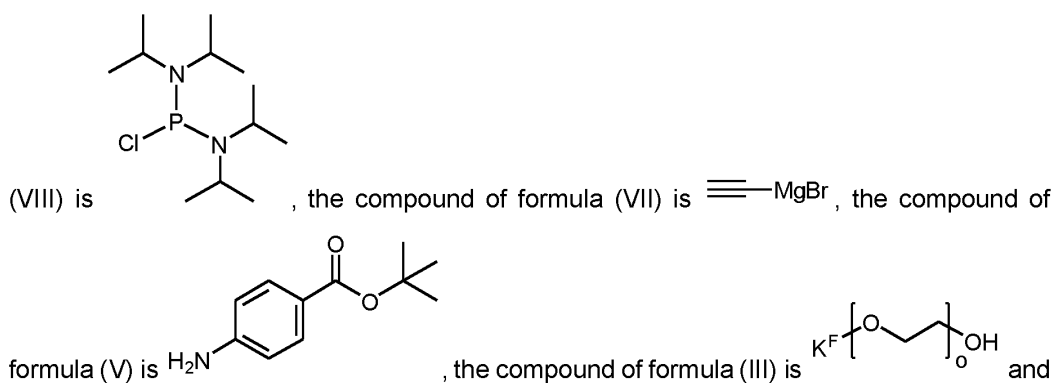
wherein:

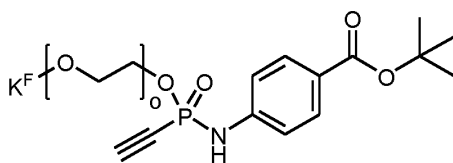


indicates the position of the O;

- K^F is selected from the group consisting of -H, a protecting group, $-\text{PO}_3\text{H}$, $-(\text{C}_1-\text{C}_{10})\text{alkyl}$, $-(\text{C}_1-\text{C}_{10})\text{alkyl}-\text{SO}_3\text{H}$, $-(\text{C}_2-\text{C}_{10})\text{alkyl}-\text{CO}_2\text{H}$, $-(\text{C}_2-\text{C}_{10})\text{alkyl}-\text{OH}$, $-(\text{C}_2-\text{C}_{10})\text{alkyl}-\text{NH}_2$, $-(\text{C}_2-\text{C}_{10})\text{alkyl}-\text{NH}(\text{C}_1-\text{C}_3)\text{alkyl}$ and $-(\text{C}_2-\text{C}_{10})\text{alkyl}-\text{N}((\text{C}_1-\text{C}_3)\text{alkyl})_2$; and
- o is an integer ranging from 1 to 100.

21. The method according to item 20, wherein K_F is H.
22. The method according to item 20, wherein K^F is a protecting group, preferably wherein K^F is selected from the group consisting of *tert*-butyl, trityl, acetyl and a silyl protecting group (e.g., trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBDMS), *tert*-butyldiphenylsilyl (TBDPS) or triisopropylsilyl (TIPS).
23. The method according to any one of items 20 to 22, wherein o ranges from 8 to 30.
24. The method according to item 23, wherein o ranges from 20 to 28.
25. The method according to item 24, wherein o is 22, 23, 24, 25 or 26.
26. The method according to item 23, wherein o ranges from 8 to 16.
27. The method according to item 26, wherein o is 10, 11, 12, 13 or 14.
28. The method according to any one of the preceding item, wherein the compound of formula





the compound of formula (I) is K^{F} , wherein K^{F} and o are as defined in any one of the preceding items; preferably wherein K^{F} is H; and/or preferably wherein o is 24 or 12.

29. The method according to any one of items 1, 2 and 5 to 28, wherein the compound of formula (V) is used in a substantially equimolar amount based on the amount of the compound of formula (VIII); preferably wherein the compound of formula (V) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); more preferably wherein the compound of formula (V) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); still more preferably wherein the compound of formula (V) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); still more preferably wherein the compound of formula (V) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); even more preferably wherein the compound of formula (V) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VIII).
30. The method according to any one of items 3 to 27, wherein the compound of formula (V) is used in a substantially equimolar amount based on the amount of the compound of formula (VI); preferably wherein the compound of formula (V) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); more preferably wherein the compound of formula (V) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); still more preferably wherein the compound of formula (V) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); still more preferably wherein the compound of formula (V) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); even more preferably wherein the compound of formula (V) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VI).
31. The method according to any one of items 1, 2 and 5 to 29, wherein the compound of formula (III) is used in a substantially equimolar amount based on the amount of the compound of formula (VIII); preferably wherein the compound of formula (III) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII);

more preferably wherein the compound of formula (III) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); still more preferably wherein the compound of formula (III) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); still more preferably wherein the compound of formula (III) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII); even more preferably wherein the compound of formula (III) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VIII).

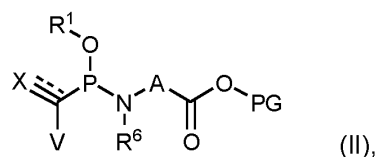
32. The method according to any one of items 3 to 27 and 30, wherein the compound of formula (III) is used in a substantially equimolar amount based on the amount of the compound of formula (VI); preferably wherein the compound of formula (III) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); more preferably wherein the compound of formula (III) is used in an amount of from 0.7 to 1.3 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); still more preferably wherein the compound of formula (III) is used in an amount of from 0.8 to 1.2 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); still more preferably wherein the compound of formula (III) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VI); even more preferably wherein the compound of formula (III) is used in an amount of about 1.0 molar equivalent based on 1.0 molar equivalent of the compound of formula (VI).
33. The method according to any one of the preceding items, wherein step (ii) is carried out in the presence of an activator, preferably wherein the activator is selected from the group consisting of 1H-tetrazole, 5-ethylthio-1H-tetrazole (ETT), 5-benzylthio-1H-tetrazole (BTT) and 4,5-dicyanoimidazole (DCI), more preferably wherein the activator is 1H-tetrazole.
34. The method according to any one of the preceding items, wherein step (iii) is carried out in the presence of an activator, preferably wherein the activator is selected from the group consisting of 1H-tetrazole, 5-ethylthio-1H-tetrazole (ETT), 5-benzylthio-1H-tetrazole (BTT) and 4,5-dicyanoimidazole (DCI), more preferably wherein the activator is 1H-tetrazole.
35. The method according to any one of the preceding items, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA), a urea-hydrogen peroxide adduct, (camphorsulfonyl)oxaziridine (CSO), iodine, tert-butylhydroperoxide (tBuOOH) and air; preferably wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA)

and a urea-hydrogen peroxide adduct; more preferably wherein the oxidizing agent is hydrogen peroxide.

36. The method according to any one of the preceding items, wherein:
- (a) step (i) is carried out in a solvent selected from the group consisting of tetrahydrofuran, diethylether, methyltetrahydrofuran, benzene, toluene, xylene, methyl-tert-butyl ether (MTBE), diisopropylether, dioxane and any combination thereof; preferably wherein step (i) is carried out in tetrahydrofuran; and/or
 - (b) step (ii) is carried out in a solvent selected from the group consisting of acetonitrile, acetone, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof; preferably wherein step (ii) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether; and/or
 - (c) step (iii) is carried out in a solvent selected from the group consisting of acetonitrile, acetone, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof; preferably wherein step (iii) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether; and/or
 - (d) step (iv) is carried out in a solvent selected from the group consisting of acetonitrile, acetone, N,N-dimethylformamide, dimethylsulfoxide, pyridine, dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane and any combination thereof; preferably wherein step (iv) is carried out in acetonitrile, optionally in combination with tetrahydrofuran and/or diethylether, optionally further in combination with water.
37. The method according to any one of items 1 to 35, wherein:
- (a) step (i) is carried out in tetrahydrofuran; and/or
 - (b) step (ii) is carried out in a solvent selected from the group consisting of tetrahydrofuran, acetonitrile and a combination thereof; preferably wherein step (ii) is carried out in tetrahydrofuran, optionally in combination with acetonitrile; and/or

