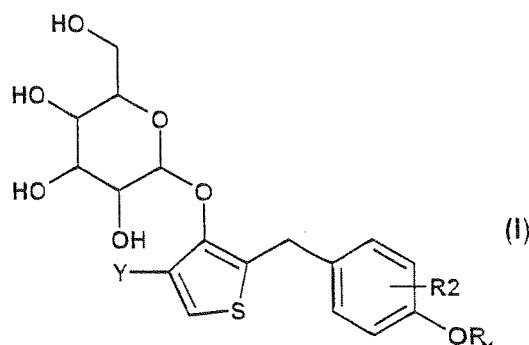


Method for producing thiophene glycoside derivatives

The present invention relates to a process for preparing thiophene-glycoside derivatives of the general formula (I)



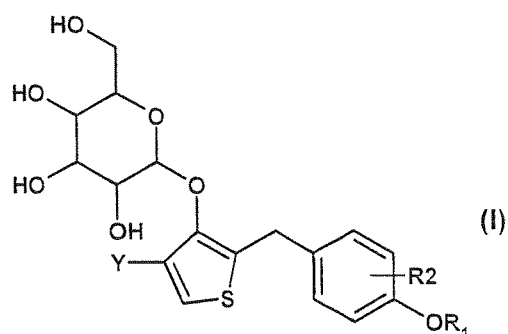
Thiophene-glycoside derivatives show biological activity which makes use possible in particular in the prevention and treatment of type 1 and 2 diabetes.

WO2004/007517 describes inter alia various processes for preparing thiophene-glycoside derivatives of the general formula (I). However, the most efficient and shortest described process (B) has various disadvantages in relation to an industrial conversion. Thus, the products are purified mainly by chromatography. The yields are moreover so low in some cases that removal of the precursors and by-products impedes simple isolation of the product. No optimization was undertaken in relation to atom economy. The use of highly toxic compounds, such as sodium cyanoborohydride, or substances with a very intense odor, such as dimethyl sulfide, furthermore impair use thereof in an industrial process.

In view of the disadvantages and problems described above, there is a need to provide a process which avoids these disadvantages and problems and which moreover, without requiring great additional complexity, can be implemented in a simple manner and makes the desired products available in high yields with high conversion and high selectivity. High yields in particular are a central requirement for the process which is sought.

Summary of the Invention

According to a first aspect, there is provided a process for preparing compounds of the general formula (I):



in which the meanings are

Y H, (C₁-C₁₀)-alkyl;

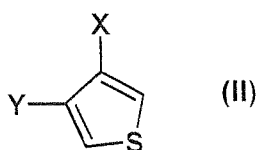
R1 (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R2 H, Cl, Br, I;

which comprises

A. Preparation of the hydroxy ketones

A.1. the thiophene component of the formula (II)

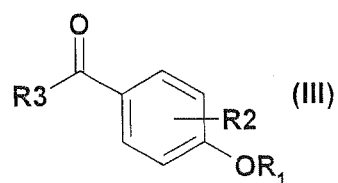


in which Y is as defined above, and

X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

being reacted with a compound of the formula (III)

1b

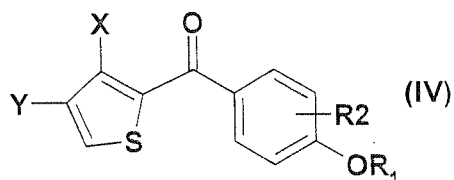


in which

R1 and R2 are as defined above, and

R3 is Cl, Br, I;

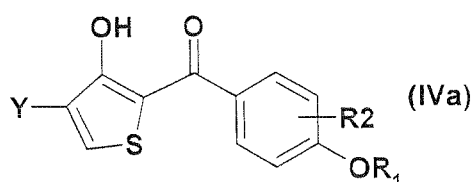
in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV),



in which X, Y, R1 and R2 are as defined above; and

this compound of the formula (IV)

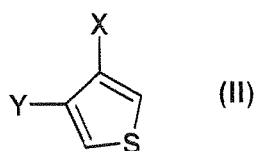
being converted in the presence of from 0.1 to 10 equivalents of one or more acids at from -50 to $+150^{\circ}\text{C}$ into the compound of the formula (IVa)



in which Y, R1 and R2 are as defined above;

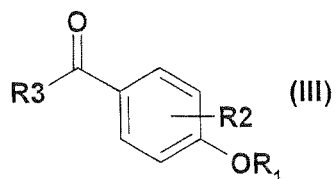
or

A.2. the thiophene component of the formula (II)



in which X and Y are as defined above under A.1.

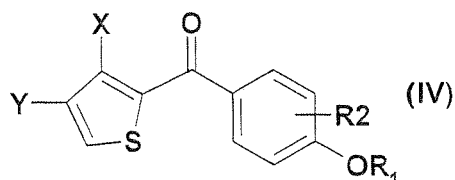
being reacted with a compound of the formula (III)



in which

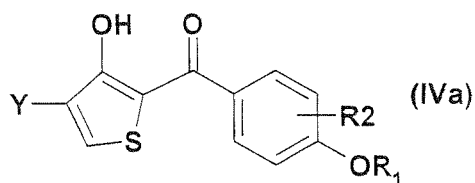
R1, R2 and R3 are as defined above under A.1.;

in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV)



in which X, Y, R1 and R2 are as defined above; and

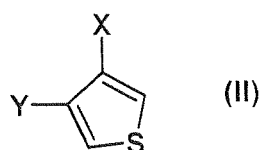
the latter being directly reacted further in the presence of an acid as defined above at from 0 to 200°C to give the compound of the formula (IVa)



in which Y, R1 and R2 are as defined above,

or

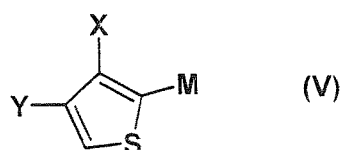
A.3. the thiophene component of the formula (II)



in which X and Y are as defined above,

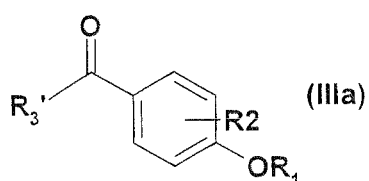
being reacted with one or more organometallic reagents from the series M-(C₁-C₈)-alkyl, MH, M-O-(C₁-C₈)-alkyl or M-N((C₁-C₈)-alkyl)₂ in which M is Li, Na, K, Zn, Mg, Ca,

in apolar solvents at temperatures of from -20 to 45°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,

and the latter being reacted further with a compound of the formula (IIIa)



in which R1 and R2 are as defined above, and

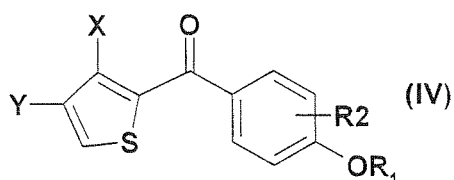
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

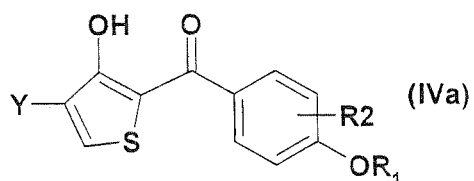
$N((C_6-C_{10})\text{-aryl})-(C_1-C_8)\text{-alkyl}$, $N((C_3-C_8)\text{-cycloalkyl})-(C_3-C_8)\text{-aryl}$, $N((C_6-C_{10})\text{-aryl})_2$, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

to give a compound of the formula (IV)



in which X, Y, R1 and R2 are as defined above; as described under A.1. at temperatures of from -20°C to $+30^{\circ}\text{C}$;

and subsequently this compound of the formula (IV) being converted in the presence of a Lewis acid into the compound of the formula (IVa)

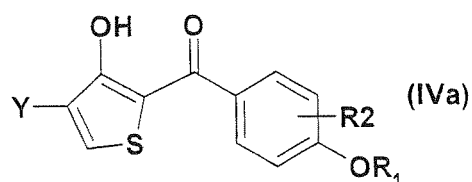


in which Y, R1 and R2 are as defined above, and where appropriate subsequently the compounds of the formula (IVa) being purified by conventional purification methods;

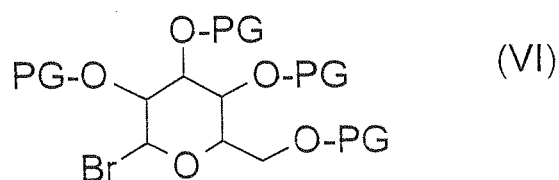
and subsequently

B. Preparation of the acetogluco ketones

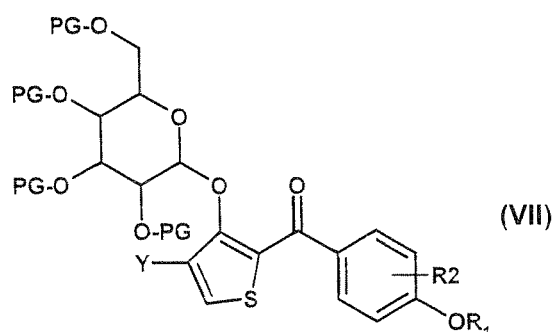
the compound of the formula (IVa)



being reacted with from 0.5 to 10 equivalents of a sugar derivative of the formula (VI)



in which PG is an OH protective group, in the presence of from 1 to 15 equivalents of an organic or inorganic base and of from 0.01 to 5 equivalents of a phase-transfer catalyst in a mixture of an organic solvent and water in the ratio of from 10 000:1 to 1:1 at from -20°C to $+80^{\circ}\text{C}$ to give the compound of the formula (VII);

