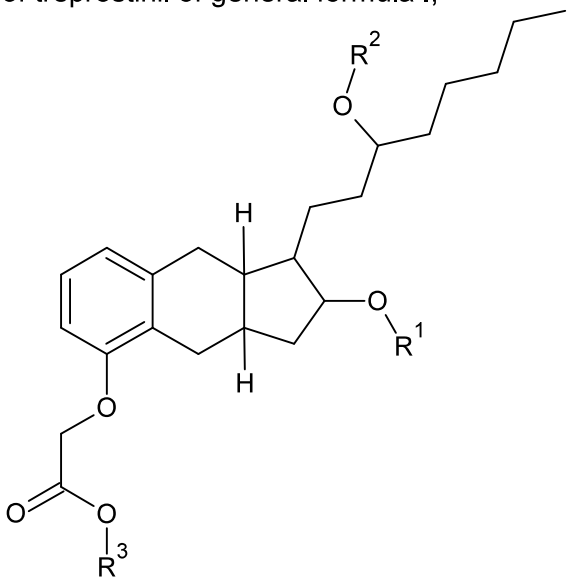
is frequently associated with subcutaneously infused treprostinil, inhalation is considered to be less effective and therefore less often prescribed.

[0009] Therefore, there still exists a need to provide a more efficacious and/or more comfortable treprostinil treatment for patients.

Summary

[0010] It is therefore an object of the present disclosure to provide an improved prodrug of treprostinil. The object is solved by the subject matter of the present disclosure.

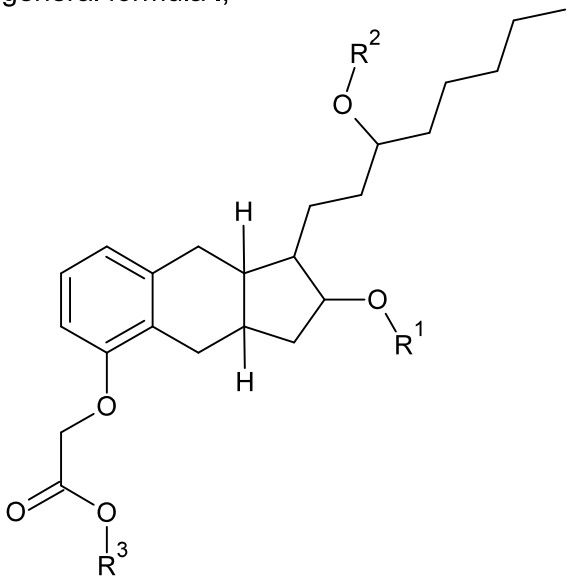
[0011] According to the disclosure, in one example, there is provided a glycoside derivative of treprostinil of general formula I,



wherein

R^1, R^2 and R^3 are independently from one another H or a carbohydrate, and wherein at least one of R^1, R^2 and R^3 is not H.

[0011a] In one aspect, the present disclosure refers to a glycoside derivative of treprostinil of general formula I,



wherein

R^1, R^2 and R^3 are independently from one another H, or a carbohydrate selected from the group consisting of cyclic monosaccharides, disaccharides, or oligosaccharides, and wherein at least one of R^1, R^2 and R^3 is not H.

[0012] In an example, the glycoside derivative is of the general formula as described above, wherein R^1 and R^2 are H and R^3 is a carbohydrate.

[0013] A further example of the disclosure relates to the treprostinil derivative as described herein, wherein the carbohydrate is a cyclic monosaccharide, disaccharide, oligosaccharide, an amino sugar or an alditol.

[0014] In one example of the disclosure the monosaccharide is a pyranoside or a furanoside.

[0015] In one example of the disclosure the carbohydrate is selected from hexoaldoses like allose, altrose, glucose, mannose, gulose, idose, galactose and talose, from hexoketoses like psicose, fructose sorbose and tagatose, from aldopentoses like ribose, arabinose, xylose, and lyxose, from ketopentoses like ribulose and xylulose, or from hexosamines, like galactosamine, glucosamine, mannosamine, neuramine acid, muramine acid, and N-acetylglucosamine.

[0016] In one example of the disclosure the pyranoside is glucose or galactose.