- (c) step (iii) is carried out in a solvent selected from the group consisting of tetrahydrofuran, acetonitrile and a combination thereof; preferably wherein step (iii) is carried out in tetrahydrofuran, optionally in combination with acetonitrile; and/or
- (d) step (iv) is carried out in a solvent selected from the group consisting of tetrahydrofuran, acetonitrile and a combination thereof; preferably wherein step (iv) is carried out in tetrahydrofuran, optionally in combination with acetonitrile and/or water.
38. The method according to any one of the preceding items, wherein:
- (a) step (i) is carried out at a temperature of from -20 to $+60$ °C, preferably of from -10 to $+40$ °C, more preferably of from -5 to $+35$ °C; and/or
- (b) step (ii) is carried out at a temperature of from 0 to $+60$ °C, preferably of from $+5$ to $+40$ °C, more preferably of from $+10$ to $+35$ °C; and/or
- (c) step (iii) is carried out at a temperature of from 0 to $+60$ °C, preferably of from $+5$ to $+40$ °C, more preferably of from $+10$ to $+35$ °C; and/or
- (d) step (iv) is carried out at a temperature of from 0 to $+60$ °C, preferably of from $+5$ to $+40$ °C, more preferably of from $+10$ to $+35$ °C.
39. The method according to any one of the preceding items, wherein steps (i) to (iv) are carried out as a one-pot process.
40. The method according to any one of the preceding items, wherein steps (i) to (iv) are carried out under an inert gas atmosphere, in particular under nitrogen or argon.
41. A method of preparing a compound of formula (I), optionally according to any one of the preceding items, comprising:

reacting a compound of formula (II) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\text{R}^4-\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when  is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

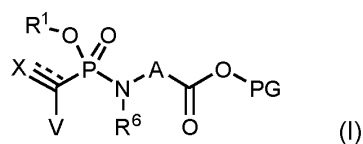
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

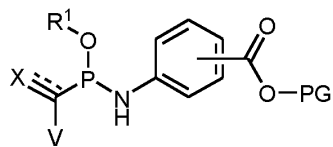
V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

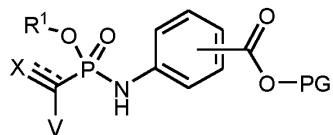
- X is R^3-C when  is a triple bond; or
- X is R^4-C when  is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-Si(R^{Si})_3$ and $(C_1-C_8)alkyl$, wherein R^{Si} is, each independently, $(C_1-C_8)alkyl$;
- R^4 is H or $(C_1-C_8)alkyl$;
- R^5 is H or $(C_1-C_8)alkyl$;
- R^6 is H or $(C_1-C_8)alkyl$;
- A is a spacer; and
- PG is a protecting group.

42. The method according to item 41, wherein , X, V, R^1 , R^3 , R^{Si} , R^4 , R^5 , R^6 , A, PG and the oxidizing agent are as defined in any one of the preceding items.

43. The method according item 41 or 42, wherein the compound of formula (II) is

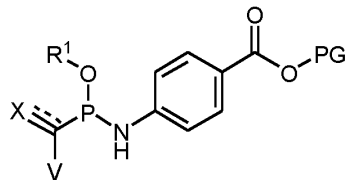


, and the compound of formula (I) is

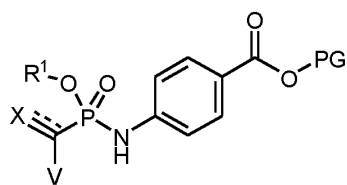


, wherein , X, V, R^1 and PG are as defined in any one of the preceding items.

44. The method according to any one of items 41 to 43, wherein the compound of formula (II) is

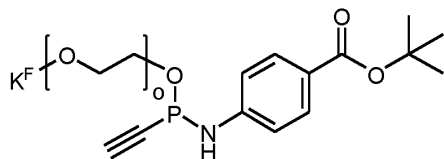


, and the compound of formula (I) is

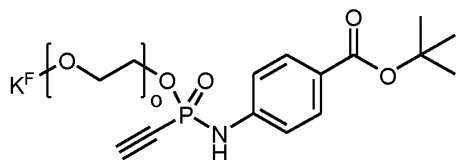


, wherein , X, V, R¹ and PG are as defined in any one of the preceding items.

45. The method according to any one of items 41 to 44, wherein the compound of formula (II) is



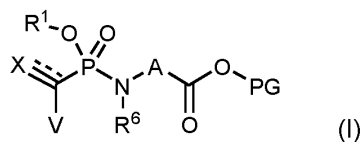
, and the compound of formula (I) is



, wherein K^F and o are as defined in any one of the preceding items; preferably wherein K^F is H; and/or preferably wherein o is 24 or 12.

- 45a. The method according to any one of the preceding items, further comprising:

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:



wherein:

 is a triple bond; or

 is a double bond;

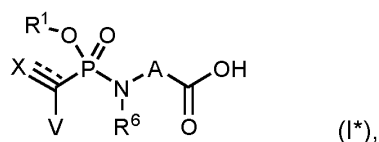
V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when $\equiv$ is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$\equiv$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when $\equiv$ is a double bond;

X is $R^3-\text{C}$ when $\equiv$ is a triple bond; or

X is $R^4-\overset{\overset{R^5}{|}}{C}$ when $\equiv$ is a double bond;

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

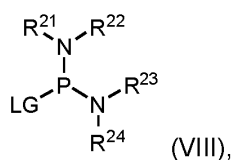
R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

A is a spacer.

45b. A method of preparing a compound of formula (I*) or a salt or solvate thereof, comprising:

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

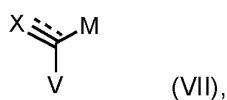


wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted ($\text{C}_1\text{--C}_8$)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and

LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or ($\text{C}_1\text{--C}_8$)alkyl when is a double bond;

X is $\text{R}^3\text{---C}$ when is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4\text{---C} \end{array}$ when is a double bond;

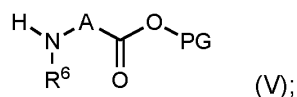
R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



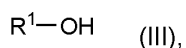
wherein:

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

A is a spacer; and

PG is a protecting group;

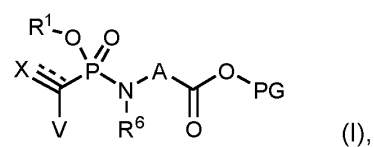
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

$\text{C}\equiv\text{C}$ is a triple bond; or

$\text{C}=\text{C}$ is a double bond;

V is absent when $\text{C}\equiv\text{C}$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $\text{C}=\text{C}$ is a double bond;

X is R³-C when $\text{C}\equiv\text{C}$ is a triple bond; or

X is $\text{R}^4\text{-C(R}^5\text{)}$ when $\text{C}=\text{C}$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

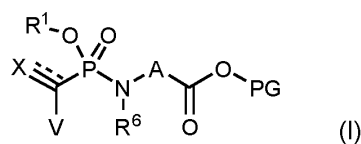
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:

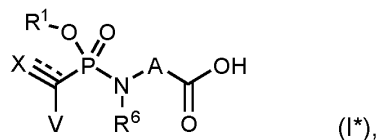


wherein:

$\text{C}\equiv\text{C}$ is a triple bond; or

- $\text{---}\text{---}\text{---}$ is a double bond;
- V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or
- V is H or (C₁-C₈)alkyl when $\text{---}\text{---}\text{---}$ is a double bond;
- X is R³-C when $\text{---}\text{---}\text{---}$ is a triple bond; or
- X is $\text{R}^4\text{---}\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when $\text{---}\text{---}\text{---}$ is a double bond;
- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;
- R⁴ is H or (C₁-C₈)alkyl;
- R⁵ is H or (C₁-C₈)alkyl;
- R⁶ is H or (C₁-C₈)alkyl;
- A is a spacer; and
- PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



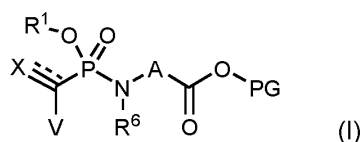
wherein:

- $\text{---}\text{---}\text{---}$ is a triple bond; or
- $\text{---}\text{---}\text{---}$ is a double bond;
- V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or
- V is H or (C₁-C₈)alkyl when $\text{---}\text{---}\text{---}$ is a double bond;
- X is R³-C when $\text{---}\text{---}\text{---}$ is a triple bond; or
- X is $\text{R}^4\text{---}\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when $\text{---}\text{---}\text{---}$ is a double bond;

- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;
- R⁴ is H or (C₁-C₈)alkyl;
- R⁵ is H or (C₁-C₈)alkyl;
- R⁶ is H or (C₁-C₈)alkyl; and
- A is a spacer.