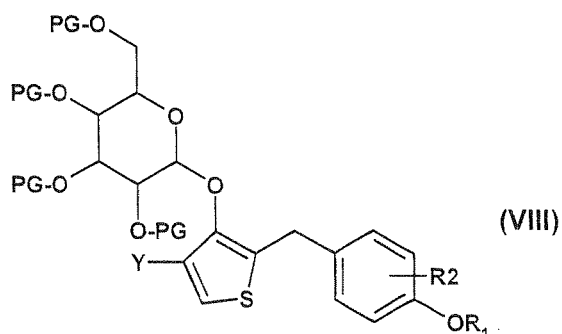


in which PG, Y, R1 and R2 are as defined above;
and subsequently

C. Preparation of the acetoglucomethylenes

the compound of the formula (VII) as described above being reacted in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine,

sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1 to 25 equivalents of one or more further acids at from -100°C to $+100^{\circ}\text{C}$ to give the compound of the formula (VIII)

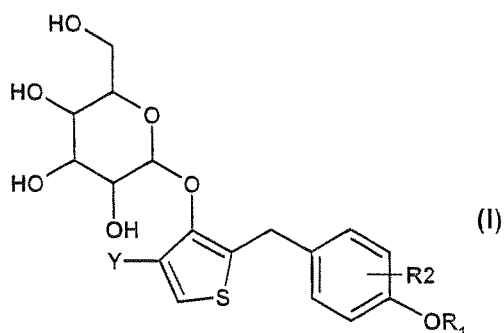


in which PG, Y, R1 and R2 are as defined above;
subsequently

D. Preparation of the thiophene-glycoside derivatives

the protective groups being eliminated under basic or acidic conditions, by oxidation or reduction or with fluoride, corresponding to known methods, in the presence of from 0.01 to 25 equivalents of an organic or inorganic base in a suitable solvent at from -50°C to $+150^{\circ}\text{C}$ and subsequently

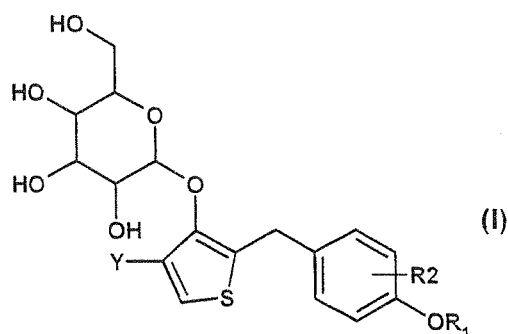
being converted into the compounds of the formula (I)



in which Y, R1 and R2 are as defined above,

and subsequently the compounds of the formula (I) being purified by conventional purification methods.

According to a second aspect, there is provided a process for preparing compounds of the general formula (I):



in which the meanings are

Y H, (C₁-C₁₀)-alkyl;

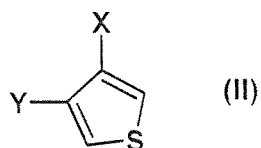
R₁ (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R₂ H, Cl, Br, I;

which comprises

A. Preparation of the hydroxy ketones

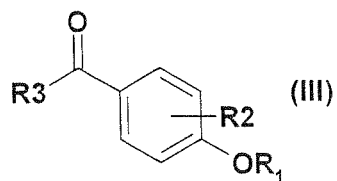
A.2. the thiophene component of the formula (II)



in which Y is as defined above, and

X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

being reacted with a compound of the formula (III)

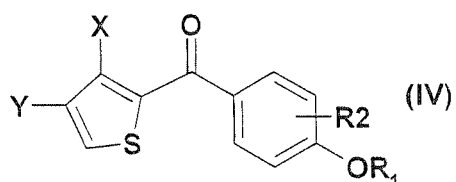


in which

R1 and R2 are as defined above, and

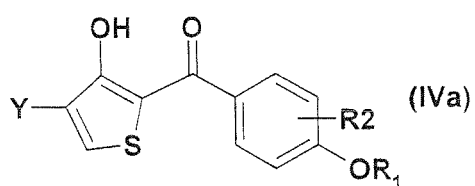
R3 is Cl, Br, I;

in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV),



in which X, Y, R1 and R2 are as defined above; and

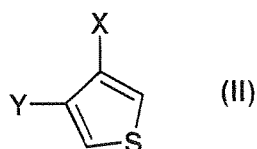
the latter being directly converted further in the presence of an acid as defined above at from 0 to 200°C into the compound of the formula (IVa)



in which Y, R1 and R2 are as defined above,

or

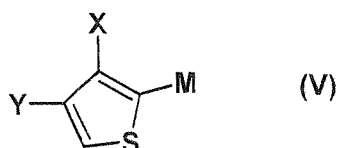
A.3. the thiophene component of the formula (II)



in which X and Y are as defined above,

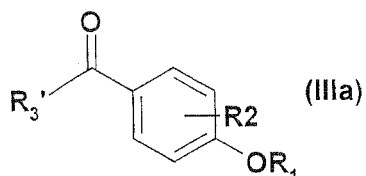
being reacted with one or more organometallic reagents from the series $M-(C_1-C_8)$ -alkyl, MH , $M-O-(C_1-C_8)$ -alkyl or $M-N((C_1-C_8)$ -alkyl) $_2$ in which M is Li, Na, K, Zn, Mg, Ca,

in apolar solvents at temperatures of from -20 to 45°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,

and the latter being reacted further with a compound of the formula (IIIa)



in which R1 and R2 are as defined above, and

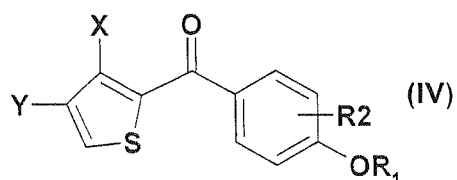
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

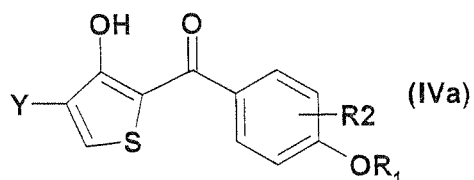
N((C₆-C₁₀)-aryl)-(C₁-C₈)-alkyl, N((C₃-C₈)-cycloalkyl)-(C₃-C₈)-aryl, N((C₆-C₁₀)-aryl)₂, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

to give a compound of the formula (IV)



in which X, Y, R₁ and R₂ are as defined above; as described under A.2. at temperatures of from -20°C to $+30^{\circ}\text{C}$;

and subsequently this compound of the formula (IV) being converted in the presence of a Lewis acid into the compound of the formula (IVa)

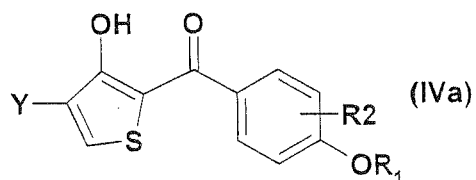


in which Y, R₁ and R₂ are as defined above, and where appropriate subsequently the compounds of the formula (IVa) being purified by conventional purification methods;

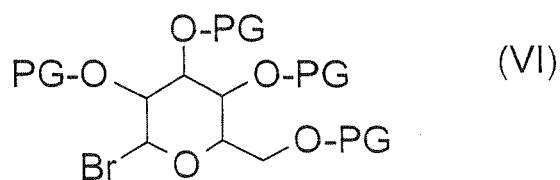
and subsequently

B. Preparation of the acetogluco ketones

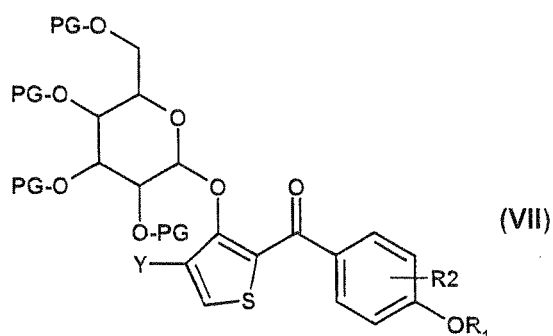
the compound of the formula (IVa)



being reacted with from 0.5 to 10 equivalents of a sugar derivative of the formula (VI)