[0017] A further example of the disclosure relates to the treprostinil derivative as described herein, wherein the treprostinil derivative has a plasma half-life of at least 60 min, specifically 70 min, 80 min, 90 min, specifically of 100 min ± 20 min.

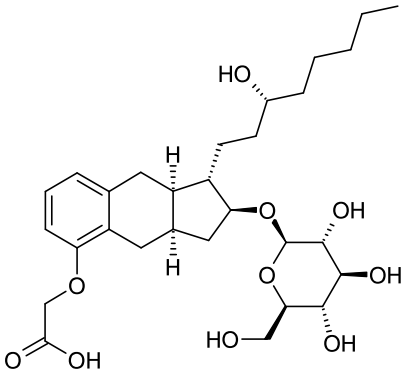
[0018] A further example of the disclosure relates to the treprostinil derivative as described herein, wherein the treprostinil derivative is being cleaved in plasma in 20 h ± 5 h for at least 50%, specifically at least 60%, 70%, 80%, more specifically at least 90%.

[0019] A further example of the disclosure relates to the treprostinil derivative as described herein, wherein the treprostinil derivative has reduced receptor binding affinity towards IP, EP2 and/or EP receptors compared to unmodified treprostinil. Specifically, the receptor binding is at least 2-fold, specifically 5-fold, 10-fold, 15-fold, more specifically about 20-fold reduced with regard to the receptor binding affinity of unmodified treprostinil.

[0020] In another aspect, the disclosure relates to a composition comprising a glycoside derivative of treprostinil as described herein.

[0021] In another aspect, the disclosure relates to a pharmaceutical composition comprising a glycoside derivative of treprostinil as described herein.

[0022] A further example of the disclosure relates to the pharmaceutical composition as described herein, wherein the treprostinil derivative is selected from



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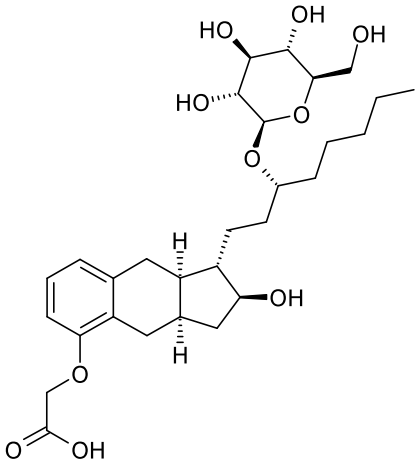

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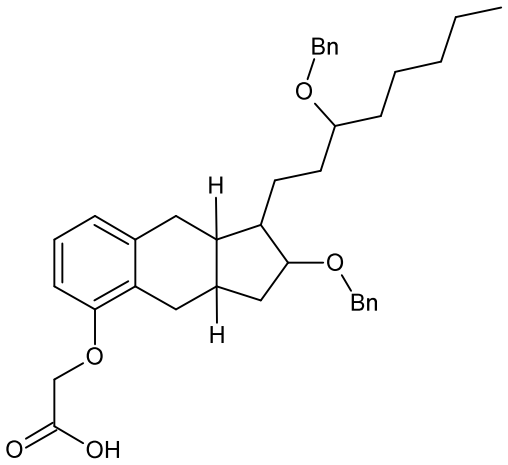
[0028] Protecting groups may be preferred which are to be split off again with the highest possible protection of the molecule at room temperature, without disturbing by-products and without appreciable pH change. The use of benzyl ether is a specific example herein, being easy to be synthesized and easy to be cleaved by heterogenic catalytic hydration.

[0029] Protecting groups for the acid function of treprostinil may be ester, eg benzyl ester, amides and hydrazides.

[0030] In yet another example, the disclosure relates to an intermediate compound of formula II,



wherein Bn is a benzyl moiety.

Brief description of drawings

[0031] Fig. 1 depicts the calibration curve of treprostinil.

[0032] Fig. 2 shows the hydrolysis of treprostinil in human plasma and in water.

[0033] Fig. 3 represents the elution profile of free treprostinil.

[0034] Fig. 4 shows the concentration of free treprostinil after incubation of treprostinil galactoside in human plasma.