46. A method, optionally according to any one of the preceding items, of preparing a compound of formula (I*), comprising:

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is $\begin{matrix} R^5 \\ | \\ R^4-C \end{matrix}$ when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

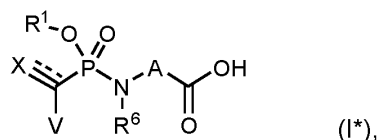
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl; and

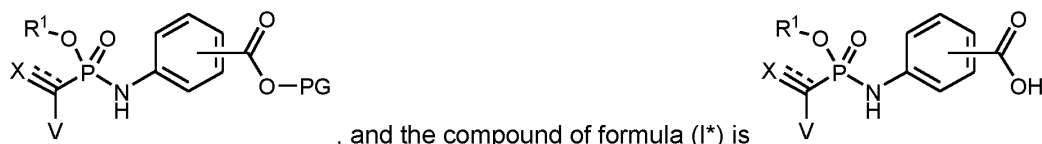
A is a spacer.

47. The method according to any one of items 45a to 46, wherein , X, V, R¹, R³, R^{Si}, R⁴, R⁵, R⁶, A and PG are as defined in any one of the preceding items.

48. The method according to any one of items 45a to 47, wherein the protecting group PG is tert-butyl, and PG is removed with an acid, preferably trifluoroacetic acid.

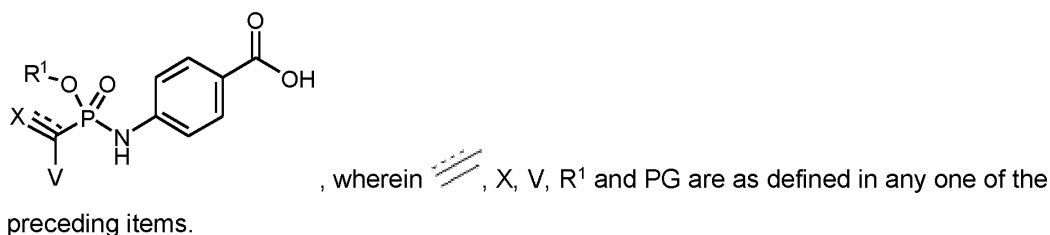
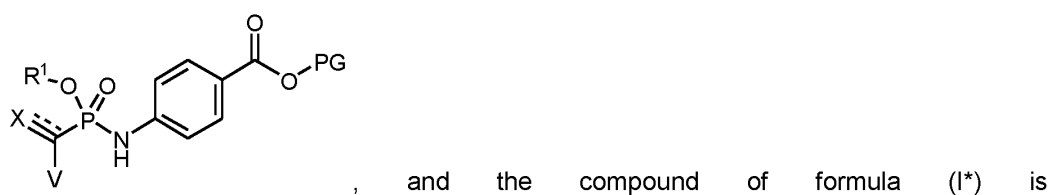
49. The method according to any one of items 45a to 48, wherein the protecting group PG is removed under an inert gas atmosphere, in particular under nitrogen or argon.

50. The method according to any one of items 45a to 49, wherein the compound of formula (I) is

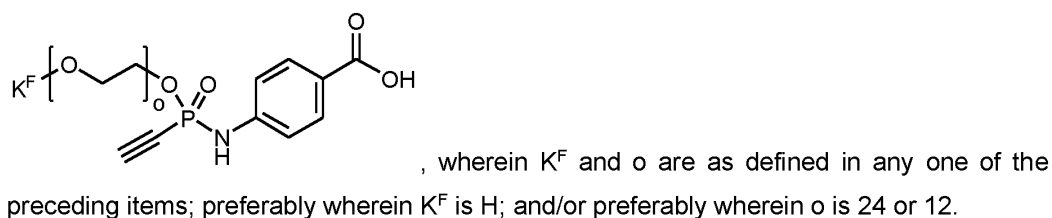
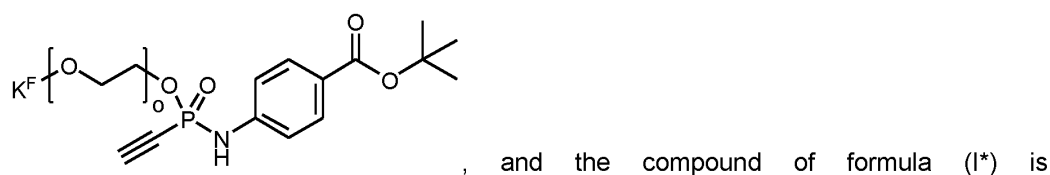


, wherein X , V, R¹ and PG are as defined in any one of the preceding items.

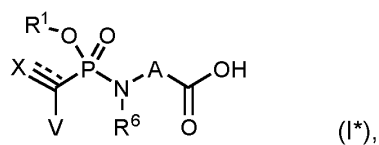
51. The method according to any one of items 45a to 50, wherein the compound of formula (I) is



52. The method according to any one of items 45a to 51, wherein the compound of formula (I) is

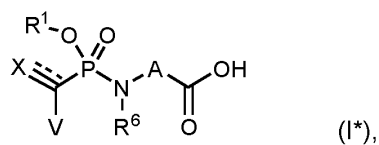


- 52a. A compound of formula (I*) or a salt or solvate thereof:



wherein , X, V, R¹, R⁶ and A are as defined in any one of the preceding items.

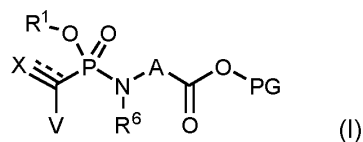
52b. A compound of formula (I*) or a salt or solvate thereof:



obtainable or being obtained by a method of any one of the preceding items,

wherein , X, V, R¹, R⁶ and A are as defined in any one of the preceding items.

53. A compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

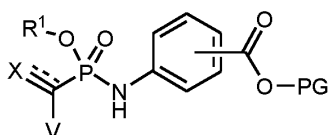
X is R³-C when is a triple bond; or

X is $\begin{matrix} R^5 \\ | \\ R^4-C \end{matrix}$ when is a double bond;

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group.

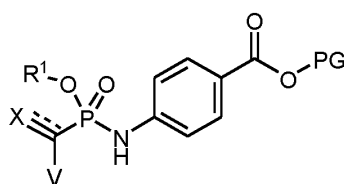
54. The compound according to item 53, wherein , X, V, R^1 , R^3 , R^{Si} , R^4 , R^5 , R^6 , A and PG are as defined in any one of the preceding items.

55. The compound according to item 53 or 54, wherein the compound of formula (I) is:



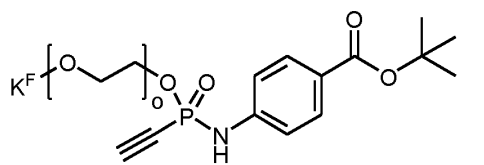
wherein X, V, R^1 and PG are as defined in any one of the preceding items.

56. The compound according to any one of items 53 to 55, wherein the compound of formula (I) is:



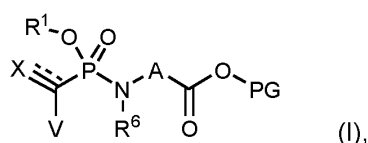
wherein X, V, R^1 and PG are as defined in any one of the preceding items.

57. The compound according to any one of items 53 to 56, wherein the compound of formula (I) is:



wherein K^F and o are as defined in any one of the preceding items; preferably wherein K^F is H; and/or preferably wherein o is 24 or 12.

58. A compound of formula (I) or a salt or solvate thereof:



obtainable or being obtained by a method of any one of items 1 to 45,

wherein , X, V, R^1 , R^6 , A and PG are as defined in any one of the preceding items.

* * *

[00135] It is noted that as used herein, the singular forms "a", "an", and "the", include plural references unless the context clearly indicates otherwise. Thus, for example, reference to "a reagent" includes one or more of such different reagents and reference to "the method" includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

[00136] Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

[00137] The term "and/or" wherever used herein includes the meaning of "and", "or" and "all or any other combination of the elements connected by said term".

[00138] The term “less than” or in turn “more than” does not include the concrete number. For example, less than 20 means less than the number indicated. Similarly, more than or greater than means more than or greater than the indicated number, e.g. more than 80 % means more than or greater than the indicated number of 80 %.

[00139] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. When used herein the term “comprising” can be substituted with the term “containing” or “including” or sometimes when used herein with the term “having”. When used herein “consisting of” excludes any element, step, or ingredient not specified.

[00140] The term “including” means “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[00141] As used herein the terms “about”, “approximately” or “essentially” mean within 20%, preferably within 15%, preferably within 10%, and more preferably within 5% of a given value or range. It also includes the concrete number, i.e. “about 20” includes the number of 20.