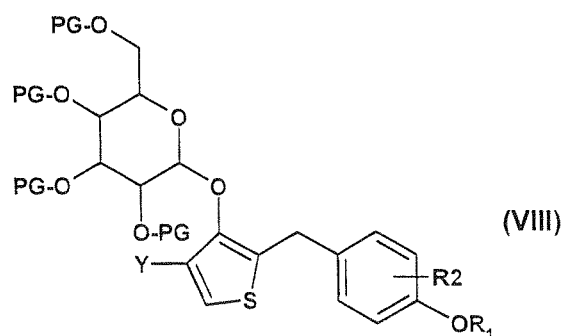
in which PG is an OH protective group, in the presence of from 1 to 15 equivalents of an organic or inorganic base and of from 0.01 to 5 equivalents of a phase-transfer catalyst in a mixture of an organic solvent and water in the ratio of from 10 000:1 to 1:1 at from -20°C to $+80^{\circ}\text{C}$ to give the compound of the formula (VII);



in which PG, Y, R₁ and R₂ are as defined above;
and subsequently

C. Preparation of the acetoglucomethylenes

the compound of the formula (VII) as described above being reacted in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1 to 25 equivalents of one or more further acids at from -100°C to $+100^{\circ}\text{C}$ to give the compound of the formula (VIII)

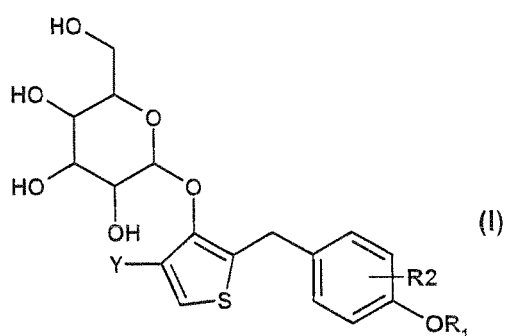


in which PG, Y, R1 and R2 are as defined above;
subsequently

D. Preparation of the thiophene-glycoside derivatives

the protective groups being eliminated under basic or acidic conditions, by oxidation or reduction or with fluoride, corresponding to known methods, in the presence of from 0.01 to 25 equivalents of an organic or inorganic base in a suitable solvent at from -50°C to $+150^{\circ}\text{C}$ and subsequently

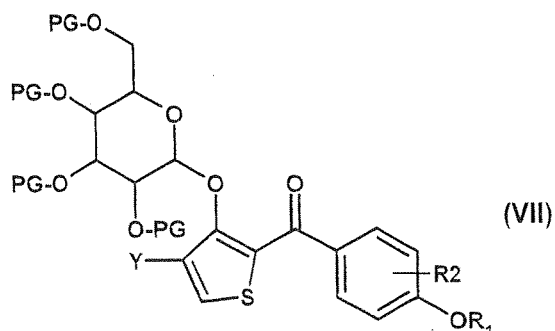
being converted into the compounds of the formula (I)



in which Y, R1 and R2 are as defined above,

and subsequently the compounds of the formula (I) being purified by conventional purification methods.

According to a third aspect, there is provided a process for preparing the intermediate compounds of the formula (VIII), which comprises a compound of the formula (VII),



in which

PG is an OH protective group;

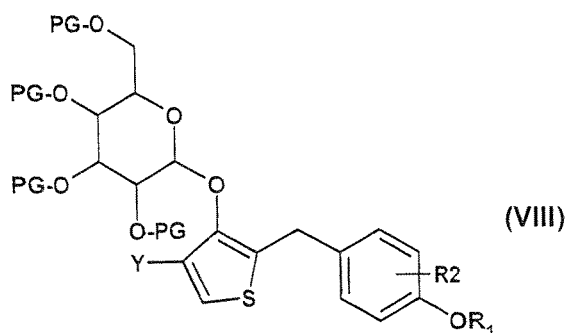
Y is H, (C₁-C₁₀)-alkyl;

R₁ is (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R₂ H, Cl, Br, I;

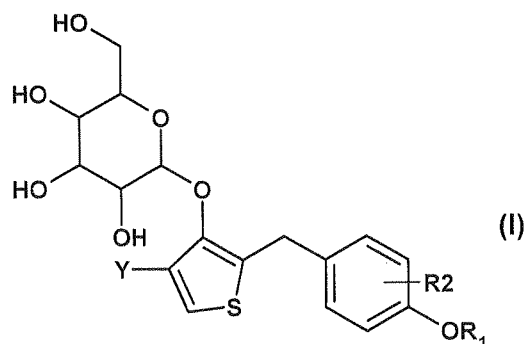
being reacted

in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1 to 25 equivalents of one or more further acids at from -100°C to +100°C to give the compound of the formula (VIII)



in which PG, Y, R₁ and R₂ are as defined above.

In one embodiment, there is provided a process for preparing compounds of the general formula (I):



in which the meanings are

Y H, (C₁-C₁₀)-alkyl;

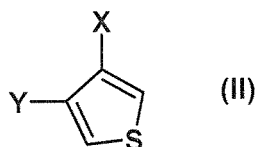
- 5 R1 (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R2 H, Cl, Br, I;

- 10 which comprises applying a multistage process in which

A. Preparation of the hydroxy ketones

A.1. the thiophene component of the formula (II)



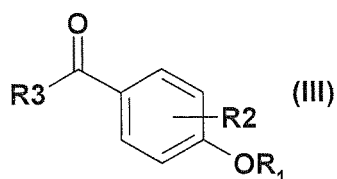
15

in which Y is as defined above, and

X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

20

is reacted with a compound of the formula (III)

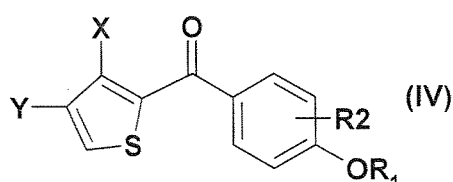


in which

R1 and R2 are as defined above, and

R3 is Cl, Br, I;

- 5 in the presence of from 0.1 to 10 equivalents, preferably 0.8 to 1.5 equivalents, of one or more acids – where one acid is preferred – preferably with Lewis acids such as SnCl₄, AlCl₃, TiCl₄, BF₃, FeCl₃, ZnCl₂, MgCl₂, ZnBr₂, MgBr₂ but also with Brönsted acids such as CF₃SO₃H, H₂SO₄, toluenesulfonic acid, particularly preferably with Lewis acids such as SnCl₄ or AlCl₃, in a suitable solvent, preferably in a halogenated
10 solvent such as, for example, dichloromethane, chloroform, 1,2-dichloroethane, at from –50°C to +150°C, preferably at from –20°C to +80 °C, particularly preferably at from 5°C to 25°C, to give a compound of the formula (IV),

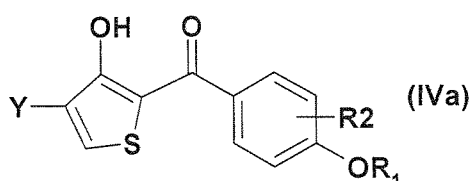


15

in which X, Y, R1 and R2 are as defined above; and

this compound of the formula (IV)

- is converted in the presence of from 0.1 to 10 equivalents, preferably 0.8 to 1.5
20 equivalents, of one or more acids – where one acid is preferred – preferably a Lewis acid such as BBr₃, BCl₃, BF₃, AlCl₃, SnCl₄, TiCl₄ at from –50°C to +150°C, preferably from –20°C to +80°C, particularly preferably at from 0°C to 25°C, into the compound of the formula (IVa)

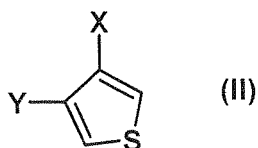


25

in which Y, R1 and R2 are as defined above,

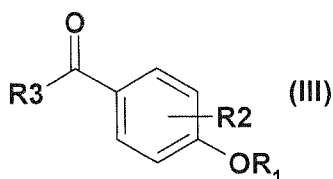
or

A.2. the thiophene component of the formula (II)



5 in which X and Y are as defined above under A.1.

is reacted with a compound of the formula (III)

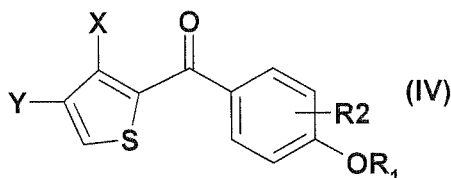


10

in which

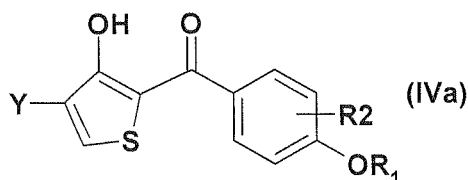
R1, R2 and R3 are as defined above under A.1.;

15 in the presence of from 0.1 to 10 equivalents, preferably 0.8 to 1.5 equivalents, of one or more acids – where one acid is preferred – preferably with Lewis acids such as SnCl₄, AlCl₃, TiCl₄, BF₃, FeCl₃, ZnCl₂, MgCl₂, ZnBr₂, MgBr₂ but also Brönsted acids such as CF₃SO₃H, H₂SO₄, toluenesulfonic acid, particularly preferably with Lewis acids such as SnCl₄ or AlCl₃, in a suitable solvent, preferably in a halogenated solvent such as, for example, dichloromethane, chloroform, 1,2-dichloroethane, at
20 from –50°C to +150°C, preferably at from –20°C to +100°C, particularly preferably at from 60°C to 75°C, to give a compound of the formula (IV)