[0035] Fig. 5: Treprostinil glucoside in plasma

[0036] Fig. 6: Treprostinil glucoside hydrolysis in plasma

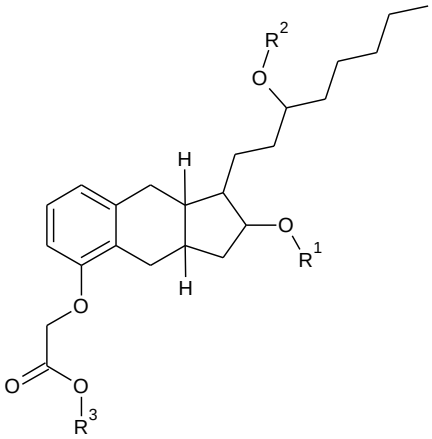
[0037] Fig. 7: Treprostinil and Treprostinil-glucoside concentration response curves in HEK293 cells transiently expressing IP receptors (n=3 independent experiments).

[0038] Fig. 8: Treprostinil and Treprostinil-glucoside concentration response curves in HEK293 cells transiently expressing EP2 receptors (n=4 independent experiments).

[0039] Fig. 9: Treprostinil and Treprostinil-glucoside concentration response curves in HEK293 cells transiently expressing EP4 receptors (n=3 independent experiments).

Claims

1. A glycoside derivative of treprostinil of general formula I,



wherein

R^1, R^2 and R^3 are independently from one another H, or a carbohydrate selected from the group consisting of cyclic monosaccharides, disaccharides, or oligosaccharides, and wherein at least one of R^1, R^2 and R^3 is not H.

2. The glycoside derivative of treprostinil according to claim 1, wherein the monosaccharide is a pyranoside or a furanoside.

3. The glycoside derivative of treprostinil according to claim 1, wherein the carbohydrate is selected from hexoaldoses like allose, altrose, glucose, mannose, gulose, idose, galactose and talose, from hexoketoses like psicose, fructose sorbose and tagatose, from aldopentoses like ribose, arabinose, xylose, and lyxose, from ketopentoses like ribulose and xylulose, or from hexosamines like galactosamine, glucosamine, mannosamine, and N-acetylglucosamine.

4. The glycoside derivative of treprostinil according to claim 2, wherein the pyranoside is glucose or galactose.

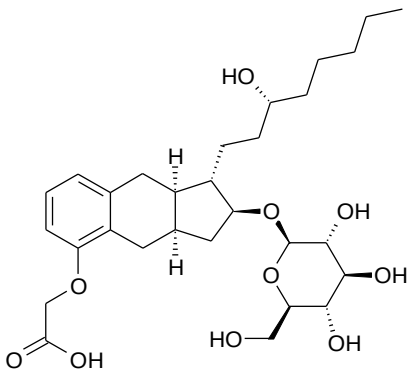
5. The glycoside derivative of treprostinil according to any one of claims 1 to 4, wherein said treprostinil derivative has a plasma half-life of at least 60 min, specifically 70 min, 80 min, 90 min, specifically of 100 min ± 20 min.

6. The glycoside derivative of treprostinil according to any one of claims 1 to 4, wherein said treprostinil derivative is being cleaved in plasma in 20 h ± 5 h for at least 50%, specifically at least 60%, 70%, 80%, more specifically at least 90%.

7. A composition comprising a glycoside derivative of treprostinil according to any of claims 1 to 6.

8. A pharmaceutical composition comprising a glycoside derivative of treprostinil according to any of claims 1 to 6.

9. The pharmaceutical composition according to claim 8, wherein the glycoside derivative of treprostinil is selected from



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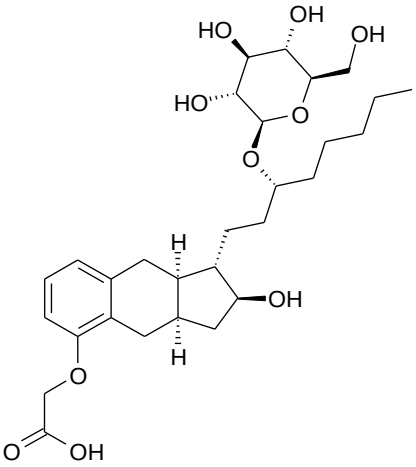