[00142] It should be understood that this invention is not limited to the particular methodology, protocols, material, reagents, and substances, etc., described herein and as such can vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

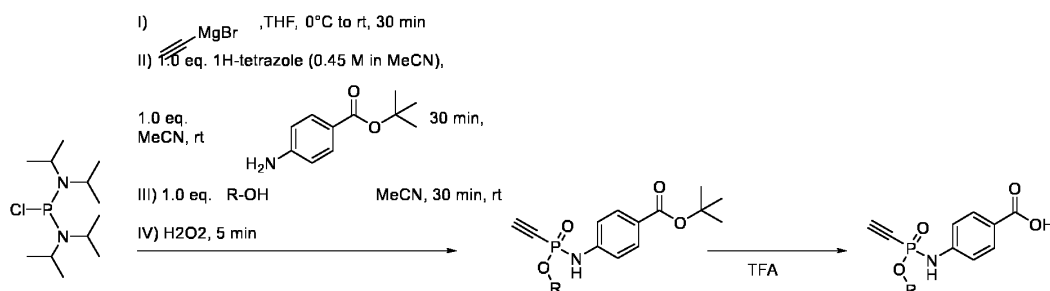
[00143] All publications cited throughout the text of this specification (including all patents, patent application, scientific publications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material.

[00144] The content of all documents and patent documents cited herein is incorporated by reference in their entirety.

EXAMPLES

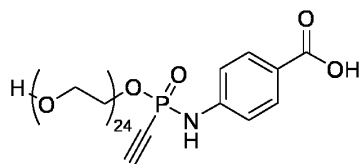
[00145] An even better understanding of the present invention and of its advantages will be evident from the following examples, offered for illustrative purposes only. The examples are not intended to limit the scope of the present invention in any way.

Example 1: General method for the synthesis of phosphonamidates via the substitution/oxidation route



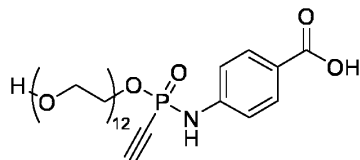
[00146] A 25 ml Schlenk tube with stirring bar was charged with 100 mg (1.0 eq., 0.38 mmol) bisdiisopropylaminochlorophosphine under a nitrogen atmosphere and cooled to 0 °C with wet ice. Slowly 0.9 ml of an ethynylmagnesiumbromide solution in THF (0.5 M, 1.2 eq., 0.45 mmol) were added. The cooling bath was removed after 5 minutes and the solution was allowed to stir at rt (rt = room temperature) for 30 minutes. 73 mg tert-butyl-4-aminobenzoate (1.0 eq., 0.38 mmol) was dissolved in 1.0 ml of 1H-tetrazole in acetonitrile solution (0.45M, 1.2 eq.), added slowly to the reaction mixture, and stirred at rt for 30 minutes. The desired alcohol (1.0 eq., 0.38 mmol) was dissolved in 1.0 ml of 1H tetrazole in acetonitrile solution (0.45M, 1,2 eq.), added to the reaction mixture slowly and stirred at rt for 30 minutes. A solution of hydrogen peroxide in water (0.2 ml, 30 %) was added to the reaction mixture and stirred for five minutes. All volatiles were removed under reduced pressure, the obtained solid was dissolved in 2 ml trifluoroacetic acid (TFA) and stirred for 30 minutes. TFA was removed in a nitrogen stream and the product purified by preparative HPLC.

[00147] Preparative HPLC was performed on a BÜCHI Pure C-850 Flash-Prep system (BÜCHI Labortechnik AG, Switzerland) using a VP 250/21 Macherey-Nagel Nucleodur C18 HTec Spum column (Macherey-Nagel GmbH & Co. Kg, Germany) the following gradients: Method D: (A = H2O + 0.1% TFA (trifluoroacetic acid), B = MeCN (acetonitrile) + 0.1% TFA, flow rate 14 ml/min, 30% B 0-5 min, 30-70% B 5-35 min, 99% B 35-45 min.

Example 2: Synthesis of P5(PEG24)-COOH

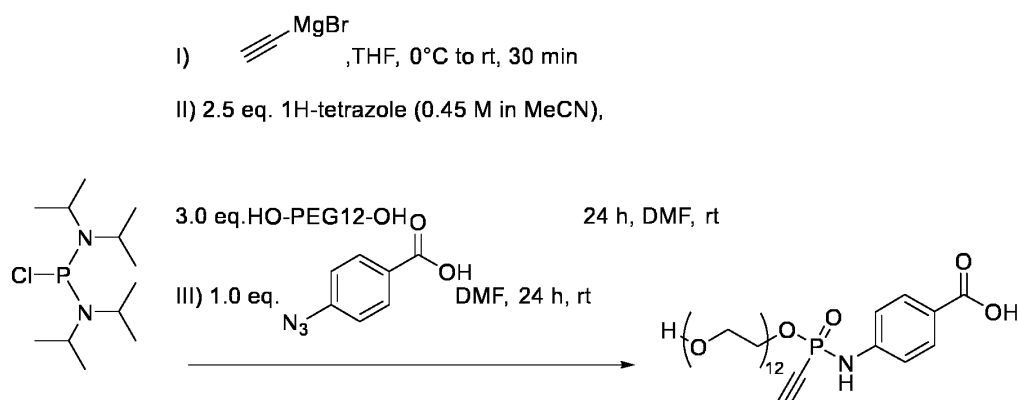
[00148] The title compound was synthesized in accordance to the general method of **Example 1** from 50 mg bis(diisopropylamino)chlorophosphine (187 μmol , 1.00 eq.), 450 μL ethynylmagnesium bromide solution (0.5 M in THF, 225 μmol , 1.20 eq.), 36 mg tert-butyl-4-amiobenzoate (187 μmol , 1.00 eq), 2x 500 μL of 1H-tetrazole in acetonitrile solution (0.45M, 1,2 eq.), and 201 mg of HO-PEG24-OH (187 μmol , 1.0 eq). The product was obtained as colourless oil after preparative HPLC and lyophilization. (53.4 mg, 40 μmol , 21%). HR-MS for $\text{C}_{57}\text{H}_{106}\text{NO}_{28}\text{P}^{2+}$ $[\text{M}+2\text{H}]^{2+}$ calcd.: 641.8314, found 641.84318.

[00149] **Figure 1** shows an HPLC chromatogram of the compound P5(PEG24)-COOH synthesized according to **Example 2**.

Example 3: Synthesis of P5(PEG12)-COOH

[00150] The title compound was synthesized in accordance to the general method of **Example 1** from 100 mg bis(diisopropylamino)chlorophosphine (376 μmol , 1.00 eq.), 900 μL ethynylmagnesium bromide solution (0.5 M in THF, 450 μmol , 1.20 eq.), 72.5 mg tert-butyl-4-amiobenzoate (376 μmol , 1.00 eq), 2x 1 mL of 1H-tetrazole in acetonitrile solution (0.45M, 450 μmol , 1.20 eq.), and 189 mg of HO-PEG12-OH (376 μmol , 1.0 eq). The product was obtained as colourless oil after preparative HPLC and lyophilization. (71.93 mg, 95.4 μmol , 25.4%). HR-MS for $\text{C}_{33}\text{H}_{57}\text{NO}_{16}\text{P}^+$ $[\text{M}+\text{H}]^+$ calcd.: 754.3410, found 754.3398

[00151] **Figure 2** shows an HPLC chromatogram of the compound P5(PEG12)-COOH synthesized according to **Example 3**.