25 in which X, Y, R1 and R2 are as defined above, and

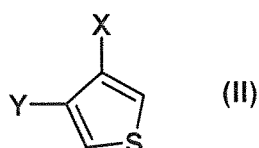
the latter is directly reacted further in the presence of an acid as defined above at from 0 to 200°C preferably at from 20°C to 120°C, particularly preferably at from 80 to 90°C, to give the compound of the formula (IVa)



5

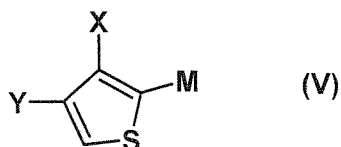
in which Y, R1 and R2 are as defined above,
or

10 **A.3.** the thiophene component of the formula (II)



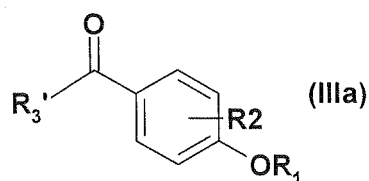
in which X and Y are as defined above,

15 is reacted with one or more organometallic reagents from the series M-(C₁-C₈)-alkyl, MH, M-O-(C₁-C₈)-alkyl or M-N((C₁-C₈)-alkyl)₂ in which M is Li, Na, K, Zn, Mg, Ca, in apolar solvents such as an ether, for example diethyl ether, tetrahydrofuran, dibutyl ether, dihexyl ether and methyl tert-butyl ether, at temperatures of from -20°C to 45°C, preferably at temperatures of from 15°C to 35°C, particularly preferably of from
20 30°C to 35°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,
and the latter is reacted further with a compound of the formula (IIIa)

25



in which R1 and R2 are as defined above, and

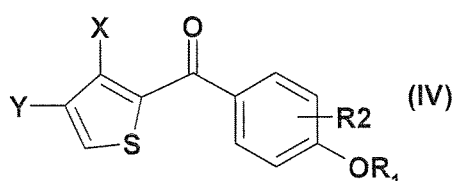
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

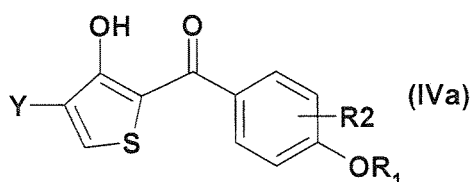
N((C₆-C₁₀)-aryl)-(C₁-C₈)-alkyl, N((C₃-C₈)-cycloalkyl)-(C₃-C₈)-aryl, N((C₆-C₁₀)-aryl)₂, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

to give a compound of the formula (IV)



in which X, Y, R1 and R2 are as defined above; as described under A.1. at temperatures of from -20°C to +30°C, preferably -5°C to +5°C;

and subsequently this compound of the formula (IV) is converted in the presence of a Lewis acid such as BBr₃, AlCl₃, SnCl₄, TiCl₄ at from 0°C to 30°C, preferably at from 5°C to 15°C, into the compound of the formula (IVa)



in which Y, R1 and R2 are as defined above;

and where appropriate subsequently the compounds of the formula (IVa) are purified by conventional purification methods such as crystallization, distillation or

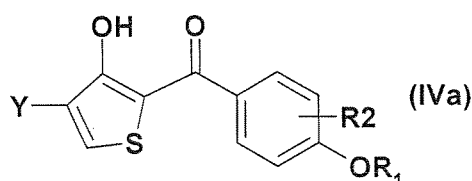
5 chromatography, preferably by crystallization from a solvent or a mixture of a plurality of solvents such as alkanes, aromatic compounds, halogenated solvents, ethers, ketones, esters, alcohols or water, particularly preferably purified by crystallization from methanol or from dichloromethane/heptane or methanol/water mixtures or by sodium salt and – after neutralization – crystallization from water;

10

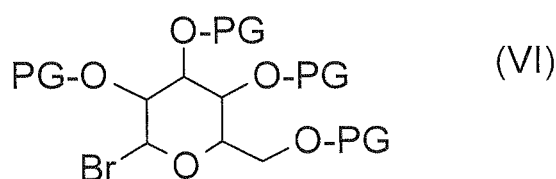
and subsequently

B. Preparation of the acetogluco ketones

15 the compound of the formula (IVa)



is reacted with from 0.5 to 10 equivalents, preferably 1 to 4 equivalents, particularly
20 preferably 1.5 to 2.0 equivalents, of a sugar derivative of the formula (VI)



25 in which PG is an OH protective group such as, for example, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), phenyldimethylsilylmethoxymethyl (SMOM), benzyloxymethyl (BOM), p-methoxybenzyloxymethyl (PMBM), t-butoxymethyl, 4-pentenylloxymethyl, 2-methoxyethoxymethyl (MEM), 2-trimethylsilylethoxymethyl (SEM), trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), triisopropylsilyl (TIPS), or similar silyl protective groups, 1-methyl-1-

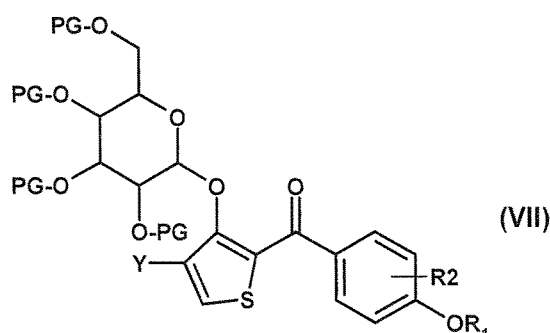
methoxyethyl (MIP), allyl, benzyl, acetyl, trifluoroacetyl, Fmoc, THP, and preferably acetyl,

in the presence of from 1 to 15 equivalents, preferably 3 to 6 equivalents, of an organic or inorganic base, preferably potassium carbonate, and from 0.01 to

5 5 equivalents, preferably 0.1 to 1 equivalents, particularly preferably 0.3 to

0.6 equivalents, of a phase transfer catalyst, preferably tetrabutylammonium bromide or chloride or benzyltributylammonium chloride or bromide, in a mixture of an organic solvent, preferably methylene chloride or 2-methyltetrahydrofuran, and water in the ratio of from 10 000:1 to 1:1, preferably 500:1 to 10:1, very particularly preferably

10 200:1 to 50:1, at from -20°C to $+80^{\circ}\text{C}$, preferably at from 5°C to 40°C , particularly preferably at from 20°C to 30°C , to give the compound of the formula (VII);



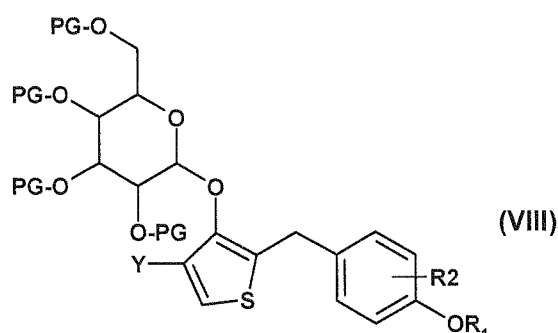
15 in which PG, Y, R1 and R2 are as defined above;
and subsequently

C. Preparation of the acetoglucomethylenes

20 the compound of the formula (VII) as described above is reacted
in an organic suitable solvent such as, for example, dichloromethane, acetonitrile, tetrahydrofuran, dimethylformamide, DMSO and chloroform, preferably in acetonitrile
with from 1 to 15 equivalents, preferably 2 to 6 equivalents, of one or more hydride
donors such as, for example, potassium borohydride, sodium borohydride, sodium
25 cyanoborohydride, triethylsilane, triacetoxymethylborohydride, preferably with sodium
cyanoborohydride or sodium borohydride, particularly preferably with sodium
borohydride, and from 0.1 to 5 equivalents, preferably 0.5 to 1.5 equivalents, of one
or more activators selected from the group of lithium chloride, bromine, sodium
bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium

triiodide or potassium triiodide, preferably with iodine, and from 1 to 25 equivalents, preferably 3 to 10 equivalents, of one or more further acids, Lewis acids or acid equivalents, such as, for example, trifluoroacetic acid, hydrogen chloride, BF_3 , halosilanes, preferably chlorosilanes, particularly preferably trimethylsilyl chloride, at
 5 from -100°C to $+100^\circ\text{C}$, preferably at from -40°C to $+40^\circ\text{C}$, particularly preferably from -15°C to $+15^\circ\text{C}$,

to give the compound of the formula (VIII),



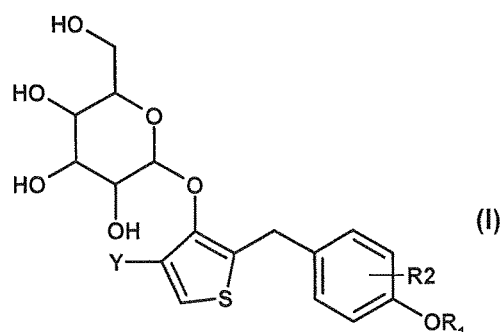
in which PG, Y, R1 and R2 are as defined above;
 subsequently