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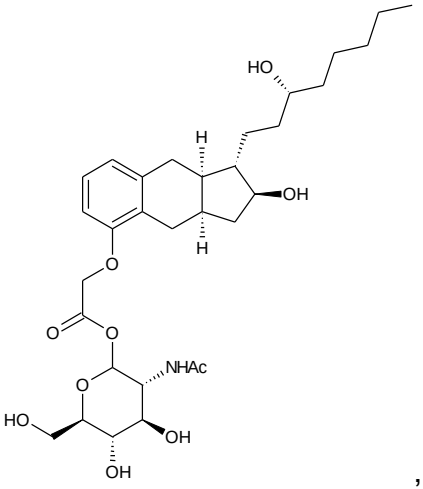

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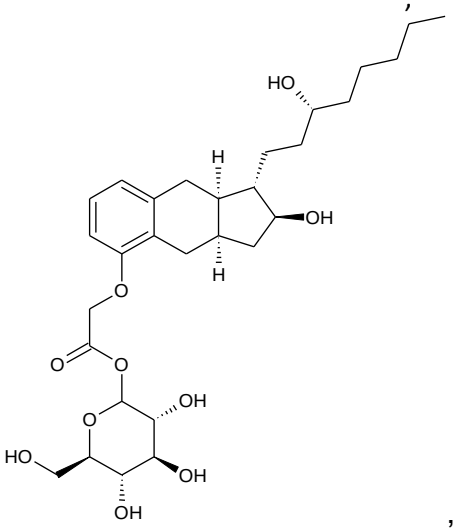

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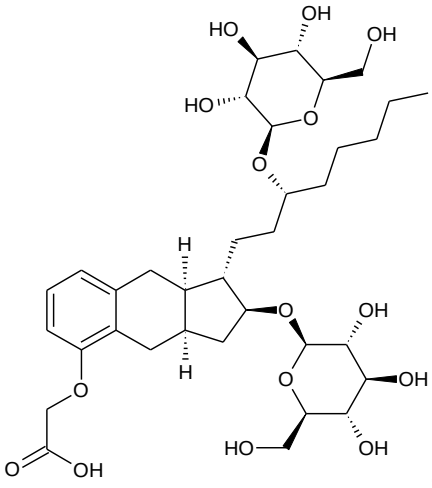

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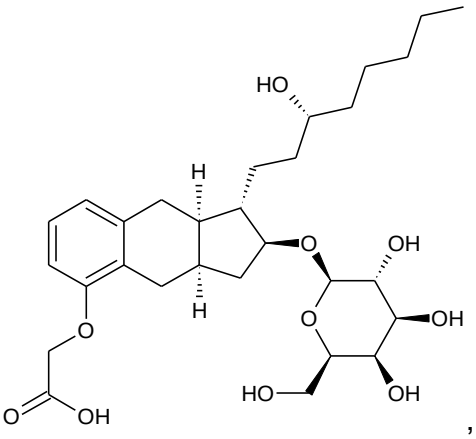