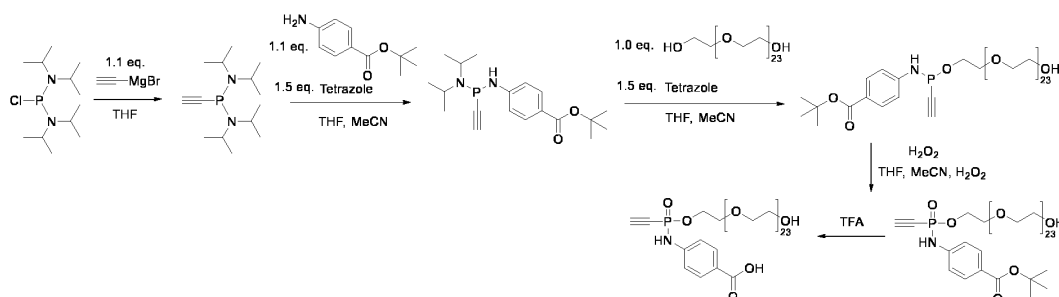
Comparative Example A: Synthesis of P5(PEG12)-COOH via the Staudinger route

[00152] A 25-ml Schlenk flask was charged with 40 mg bis(diisopropylamino)chlorophosphine (150 μ mol, 1.00 eq.) under an argon atmosphere, cooled to 0 °C and 0.36 mL ethynylmagnesium bromide solution (0.5 M in THF, 180 μ mol, 1.2 eq.) was added drop wise. The yellowish solution was allowed to warm to room temperature and stirred for further 30 minutes. 245 mg of HO-PEG12-OH (450 μ mol, 3.0 eq), dissolved in 0.83 mL 1H tetrazole solution (0.45 M in MeCN, 375 μ mol, 2.50 eq.) were added and the white suspension was stirred overnight at room temperature. 39 mg 4-azidobenzoic-acid (150 μ mol, 1.00 eq.) dissolved in 0.5 mL of DMF was added and the suspension further stirred for 24h at room temperature. The crude reaction mixture was purified using preparative HPLC as described under 2.1. The product was obtained as colourless oil after lyophilization. (25 mg, 34 μ mol, 23%). HR-MS for $C_{33}H_{57}NO_{16}P^+$ $[M+H]^+$ calcd.: 754.3410, found 754.3398

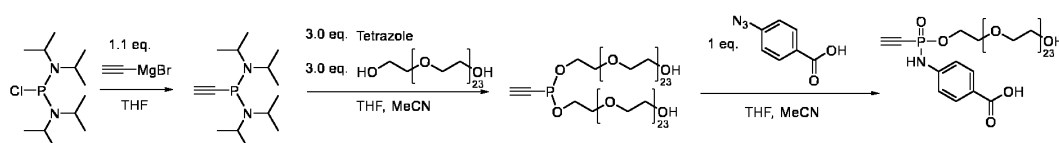
[00153] **Figure 3** shows an HPLC chromatogram of the compound P5(PEG12)-COOH synthesized according to Comparative **Example A** via the Staudinger route.

Interpretation:

[00154] Comparison of the preparation of P5(PEG12)-COOH according to **Example 3**, which was carried out in accordance with the present invention, with the preparation of P5(PEG12)-COOH according to **Comparative Example A**, which was carried out in accordance with the Staudinger route, shows that the yield was increased by using the method in accordance with the present invention.

Example 4: Synthesis of P5(PEG24)-COOH

[00155] A 25-ml Schlenk flask was charged with 50 mg bis(diisopropylamino)chlorophosphine (0.188 mmol, 1.00 eq.) under an argon atmosphere, cooled to 0 °C and 420 μ l ethynylmagnesium bromide solution (0.5 M in THF, 0.207 mmol, 1.10 eq.) was added drop wise. The yellowish solution was allowed to warm to room temperature and stirred for further 30 minutes. 40 mg tert-butyl-4-aminobenzoate (1.1 eq., 0.207 mmol) was dissolved in 625 μ l of 1H-Tetrazole in Acetonitrile solution (0.45 M in MeCN, 0.282 mmol, 1.5 eq.), added slowly to the reaction mixture, and stirred at rt for 30 minutes. 202 mg HO-PEG24-OH (0.188 mmol, 1.0 eq.), dissolved in 625 μ l 1H tetrazole solution (0.45 M in MeCN, 0.282 mmol, 1.5 eq.) was added to the reaction mixture and stirred at rt for 30 minutes. A solution of hydrogen peroxide in water (0.2 ml, 30 %) was added to the reaction mixture and stirred for five minutes. All volatiles were removed under reduced pressure, the obtained solid was dissolved in 2 ml TFA and stirred for 30 minutes. TFA was removed in a nitrogen stream and the crude reaction mixture was purified using preparative HPLC to afford 72.0 mg (0.0561 mmol, 29.8%) of the desired compound as colorless oil after lyophilization.

Comparative Example B: Synthesis of P5(PEG24)-COOH via the Staudinger route

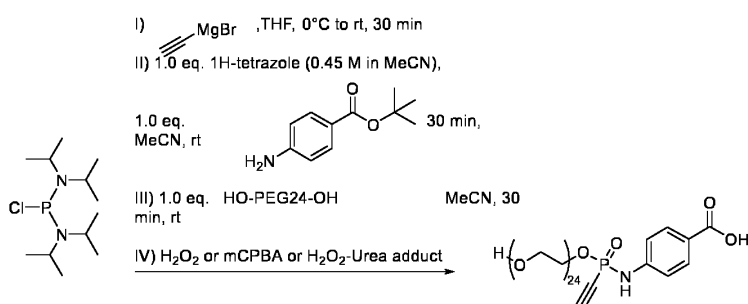
[00156] A 25-ml Schlenk flask was charged with 50 mg bis(diisopropylamino)chlorophosphine (0.188 mmol, 1.00 eq.) under an argon atmosphere, cooled to 0 °C and 420 μ l ethynylmagnesium bromide solution (0.5 M in THF, 0.207 mmol, 1.10 eq.) was added drop wise. The yellowish solution was allowed to warm to room temperature and stirred for further 30 minutes. 606 mg HO-PEG24-OH (0.564 mmol, 3.0 eq.), dissolved in 1.25 mL 1H tetrazole solution (0.45 M in MeCN, 0.564 mmol, 3.0 eq.). 33 mg of 4-azidobenzoic acid (0.188 mmol, 1.00 eq.) were dissolved in THF and added to the reaction mixture and the yellow suspension was further stirred for 24h at room temperature. The

crude reaction mixture was purified using preparative HPLC to afford 36.6 mg (0.0285 mmol, 15.1%) of the desired compound as colorless oil after lyophilization.

Interpretation:

[00157] The head-to-head comparison of the preparation of P5(PEG24)-COOH according to **Example 4**, which was carried in accordance with the present invention, with the preparation of P5(PEG24)-COOH according to **Comparative Example B**, which was carried out in accordance with the Staudinger route, and wherein both preparations start with the same amount of the bis(diisopropylamino)chlorophosphine, clearly shows the advantage of the new synthesis of phosphonamidates described herein, since a significant increase in yield from 15.1 to 29.8% could be achieved.

Example 5: Use of different oxidizing agents



[00158] A 25 ml Schlenk tube with stirring bar was charged with 100 mg (1.0 eq., 0.38 mmol) bisdiisopropylaminochlorophosphine under a nitrogen atmosphere and cooled to 0 °C with wet ice. Slowly 0.9 ml of an ethynylmagnesiumbromide solution in THF (0.5 M, 1.2 eq., 0.45 mmol) were added. The cooling bath was removed after 5 minutes and the solution was allowed to stir at rt for 30 minutes. 80 mg tert-butyl-4-aminobenzoate (1.1 eq., 0.42 mmol) was dissolved in 1.25 ml of 1H-tetrazole in acetonitrile solution (0.45M, 0.57 mmol, 1.5 eq.), added slowly to the reaction mixture, and stirred at rt for 30 minutes. 458 mg HO-PEG24-OH (1.1 eq., 0.42 mmol) was dissolved in 1.25 ml of 1H-tetrazole in acetonitrile solution (0.45M, 0.57 mmol, 1.5 eq.), added to the reaction mixture slowly and stirred at rt for 30 minutes.

[00159] Three reactions were carried out in parallel, as described above, and treated in the following manner:

A) 0.2 ml of a 30% solution of hydrogen peroxide in water (CAS: 7722-84-1) was added

B) A solution of 80 mg mCPBA (CAS: 937-14-4) in THF was added

C) A solution of 80 mg Urea-Hydrogenperoxide (CAS: 124-43-6) adduct in DMF was added

All three reaction mixtures were stirred for 30 minutes. All volatiles were removed under reduced pressure and the product purified by preparative HPLC.