15 D. Preparation of the thiophene-glycoside derivatives

the protective groups are eliminated under basic or acidic conditions, by oxidation or reduction or with fluoride, in accordance with known methods as described for example in T.W. Greene, P. Wuts, *Protective Groups in Organic Synthesis* 1999,
 20 Wiley, New York;

preferably as described above with PG = acetyl in the presence of from 0.01 to 25 equivalents, preferably 0.05 to 5 equivalents, particularly preferably 0.1 to 0.5 equivalents, of an organic or inorganic base, preferably such as, for example,
 25 sodium methanolate or potassium methanolate, sodium hydroxide or potassium hydroxide, preferably sodium methanolate, in a suitable solvent, preferably methanol, at from -50°C to $+150^\circ\text{C}$, preferably at from -20°C to $+80^\circ\text{C}$, particularly preferably 0°C to 50°C ; and subsequently

converted into the compounds of the formula (I)



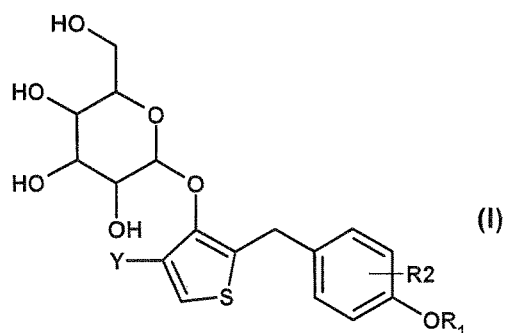
5 in which Y, R1 and R2 are as defined above;

and subsequently the compounds of the formula (I) are purified by conventional purification methods such as crystallization or chromatography, preferably by crystallization from a solvent or a mixture of a plurality of solvents such as alkanes,
 10 aromatic compounds, halogenated solvents, ethers, ketones, esters, alcohols or water, particularly preferably by crystallization from alcohols or alcohols/water mixtures, very particularly preferably by crystallization from methanol/water.

Preference is given to a multistage process for preparing the compounds of the
 15 formula (I), in which step **A**. Preparation of the hydroxy ketones consists of variants **A2** or **A3** described above:

Process for preparing compounds of the general formula (I):

20



in which the meanings are

Y H, (C₁-C₁₀)-alkyl;

R1 (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R2 H, Cl, Br, I;

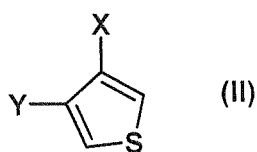
5

which comprises

A. Preparation of the hydroxy ketones

A.2. the thiophene component of the formula (II),

10

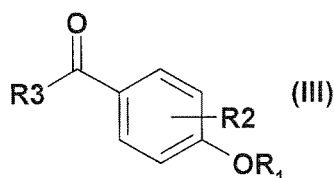


in which Y is as defined above, and

X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

15

being reacted with a compound of the formula (III)



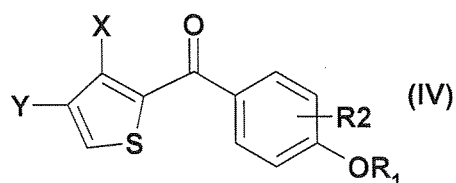
20

in which

R1 and R2 are as defined above, and

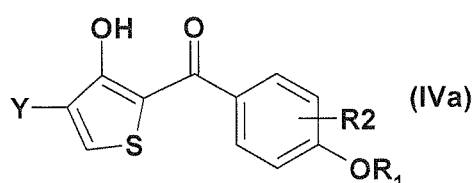
R3 is Cl, Br, I;

25 in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to +150°C to give a compound of the formula (IV)



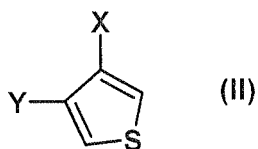
in which X, Y, R₁ and R₂ are as defined above; and

- 5 the latter being directly converted further in the presence of an acid as defined above at from 0 to 200°C into the compound of the formula (IVa)



- 10 in which Y, R₁ and R₂ are as defined above,
or

A.3. the thiophene component of the formula (II)



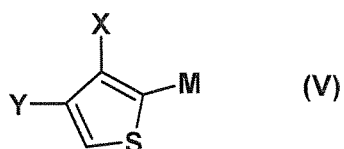
15

in which X and Y are as defined above,

being reacted with one or more organometallic reagents from the series M-(C₁-C₈)-alkyl, MH, M-O-(C₁-C₈)-alkyl or M-N((C₁-C₈)-alkyl)₂, in which M is Li, Na, K, Zn, Mg,

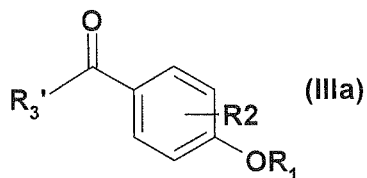
20 Ca,

in apolar solvents at temperatures of from -20 to 45°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,

and the latter being reacted further with a compound of the formula (IIIa)



in which R1 and R2 are as defined above, and

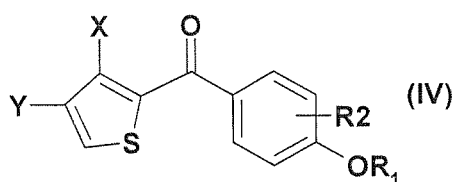
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

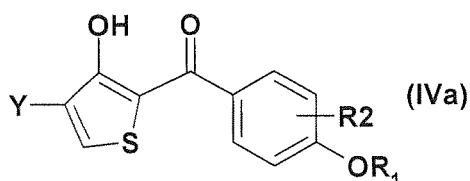
N((C₆-C₁₀)-aryl)-(C₁-C₈)-alkyl, N((C₃-C₈)-cycloalkyl)-(C₃-C₈)-aryl, N((C₆-C₁₀)-aryl)₂, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

to give a compound of the formula (IV),



in which X, Y, R1 and R2 are as defined above; as described under A.2. at temperatures of from -20°C to +30°C;

and subsequently this compound of the formula (IV) being converted in the presence of a Lewis acid into the compound of the formula (IVa)

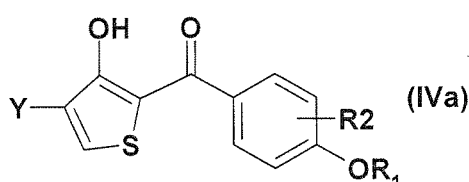


in which Y, R1 and R2 are as defined above, and where appropriate subsequently
the compounds of the formula (IVa) being purified by conventional purification
5 methods;

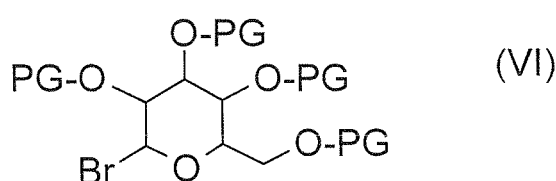
and subsequently

B. Preparation of the acetogluco ketones

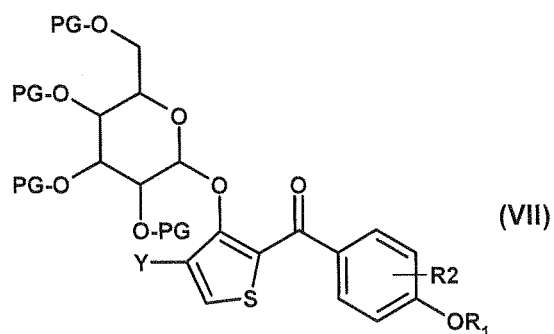
the compound of the formula (IVa)



being reacted with from 0.5 to 10 equivalents of a sugar derivative of the formula (VI)



in which PG is an OH protective group in the presence of from 1 to 15 equivalents of
an organic or inorganic base and from 0.01 to 5 equivalents of a phase-transfer
catalyst in a mixture of an organic solvent and water in the ratio of 10 000:1 to 1:1 at
from -20°C to +80°C to give the compound of the formula (VII);



in which PG, Y, R1 and R2 are as defined above;
and subsequently

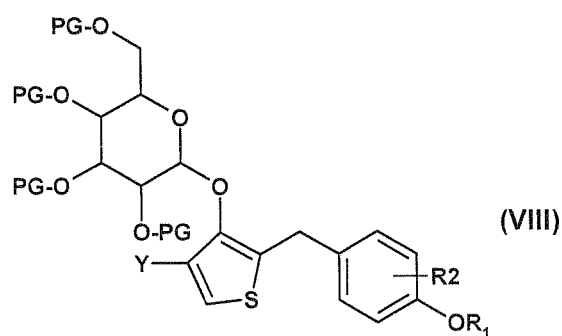
5

C. Preparation of the acetoglucomethylenes

the compound of the formula (VII) as described above being reacted

10 in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide, preferably with iodine and from 1 to 25 equivalents of one or more further acids at from -100°C

15 to $+100^{\circ}\text{C}$ to give the compound of the formula (VIII)