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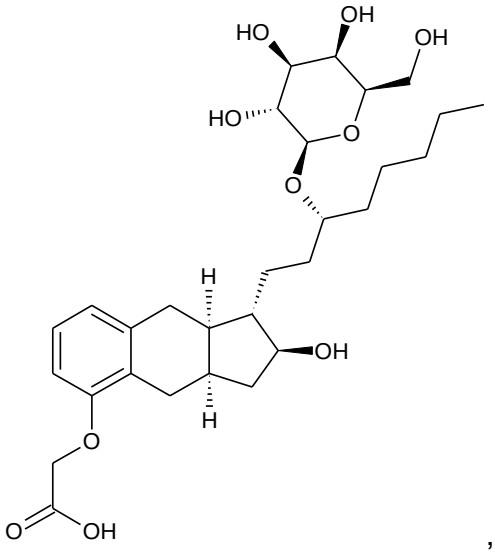
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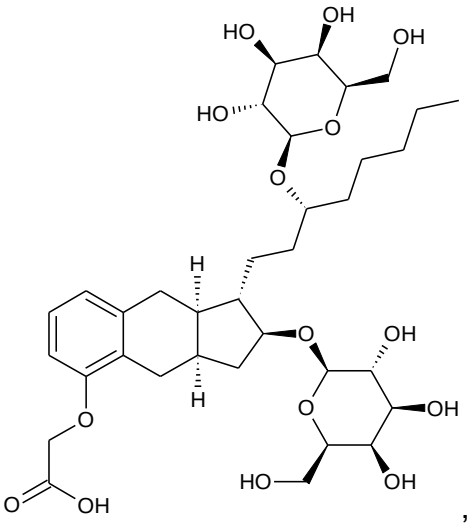
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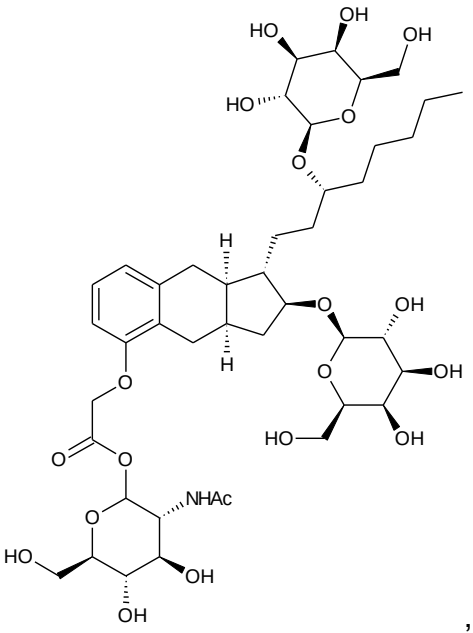
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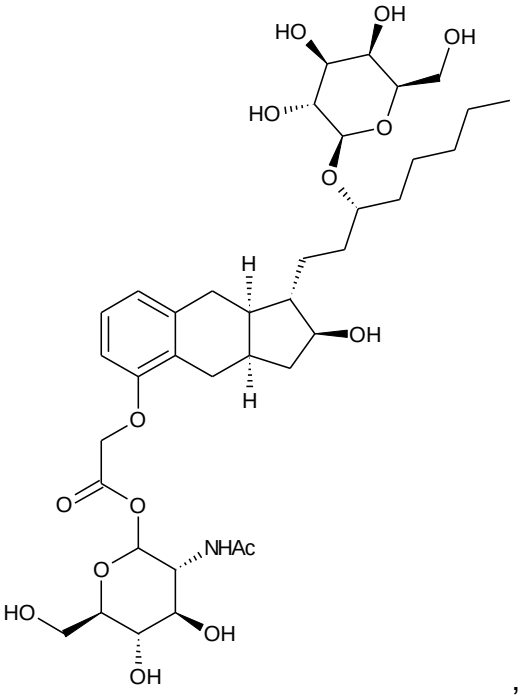
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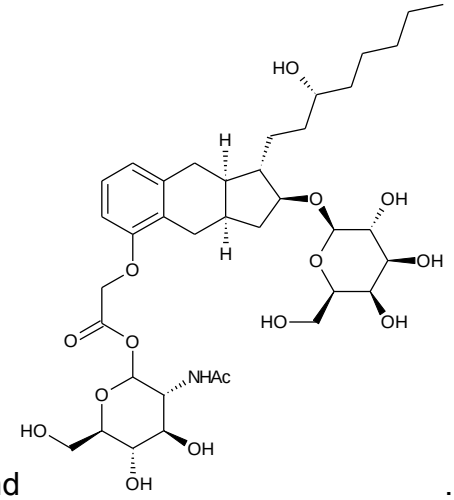
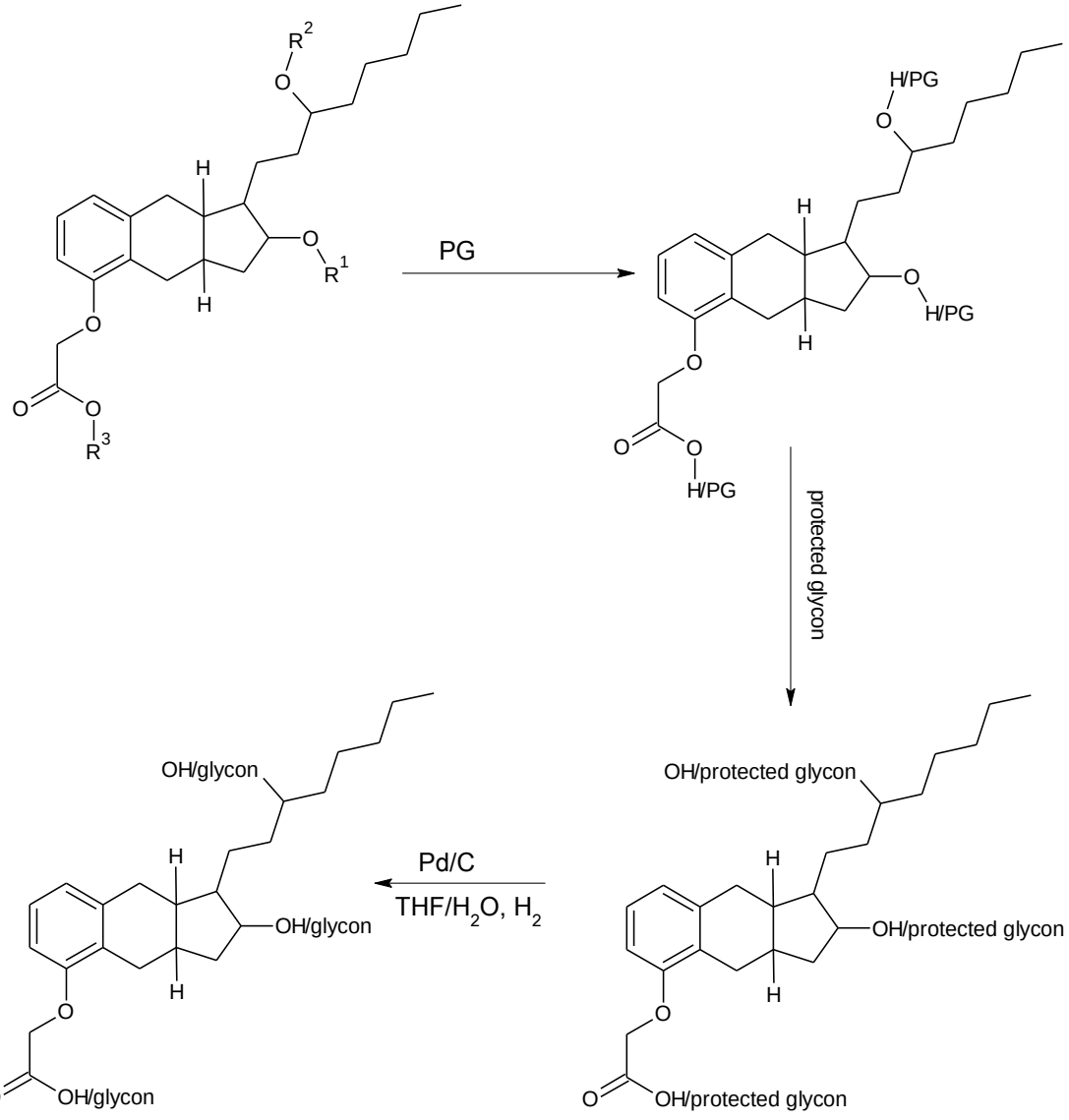


and .

10. A method for producing a compound of formula I, wherein at least one of R^1, R^2, or R^3 is H, comprising the following reaction steps:



wherein PG is a protecting group,

R^1, R^2 and R^3 are as defined in claim 1.

11. The method according to claim 10, wherein the protecting group is benzyl ether selected from the group consisting of substituted methyl ether, substituted ethyl ether, substituted benzyl ether, various silyl ethers, ester selected from the group consisting of acetate, substituted acetate, benzoate, carbonate, sulfonate, cyclic acetal, acetal from ketones, ester, amide, hydracid, benzyl ester.
12. The method according to claim 11, wherein the glycoside is a pyranoside, specifically a glucose or a galactose.