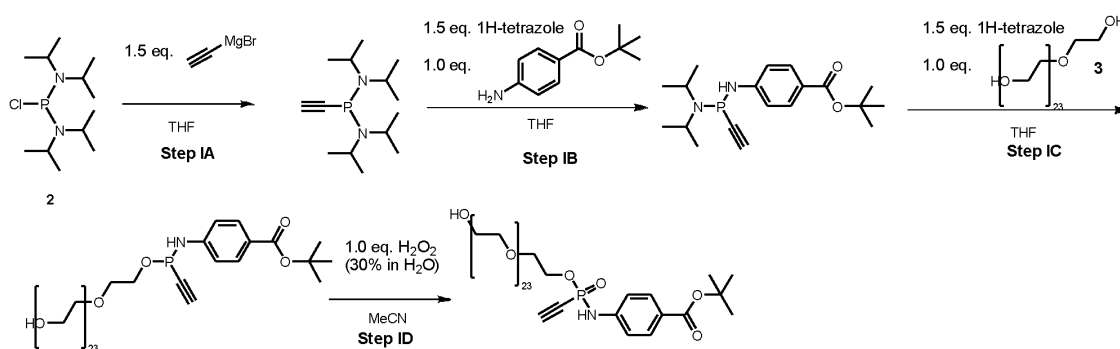
[00160] Preparative HPLC was performed on a BÜCHI Pure C-850 Flash-Prep system (BÜCHI Labortechnik AG, Switzerland) using a VP 250/21 Macherey-Nagel Nucleodur C18 HTec Spum column (Macherey-Nagel GmbH & Co. Kg, Germany) the following gradients: Method D: (A = H₂O + 0.1% TFA (trifluoroacetic acid), B = MeCN (acetonitrile) + 0.1% TFA, flow rate 14 ml/min, 30% B 0-5 min, 30-70% B 5-35 min, 99% B 35-45 min. The following yields were achieved after lyophilization:

A) 50.76 mg, 0.037946 mmol, 30.2 %

B) 31.86 mg, 0.023803 mmol, 19.0 %

C) 54.24 mg, 0.040547 mmol, 32.4 %

Example 6: P5(PEG24)-COOtBu synthesis on large scale



[00161] The first four steps (IA-ID) can be conducted in a one-pot process. The largest scale assessed so far is 450 g of the chlorophosphine **2**, with a yield of 53% after purification (1200 g of P5(PEG24)-COOtBu) by flash column on silica. Purity: >80% (HPLC). The process is described in the following table.

Large scale process for the synthesis of P5(PEG24)-COOtBu	
1.	Charge 2 under N ₂ into reactor 1.
2.	Charge tetrahydrofuran (THF) into reactor 1.
3.	Adjust reactor 1 to 0°C.
4.	Charge 1.5 eq. of ethynylmagnesium bromide solution in THF (0.5 mol/L) dropwise into reactor 1.
5.	Adjust reactor 1 Stir for 0.5h at 0°C.
6.	Adjust reactor 1 to 20-30°C
7.	Stir reactor 1 for 30 min. at 20-30°C
8.	Charge tert.-butyl-4-amino-benzoate (1 eq.) into reactor 2.
9.	1H tetrazole (1.5 eq.) in 50 mL THF was charged to reactor 2
10.	The mixture from reactor 2 was slowly added to reactor 1.
11.	Stir reactor 1 for 1 hr. at 20 to 30°C.
12.	Charge PEG24 (1 eq.) into reactor 3.
13.	1H tetrazole (1.5 eq.) in THF was charged to reactor 3.
14.	The mixture from reactor 3 was slowly added to reactor 1.
15.	Stir reactor 1 for 1 hr. at 20 to 30°C
16.	Filter
17.	Charge (1.0 eq., 30%) of H ₂ O ₂ into reactor 1.
18.	Stir reactor1 for 10 min. at 20 to 30°C.
19.	Concentrate reactor 1 below 30~40 °C under vacuum.
20.	Crude was purified by column chromatography. DCM/EtOH: Silica gel (25-35 times the weight of the crude material), elution with DCM gradient to DCM/EtOH=10:1 (DCM = dichloromethane, EtOH = ethanol).

MS analysis for C₆₁H₁₁₄NO₂₈P²⁺ [M+2H]²⁺ calcd.: 669.9, found 670.5.

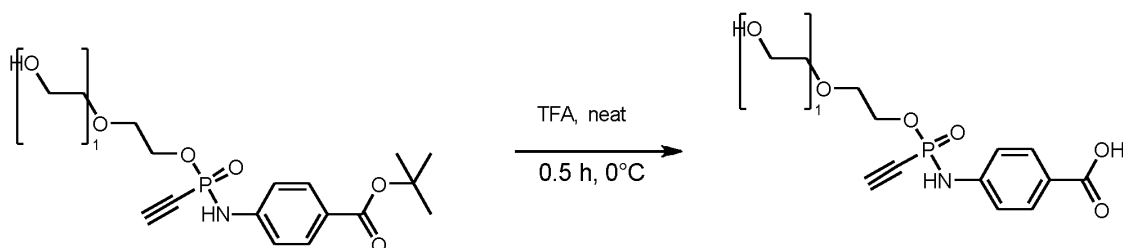
Method for characterization

[00162] LC/UV-MS analysis has been performed on an Agilent 1260/6125MS system, using a Waters XBridge C18 column, 4.6 × 150 mm, 3.5 μm, eluting at 1.0 ml/min. The following gradient was used: A: 0.03% TFA in H₂O; B: 0.03% TFA in MeCN. 20-30% B 0-5 min, 30-40% B 5-10 min, 40-45% B 10-20 min, 45-95% B 20-25 min, 95% B 25-30min, 95-20% B 30-31 min, 20%B 31-35 min. UV wavelength: 264 nm. MS parameters: Ion source: ESI, Mode: Scan, Polarity: Positive, Fragmentor: 135V, Drying gas flow: 12.0 L/min, Nebulizer pressure: 50 psig, Drying gas temperature: 350°C, Capillary voltage: 4000 V

Figure 4 shows a chromatogram of P5(PEG24)-COOtBu obtained by HPLC/UV analysis. P5(PEG24)-COOtBu was synthesized according to Example 6.

Figure 5 shows a mass spectrum of P5(PEG24)-COOtBu synthesized according to Example 6.

Example 7: P5(PEG24)-COOH synthesis on large scale



[00163] Tert-butyl deprotection is achieved by treatment with trifluoroacetic acid (TFA) at 0°C for 0.5 hours. Afterwards, the reaction is stopped by dilution with acetonitrile/water (ACN/H₂O) and storage at reduced temperature. It is important that the reaction is stopped to avoid at least partial decomposition of the product. The resulting mixture is directly injected into preparative HPLC for purification. The largest scale tested to date is 600 g of P5(PEG24)-COOtBu. After preparative HPLC and lyophilization, the yield was 55% (317g) and purity >98%.

[00164] The large scale process for the preparation of P5(PEG24)-COOH is further described in the following table:

1. Degas reactor 1 with N ₂ three times.
2. Charge P5(PEG24)-OOtBu into reactor 1 under N ₂ protection.
3. Adjust reactor 1 to –5 to +5°C under N ₂ protection.
4. Charge trifluoroacetic acid (TFA) into reactor 1 under N ₂ protection.
5. Stir reactor 1 at –5 to 5°C under N ₂ protection for 0.5 to 1h.
6. Charge purified water (20-30X) into reactor 2 under N ₂ protection.
7. Charge acetonitrile (ACN) (50g, 5-8X) into reactor 2 under N ₂ protection.
8. Adjust reactor 2 to 0 to +10°C under N ₂ protection.
9. Stir reactor 2 at 0 to +10°C under N ₂ protection for 0.5 to 1h.
10. Dropwise addition of the ACN/H ₂ O solution into reactor 1 at –5 to +5°C.
11. Stir reactor 1 at –5 to +5°C under N ₂ protection for 10 to 30min.
12. Purify the solution via preparative HPLC

Instrument: YMC Triart C18 250*150mm*7 μ m, Flow rate: 800 ml/min, Eluent A: Purified water
Eluent B: Acetonitril, Wavelength: 220,254nm

	Time/min	A (%)	B (%)	Flow rate: (A+B) (mL/min)
Gradient program	0.0	30	70	800
	15	35	65	800
	15.1	5	95	800
	20	5	95	800
	20.1	30	70	800
	25	30	70	800

13. Collect product containing fractions and lyophilize

The overall yield from starting material 2 over the two steps outlined in **Example 6** and **Example 7** is 29.2%.

The analytical characterization of the compound P5(PEG24)-COOH is shown in **Figures 6 to 9**.