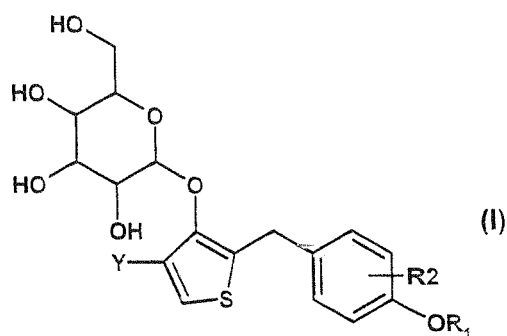


in which PG, Y, R1 and R2 are as defined above;
20 subsequently

D. Preparation of the thiophene-glycoside derivatives

the protective groups being eliminated under basic or acidic conditions, by oxidation or reduction or with fluoride, in accordance with known methods, in the presence of from 0.01 to 25 equivalents of an organic or inorganic base in a suitable solvent at from -50°C to $+150^{\circ}\text{C}$ and subsequently

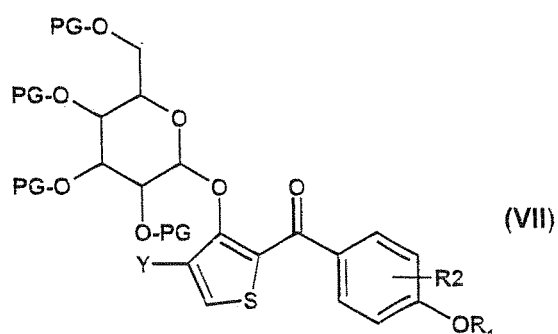
being converted into the compounds of the formula (I)



in which Y, R1 and R2 are as defined above,

and subsequently the compounds of the formula (I) being purified by conventional purification methods.

The disclosure also relates to a process for preparing the intermediate compounds of the formula (VIII), in which a compound of the formula (VII)



in which

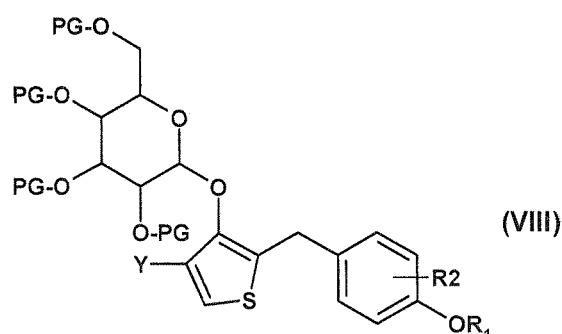
PG is an OH protective group;

Y is H, (C₁-C₁₀)-alkyl;

R1 is (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

5 R2 H, Cl, Br, I;

is reacted in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1
10 to 25 equivalents of one or more further acids at from -100°C to +100°C to give the compound of the formula (VIII)



15 in which PG, Y, R1 and R2 are as defined above.

In a preferred process for preparing the intermediate compounds of the formula (VIII), iodine is used as activator.

20

A further preferred embodiment is a process for preparing the compounds of the formula (I) in which the meanings are

25 Y H;

R1 (C₁-C₄)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine, preferably CH₃, C₂H₅, CF₃;

R2 H.

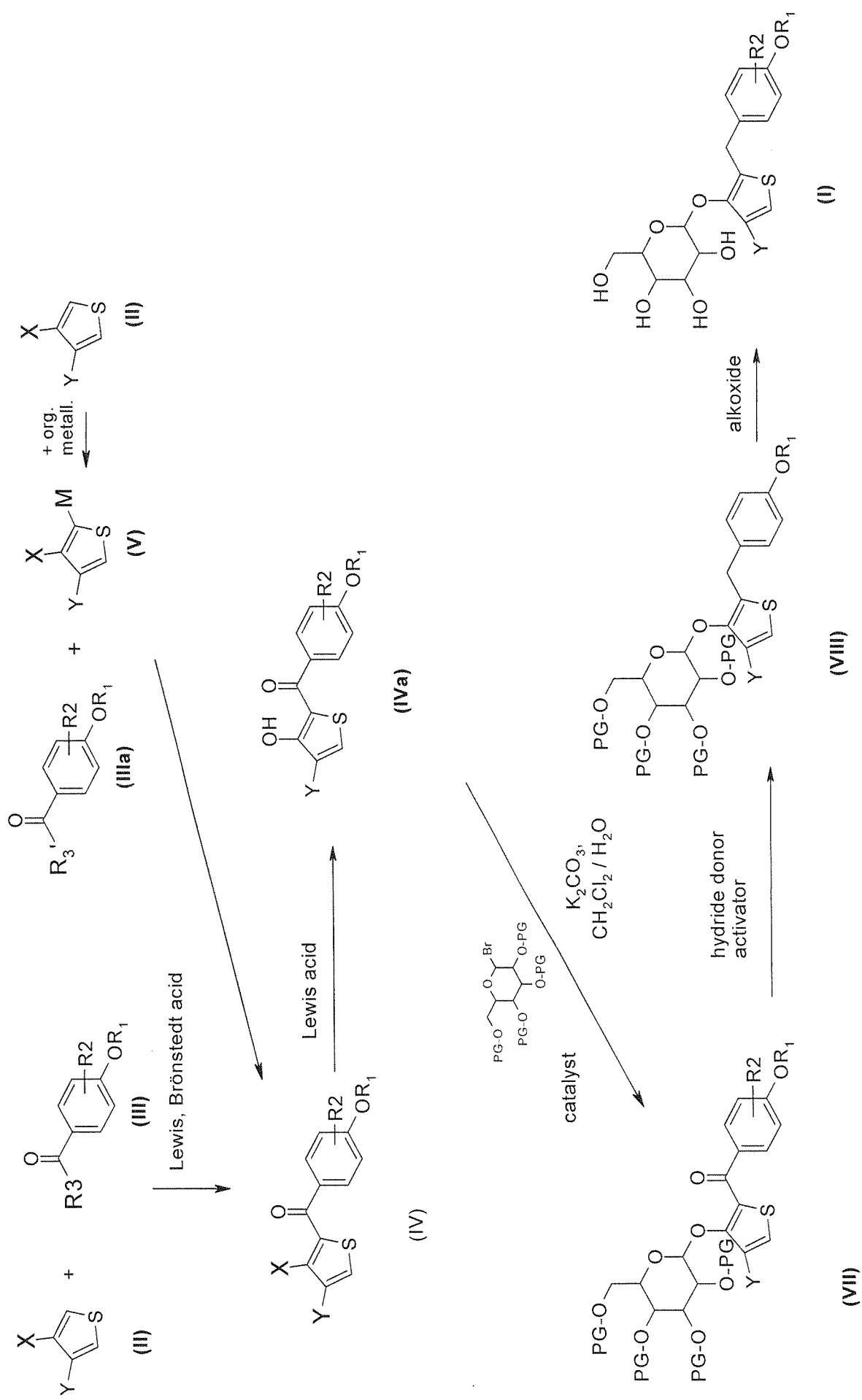
The disclosure relates to compounds of the formula (I) in the form of their racemates, racemic mixtures and pure enantiomers, to their diastereomers and mixtures thereof, and the alkali metal, alkaline earth metal, ammonium, iron and similar pharmacologically acceptable salts thereof.

The alkyl radicals, including alkoxy, alkenyl and alkynyl, in the substituents R¹, R^{3'}, X, Y and M may be either straight-chain or branched.

The sugar residues in the compounds of the formula (I) represent both L- and D-sugars in their alpha(α) and beta(β) forms, such as, for example, allose, altrose, glucose, mannose, gulose, idose, galactose, talose. Those which may be mentioned as preferred are: D-glucose, D-galactose, D-allose and D-mannose, particularly preferably β -D-glucose and β -D-galactose, very particularly preferably β -D-glucose.

The process of the disclosure is notable in particular for making an industrially feasible route possible to thiophene-glycoside derivatives in high yields. The alternative processes for preparing the compound (IV) provide the option of employing a large number of acid- or base-labile precursors of the compound (III).

The following examples illustrate the process without restricting it:



Example 1:

a) (4-Methoxyphenyl)(3-methoxythiophen-2-yl)methanone (variant A1)

24.4 parts by weight of tin tetrachloride are dissolved in 300 parts by volume of
 5 dichloromethane in a reaction vessel and, at an internal temperature of 5-10°C,
 15.0 parts by weight of p-anisoyl chloride are added. Then 9.56 parts by weight of
 3-methoxythiophene are added at an internal temperature of 5-10°C, and the
 reaction mixture is stirred at 20-25°C for 3-5 h. After conversion is complete (check of
 conversion), 135 parts by volume of water are added to the reaction mixture. It is
 10 then washed with 25 parts by volume of 30% strength hydrochloric acid. The organic
 and aqueous phase are separated, and the organic phase is washed with 100 parts
 by volume of water, 100 parts by volume of 8% strength sodium bicarbonate solution
 and 100 parts by volume of water. The organic phase is concentrated by distillation
 to 40 parts by volume and, at 40°C, 210 parts by volume of heptane are metered in.
 15 The suspension is cooled to 0°C, and the solid is freed of solvent. The pale yellow
 solid is then dried. The product is obtained in 94% yield; m.p. 98-99°C, ¹H-NMR
 (CDCl₃): δ = 8.37 (d, J = 6.3 Hz, 1H), 7.96 (d, J = 6.9 Hz, 2H), 6.96 (d, J = 6.9 Hz,
 2H), 6.37 (d, J = 6.3 Hz, 1H), 3.91, 3.88 (s, 6H) ppm.