Figure 6 shows a ^1H NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

Figure 7 shows a ^{31}P NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

Figure 8 shows a ^{13}C NMR spectrum of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

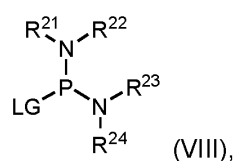
Figure 9 shows an HPLC chromatogram of the compound P5(PEG24)-COOH synthesized according to **Examples 6 and 7**.

CLAIMS

What is claimed is:

1. A method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

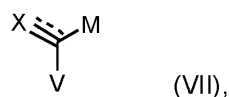


wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted ($\text{C}_1\text{-C}_8$)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and

LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;



is absent when  is a triple bond; or



is H or ($\text{C}_1\text{-C}_8$)alkyl when  is a double bond;

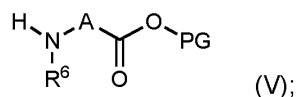


is $\text{R}^3\text{-C}$ when  is a triple bond; or

- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when  is a double bond;
- R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

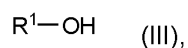
(ii) reacting the product obtained in step (i) with a compound of formula (V) or a salt or solvate thereof:



wherein:

- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group;

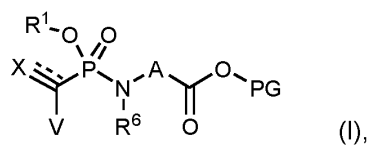
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4-\text{C} \end{array}$ when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

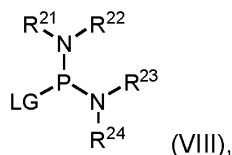
A is a spacer; and

PG is a protecting group.

2. A method of preparing a compound of formula (I) or a salt or solvate thereof, comprising:

(a)

(i) reacting a compound of formula (VIII) or a salt or solvate thereof:

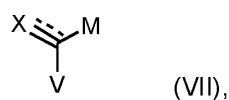


wherein:

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ; and

LG is a leaving group

with a compound of formula (VII):



wherein:



is a triple bond; or



is a double bond;

V is absent when  is a triple bond; or

V is H or (C₁-C₈)alkyl when  is a double bond;

X is R³-C when  is a triple bond; or

X is $\begin{array}{c} \text{R}^5 \\ | \\ \text{R}^4\text{---C} \end{array}$ when  is a double bond;

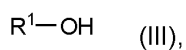
R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl; and

M is a metal-containing group capable of transferring the group  to the phosphorus atom to replace the leaving group LG;

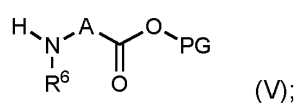
(ii) reacting the product obtained in step (i) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



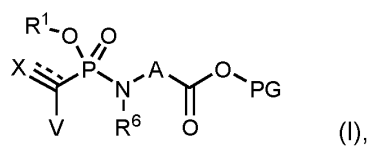
wherein:

R^6 is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

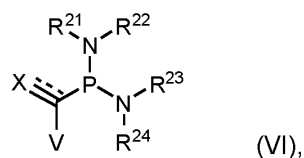
V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

- X is $R^4-\overset{\overset{R^5}{|}}{C}$ when $\equiv$ is a double bond;
- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group; or

(b)

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

 $\equiv$ is a triple bond; or $\equiv$ is a double bond;V is absent when $\equiv$ is a triple bond; orV is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when $\equiv$ is a double bond;X is R^3-C when $\equiv$ is a triple bond; orX is $R^4-\overset{\overset{R^5}{|}}{C}$ when $\equiv$ is a double bond;

R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted $(\text{C}_1\text{-C}_8)\text{alkyl}$;

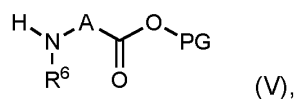
optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$

with a compound of formula (V) or a salt or solvate thereof:



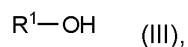
wherein:

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

A is a spacer; and

PG is a protecting group;

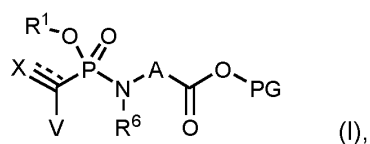
(iii) reacting the product obtained in step (ii) with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:

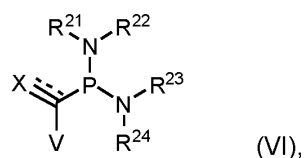


wherein:

-  is a triple bond; or
 is a double bond;
- V is absent when  is a triple bond; or
 V is H or (C₁-C₈)alkyl when  is a double bond;
- X is R³-C when  is a triple bond; or
 X is R⁴-C^{R⁵} when  is a double bond;
- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
 R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is each, independently, (C₁-C₈)alkyl;
 R⁴ is H or (C₁-C₈)alkyl;
 R⁵ is H or (C₁-C₈)alkyl;
 R⁶ is H or (C₁-C₈)alkyl;
 A is a spacer; and
 PG is a protecting group; or

(c)

(ii) reacting a compound of formula (VI) or a salt or solvate thereof:



wherein:

-  is a triple bond; or
 is a double bond;
- V is absent when  is a triple bond; or
 V is H or (C₁-C₈)alkyl when  is a double bond;

X is R^3-C when  is a triple bond; or

X is $R^4-\overset{\overset{R^5}{|}}{C}$ when  is a double bond;

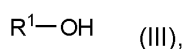
R^{21} , R^{22} , R^{23} and R^{24} are, each independently, H or optionally substituted (C₁-C₈)alkyl; optionally R^{21} and R^{22} may together form a ring; and/or optionally R^{23} and R^{24} may together form a ring; and/or optionally one of R^{21} and R^{22} may form a ring together with one of R^{23} and R^{24} ;

R^3 is selected from the group consisting of H, $-\text{Si}(R^{\text{Si}})_3$ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R^4 is H or (C₁-C₈)alkyl; and

R^5 is H or (C₁-C₈)alkyl

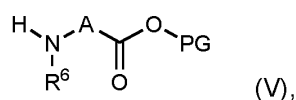
with a compound of formula (III) or a salt or solvate thereof:



wherein:

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue; and

(iii) reacting the product obtained in step (ii) with a compound of formula (V) or a salt or solvate thereof:



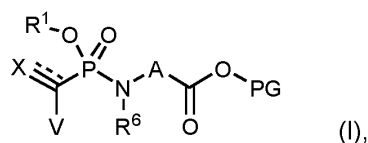
wherein:

R^6 is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group; and

(iv) reacting the product obtained in step (iii) with an oxidizing agent to give a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

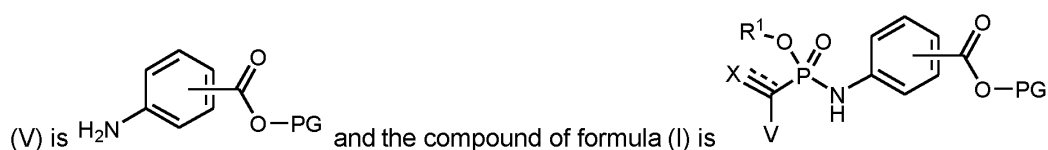
PG is a protecting group.

3. The method according to claim 1 or 2, wherein:

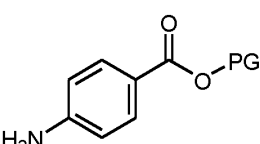
(a) is a triple bond; V is absent; X is R³-C; and R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl; preferably R³ is H or -Si(R^{Si})₃, wherein R^{Si} is, each independently, (C₁-C₈)alkyl; more preferably R³ is H; or

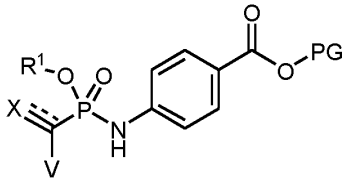
(b) is a double bond; V is H or (C₁-C₈)alkyl, preferably V is H; X is ; R⁴ is H or (C₁-C₈)alkyl, preferably R⁴ is H and R⁵ is H or (C₁-C₈)alkyl, preferably R⁵ is H.

4. The method according to any one of the preceding claims, wherein
- (a) the leaving group LG is selected from the group consisting of halogen (e.g., F, Cl, Br or I) and optionally substituted phenoxy; preferably wherein the leaving group LG is Cl; and/or
- (b) M is MgY, wherein Y is halogen, preferably wherein Y is Br; or M is Li; and/or
- (c) R⁶ is H.
5. The method according to any one of the preceding claims, wherein the spacer A is selected from the group consisting of optionally substituted -(C₆-C₁₀)arylene-, optionally substituted -(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)carbocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₆-C₁₀)arylene-, optionally substituted -(C₆-C₁₀)arylene-(C₁-C₁₀)alkylene-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)carbocyclo-, optionally substituted -(C₃-C₈)carbocyclo-(C₁-C₁₀)alkylene-, optionally substituted -(C₃-C₈)heterocyclo-, optionally substituted -(C₁-C₁₀)alkylene-(C₃-C₈)heterocyclo- and optionally substituted -(C₃-C₈)heterocyclo-(C₁-C₁₀)alkylene-;
- preferably wherein the spacer A is optionally substituted -phenylene-.
6. The method according to any one of the preceding claims, wherein PG is optionally substituted (C₁-C₈)alkyl,
- preferably wherein PG is tert-butyl.
7. The method according to any one of the preceding claims, wherein the compound of formula

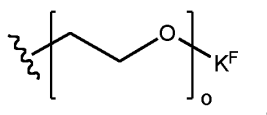


, wherein , X, V, R¹ and PG are as defined in any one of the preceding claims;

preferably wherein the compound of formula (V) is , and the

compound of formula (I) is , wherein , X, V, R¹ and PG are as defined in any one of the preceding claims.

8. The method according to any one of the preceding claims, wherein R¹ is:



wherein:



indicates the position of the O;

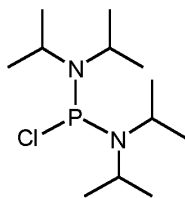
K^F is selected from the group consisting of -H, a protecting group, -PO₃H, -(C₁-C₁₀)alkyl, -(C₁-C₁₀)alkyl-SO₃H, -(C₂-C₁₀)alkyl-CO₂H, -(C₂-C₁₀)alkyl-OH, -(C₂-C₁₀)alkyl-NH₂, -(C₂-C₁₀)alkyl-NH(C₁-C₃)alkyl and -(C₂-C₁₀)alkyl-N((C₁-C₃)alkyl)₂; and

o is an integer ranging from 1 to 100;

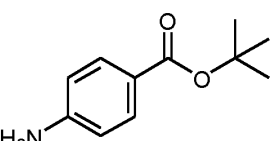
preferably wherein K_F is H; and/or

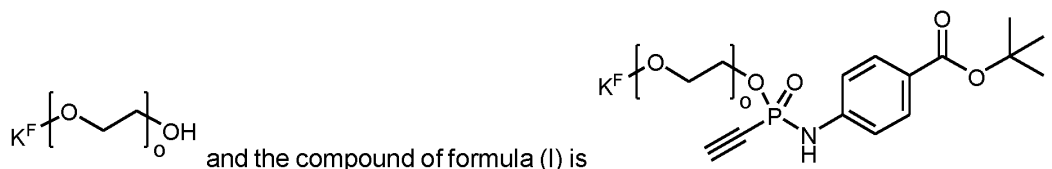
preferably wherein o ranges from 8 to 30, more preferably wherein o ranges from 20 to 28.

9. The method according to any one of claims 1, 2 item (a) and 3 to 8, wherein the compound



of formula (VIII) is MgBr, the

compound of formula (V) is , the compound of formula (III) is



, wherein K^F and o are as defined in claim 8; preferably wherein K^F is H; and/or preferably wherein o is 24 or 12.

10. The method according to any one of claims 1, 2 item (a), and 3 to 9, wherein the compound of formula (III) is used in a substantially equimolar amount based on the amount of the compound of formula (VIII);

preferably wherein the compound of formula (III) is used in an amount of from 0.5 to 1.5 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII);

still more preferably wherein the compound of formula (III) is used in an amount of from 0.9 to 1.1 molar equivalents based on 1.0 molar equivalent of the compound of formula (VIII).

11. The method according to any one of the preceding claims, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA), a urea-hydrogen peroxide adduct, (camphorsulfonyl)oxaziridine (CSO), iodine, tert-butylhydroperoxide (tBuOOH) and air;

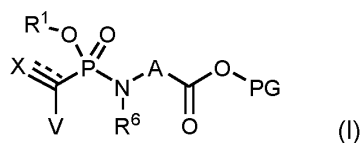
preferably wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, meta-chloroperoxybenzoic acid (mCPBA) and a urea-hydrogen peroxide adduct;

more preferably wherein the oxidizing agent is hydrogen peroxide.

12. The method according to any one of the preceding claims, wherein steps (i) to (iv) are carried out as a one-pot process.

13. The method according to any one of the preceding claims, further comprising:

(v) removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:



wherein:

is a triple bond; or

is a double bond;

V is absent when is a triple bond; or

V is H or (C₁-C₈)alkyl when is a double bond;

X is R³-C when is a triple bond; or

X is when is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

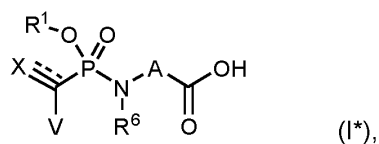
R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



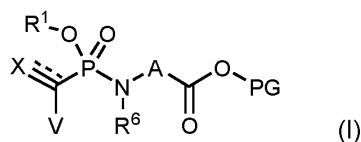
wherein:

is a triple bond; or

- $\text{---}\text{---}\text{---}$ is a double bond;
- V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or
- V is H or (C₁-C₈)alkyl when $\text{---}\text{---}\text{---}$ is a double bond;
- X is R³-C when $\text{---}\text{---}\text{---}$ is a triple bond; or
- X is $\text{R}^4\text{---}\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when $\text{---}\text{---}\text{---}$ is a double bond;
- R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;
- R⁴ is H or (C₁-C₈)alkyl;
- R⁵ is H or (C₁-C₈)alkyl;
- R⁶ is H or (C₁-C₈)alkyl; and
- A is a spacer.

14. A method of preparing a compound of formula (I*), comprising:

removing a protecting group PG from a compound of formula (I) or a salt or solvate thereof:

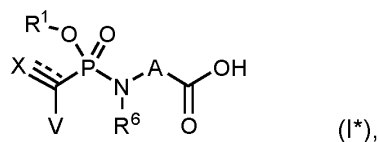


wherein:

- $\text{---}\text{---}\text{---}$ is a triple bond; or
- $\text{---}\text{---}\text{---}$ is a double bond;
- V is absent when $\text{---}\text{---}\text{---}$ is a triple bond; or
- V is H or (C₁-C₈)alkyl when $\text{---}\text{---}\text{---}$ is a double bond;
- X is R³-C when $\text{---}\text{---}\text{---}$ is a triple bond; or
- X is $\text{R}^4\text{---}\overset{\text{R}^5}{\underset{|}{\text{C}}}$ when $\text{---}\text{---}\text{---}$ is a double bond;

- R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;
- R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;
- A is a spacer; and
- PG is a protecting group

to give a compound of formula (I*) or a salt or solvate thereof:



wherein:



is a triple bond; or



is a double bond;

V is absent when is a triple bond; or

V is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$ when is a double bond;

X is $\text{R}^3\text{-C}$ when is a triple bond; or

X is $\text{R}^4\text{-C}$ when is a double bond;

R^1 is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R^3 is selected from the group consisting of H, $-\text{Si}(\text{R}^{\text{Si}})_3$ and $(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein R^{Si} is, each independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$;

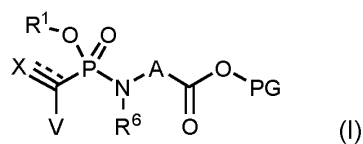
R^4 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^5 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$;

R^6 is H or $(\text{C}_1\text{-C}_8)\text{alkyl}$; and

A is a spacer.

15. A compound of formula (I) or a salt or solvate thereof:



wherein:

$\equiv$ is a triple bond; or

$=$ is a double bond;

V is absent when $\equiv$ is a triple bond; or

V is H or (C₁-C₈)alkyl when $=$ is a double bond;

X is R³-C when $\equiv$ is a triple bond; or

X is $\begin{matrix} R^5 \\ | \\ R^4-C \end{matrix}$ when $=$ is a double bond;

R¹ is an optionally substituted aliphatic residue or an optionally substituted aromatic residue;

R³ is selected from the group consisting of H, -Si(R^{Si})₃ and (C₁-C₈)alkyl, wherein R^{Si} is, each independently, (C₁-C₈)alkyl;

R⁴ is H or (C₁-C₈)alkyl;

R⁵ is H or (C₁-C₈)alkyl;

R⁶ is H or (C₁-C₈)alkyl;

A is a spacer; and

PG is a protecting group.