20 b) (3-Hydroxythiophen-2-yl)-(4-methoxyphenyl)methanone

1.86 parts by weight of boron tribromide are added to a solution of 1.84 parts by
 weight of (4-methoxyphenyl)(3-methoxythiophen-2-yl)methanone in 25 parts by
 volume of dichloromethane at 0-5°C, and the mixture is stirred at 5-15°C for 60 min.
 It is then stirred at 20-25°C for a further 3 h, and then 1.0 parts by volume of
 25 methanol and 12 parts by volume of water are added. A pH of 8 is adjusted with
 about 1.4 parts by volume of 33% strength sodium hydroxide solution. The phases
 are separated, and the organic phase is washed twice with 10 parts by volume of
 water each time. The organic phase is concentrated in vacuo, and the residue is
 taken up in 20 parts by volume of methanol. The solution is heated to 60°C, and
 30 4 parts by volume of water are added. After cooling to 0°C, the precipitated solid is
 separated off and dried. The product is obtained as a dark gray solid in 91% yield;
 m.p.: 86-87 °C. ¹H-NMR (DMSO-d₆): δ = 11.85 (s, 1H, OH), 7.96 (d, J = 5.4 Hz, 1H),
 7.89 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 5.4 Hz, 1H), 3.85 (s,
 3H) ppm.

Example 2:

(3-Hydroxythiophen-2-yl)(4-trifluoromethoxyphenyl)methanone (variant A2)

0.86 parts by weight of 4-trifluoromethoxybenzoyl chloride are added to a solution of
 5 1.0 parts by weight of tin tetrachloride in 10.8 parts by volume of 1,2-dichloroethane.
 The solution is heated to 68-70°C and, at this temperature, 0.4 part by weight of
 3-methoxythiophene are added over 2 h. The reaction mixture is refluxed at 70°C for
 3 h (check of conversion to (IV)) and for a further 8 h (80-85°C, check of conversion
 to (IVa)). At 25°C, 3.7 parts by weight of water and 6.3 parts by volume of 30%
 10 strength hydrochloric acid are added. After addition of 24 parts by volume of heptane,
 the phases are separated, and the organic phase is washed with 10 parts by volume
 of deionized water. The solvent is concentrated to 16 parts by volume. Filtration and
 washing with heptane are carried out. The filtrate is stirred with 25 parts by volume of
 0.8% strength sodium hydroxide solution, and the phases are separated. The
 15 aqueous phase is washed with heptane. A pH of 9.0 is adjusted with 7.5% strength
 hydrochloric acid, whereupon the product precipitates again. The product is filtered
 off with suction, washed and dried (3-hydroxythiophen-2-yl)(4-
 trifluoromethoxyphenyl)methanone is isolated as brownish to yellowish solid in 53%
 yield. m.p.: 67-70°C; ¹H-NMR (DMSO-d₆): δ = 11.45 (br s, 1H, OH), 7.97 (d, J = 5.4
 20 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 5.4 Hz, 1H)
 ppm.

Example 3:

a) (4-Trifluoromethoxyphenyl)-(3-methoxythiophen-2-yl)methanone (variant A3)

25 8 parts by volume of n-BuLi (1.6 M in hexane) are added to 7 parts by volume of
 3-methoxythiophene in 150 parts by volume of diethyl ether at 20-25°C under a
 protective gas atmosphere, and the solution is heated at 40°C for 30 min. The
 reaction mixture is added to an ice-cooled solution (0-5°C) of 8.3 parts by weight of
 N-methoxy-N-methyl-4-trifluoromethoxybenzamide in 100 parts by volume of diethyl
 30 ether. The mixture is then stirred at room temperature for 1h (check of conversion).
 50 parts by volume of water are added, the phases are separated and the aqueous
 phase is extracted 3x with dichloromethane, the combined organic phases are dried
 over Na₂SO₄, and the solvent is removed in vacuo. 76% of the product are isolated

as a yellowish oil. $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 8.04$ (d, $J = 5.5$ Hz, 1H), 7.82 (d, $J = 8.6$ Hz, 2H), 7.45 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 5.5$ Hz, 1H), 3.79 (s, 3H) ppm.

b) (3-Hydroxythiophen-2-yl)(4-trifluoromethoxyphenyl)methanone

- 5 7.56 parts by weight of (3-methoxythiophen-2-yl)(4-trifluoromethoxyphenyl)-methanone in 100 parts by volume of dichloromethane are slowly added to a solution of 8.2 parts by weight of $\text{BBr}_3 \times \text{DMS}$ in 500 parts by volume of dichloromethane at 20-25°C. The dark solution is stirred at 20-25°C for 7 h (check of conversion) and then 80 parts by volume of saturated sodium bicarbonate solution are added in one
- 10 portion. The phases are separated, the organic phase is washed with 100 parts by volume of water and dried, and the solvent is removed in vacuo. The solid is recrystallized in methanol, and 86% of a pale yellow solid are obtained.

Example 4:

- 15 4,5-Diacetoxy-6-acetoxymethyl-2-[2-(4-methoxybenzoyl)thiophen-3-yloxy]tetrahydropyran-3-yl acetate
- 3.9 parts by weight of benzyltributylammonium chloride, 19.4 parts by weight of potassium carbonate and 2.6 parts by volume of water are added to a solution of 7.3 parts by weight of (3-hydroxythiophen-2-yl)(4-methoxyphenyl)methanone in
- 20 280 parts by volume of dichloromethane at 20-25°C. Over the course of 2 h, 22.5 parts by weight of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide are added. The reaction mixture is stirred at 20-25°C for 16 h (check of conversion), solids are removed and the organic phase is washed 3x with water. The organic phase is concentrated and taken up in 95 parts by volume of methanol. After
- 25 crystallization, the solution is cooled to 0°C. The solid is separated off and dried. 81% of the product are obtained as a colorless solid; m.p.: 149 – 151°C, $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 8.0$ (d, 1H), 7.7 (d, 2H), 7.1 (d, 2H), 7.0 (d, 1H), 5.6 (d, 1H), 5.3 (dd, 1H), 4.9 (m, 1H), 4.7 (dd, 1H), 4.2 (m, 2H), 4.1 (m, 1H), 3.8 (s, 3H, O-CH₃), 2.05, 2.00, 1.90, 1.85 (s, 12H, acetyl-CH₃) ppm.

30

Example 5:

4,5-Diacetoxy-6-acetoxymethyl-2-[2-(4-trifluoromethoxybenzoyl)thiophen-3-yloxy]-tetrahydropyran-3-yl acetate

3.5 parts by weight of benzyltributylammonium chloride, 15.3 parts by weight of potassium carbonate and 2.5 parts by volume of water are added to a solution of 7.1 parts by weight of (3-hydroxythiophen-2-yl)(4-trifluoromethoxyphenyl)methanone in 250 parts by volume of dichloromethane at 20-25°C. Over the course of 2 h,
 5 18.7 parts by weight of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide are added. The reaction mixture is stirred at 20-25°C for 16 h (check of conversion), solids are removed and the organic phase is washed 3x with water. The organic phase is concentrated and taken up in 100 parts by volume of isopropanol. At 40-45°C, 75 parts by weight of water are added, and the solution is cooled to 0°C. The
 10 solid is separated off and dried. 90% of the product are obtained as a colorless solid; m.p.: 90-93°C, $^1\text{H-NMR}$ (DMSO- d_6): δ = 8.09 (d, J = 5.5 Hz, 1H), 7.78 (d, J = 6.7 Hz, 2H), 7.43 (d, J = 6.7 Hz, 2H), 7.13 (d, J = 5.5 Hz, 1H), 5.60 (d, J = 7.9 Hz, 1H), 5.27 (dd, J = 9.5/9.5 Hz, 1H), 4.94-4.90 (m, 1H), 4.63 (dd, J = 9.6/9.5 Hz, 1H), 4.21-4.17 (m, 2H), 4.06-4.04 (m, 1H), 2.02, 1.99, 1.90, 1.84 (s, 12H, acetyl-CH₃) ppm.

15

Example 6:

4,5-Diacetoxy-6-acetoxymethyl-2-[2-(4-methoxybenzyl)thiophen-3-yloxy]tetrahydropyran-3-yl acetate

4.5 parts by weight of iodine and 2.1 parts by weight of sodium borohydride (added
 20 over 60 min), and 11.5 parts by weight of trimethylsilyl chloride (added over 45 min) are added to a solution of 10.3 parts by weight of 4,5-diacetoxy-6-acetoxymethyl-2-[2-(4-methoxybenzoyl)thiophen-3-yloxy]tetrahydropyran-3-yl acetate in 57 parts by weight of acetonitrile at from -10 to 0°C. After being stirred at 0°C for 90 min, the reaction mixture is diluted with 75 parts by volume of dichloromethane and, while
 25 cooling, 75 parts by volume of water are added dropwise. After washing with water several times, the solvent is removed in vacuo, and the residue in 51 parts by volume of methanol. The crude product is recrystallized at 50-60°C and then filtered off with suction at -5°C. The colorless solid is dried and obtained in a yield of 83%. m.p.: 116-118°C; $^1\text{H-NMR}$ (DMSO- d_6): δ = 7.29 (d, J = 5.5 Hz, 1H), 7.09 (d, J = 6.7 Hz,
 30 2H), 6.87 (d, J = 5.5 Hz, 1H), 6.84 (d, J = 6.7 Hz, 2H), 5.41-5.33 (m, 2H), 5.07-4.97 (m, 2H), 4.21-4.17 (m, 2H), 4.09 (d, J = 9.7 Hz, 1H), 3.91-3.79 (m, 2H), 3.71 (s, 3H), 2.00, 1.99, 1.96, 1.95 (s, 12H, acetyl-CH₃) ppm.

Example 7:

4,5-Diacetoxy-6-acetoxymethyl-2-[2-(4-trifluoromethoxybenzyl)thiophen-3-yloxy]-tetrahydropyran-3-yl acetate

3.24 parts by weight of iodine and 2.0 parts by weight of sodium borohydride (added over 60 min), and 11.1 parts by weight of trimethylsilyl chloride (added over 45 min) are added to a solution of 7.98 parts by weight of 4,5-diacetoxy-6-acetoxymethyl-2-[2-(4-trifluoromethoxybenzoyl)thiophen-3-yloxy]tetrahydropyran-3-yl acetate in 41.6 parts by weight of acetonitrile at from -10 to 0°C . After stirring at 0°C for 90 min, the reaction mixture is diluted with 77 parts by volume of dichloromethane and, while cooling, 77 parts by volume of water are added dropwise. After washing with water several times, the solvent is removed in vacuo and the residue is taken up in 35 parts by volume of methanol. The crude product is recrystallized at $40 - 50^{\circ}\text{C}$ and then filtered off with suction at -10°C . The colorless solid is dried and 81% of a colorless solid are obtained. m.p.: $113-114^{\circ}\text{C}$; $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 7.47$ (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 5.5$ Hz, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 6.86 (d, $J = 5.5$ Hz, 1H), 5.89 (d, $J = 3.6$ Hz, 1H), 5.45 (dd, $J = 9.8/9.3$ Hz, 1H), 5.38 (d, $J = 8.0$ Hz, 1H), 5.11 (dd, $J = 8.0/9.8$ Hz, 1H), 5.04 (dd, $J = 9.3/9.3$ Hz, 1H), $4.21-4.17$ (m, 2H), 4.10 (dd, $J = 5.0/9.8$ Hz, 1H), 3.33 (s, 2H), 2.09 , 2.01 , 2.00 , 1.99 (s, 12H, acetyl- CH_3) $^{13}\text{C-NMR}$ (DMSO-d_6): $\delta = 170.0$, 169.6 , 169.3 , 169.3 , 148.9 , 147.2 , 144.1 , 129.5 , 127.4 , 123.8 , 120.7 , 118.9 , 99.6 , 71.8 , 70.9 , 70.8 , 68.1 , 66.1 , 61.7 , 20.4 , 20.4 , 20.3 , 20.3 ppm.

Example 8:

2-Hydroxymethyl-6-[2-(4-methoxybenzyl)thiophen-3-yloxy]tetrahydropyran-3,4,5-triol 0.97 parts by weight of sodium methanolate (30% in methanol) are added to a suspension of 14.5 parts by weight of 4,5-diacetoxy-6-acetoxymethyl-2-[2-(4-methoxybenzyl)thiophen-3-yloxy]tetrahydropyran-3-yl acetate in 91 parts by weight of methanol at 0°C . The reaction mixture is stirred at 0°C for 90 min and then a pH of 7 is adjusted with 0.76 parts by weight of acetic acid. The product is precipitated by adding water and is filtered off with suction at 0°C . The colorless solid is dried and obtained in a yield of 83%. m.p.: $154-155^{\circ}\text{C}$; $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 7.16-7.14$ (m, 3H), 6.91 (d, $J = 5.5$ Hz, 1H), 6.80 (d, $J = 8.6$ Hz, 2H), 5.35 (s, 1H), 5.05 (s, 1H), 4.99 (s, 1H), $4.63-4.53$ (m, 2H), $4.01-3.97$ (m, 2H), 3.71 (s, 3H), 3.66 (s, 1H), $3.49-3.44$ (m, 1H), $3.32-3.05$ (m, 4H) ppm.

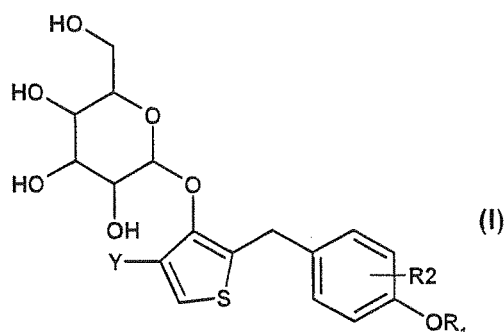
Example 9:

2-Hydroxymethyl-6-[2-(4-trifluoromethoxybenzyl)thiophen-3-yloxy]tetrahydropyran-3,4,5-triol

- 1.5 parts by weight of sodium methanolate (30% in methanol) are added to a suspension of 12.3 parts by weight of 4,5-diacetoxy-6-acetoxymethyl-2-[2-(4-trifluoromethoxybenzyl)thiophen-3-yloxy]tetrahydro-pyran-3-yl acetate in 83.2 parts by weight of methanol at 0°C. The reaction mixture is stirred at 10°C for 90 min and then a pH of 7 is adjusted with 1.58 parts by weight of acetic acid. The product is precipitated by adding water and is filtered off with suction at 0°C. The colorless solid is dried and obtained in a yield of 89%. m.p.: 144-145°C; ¹H-NMR (DMSO-d₆): δ = 7.41 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 5.5 Hz, 1H), 6.97 (d, J = 5.5 Hz, 1H), 5.37 (d, J = 4.9 Hz, 1H), 5.05 (d, J = 4.5 Hz, 1H), 4.98 (d, J = 5.3 Hz, 1H), 4.64 (d, J = 7.3 Hz, 1H), 4.56 (dd, J = 5.7/5.7 Hz, 1H), 4.12-4.04 (m, 2H), 3.72-3.68 (m, 1H), 3.51-3.47 (m, 1H), 3.32-3.12 (m, 4H); ¹⁹F-NMR (DMSO-d₆): δ = 56.8 ppm.

Claims:

1. A process for preparing compounds of the general formula (I):



in which the meanings are

Y H, (C₁-C₁₀)-alkyl;

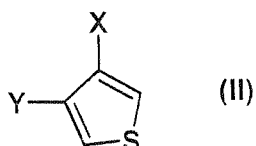
- 10 R1 (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R2 H, Cl, Br, I;

- 15 which comprises

A. Preparation of the hydroxy ketones

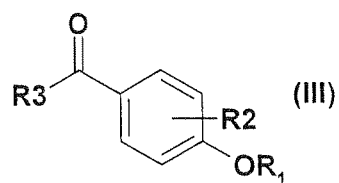
A.1. the thiophene component of the formula (II)



in which Y is as defined above, and

X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

being reacted with a compound of the formula (III)

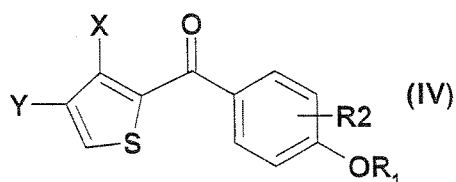


in which

R1 and R2 are as defined above, and

5 R3 is Cl, Br, I;

in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV),

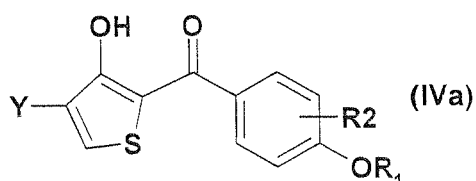


10

in which X, Y, R1 and R2 are as defined above; and

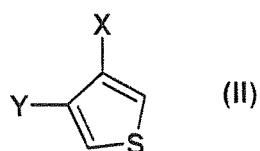
this compound of the formula (IV)

15 being converted in the presence of from 0.1 to 10 equivalents of one or more acids at from -50 to $+150^{\circ}\text{C}$ into the compound of the formula (IVa)



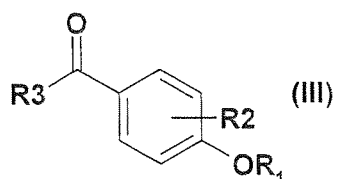
20 in which Y, R1 and R2 are as defined above;
or

A.2. the thiophene component of the formula (II)



in which X and Y are as defined above under A.1.

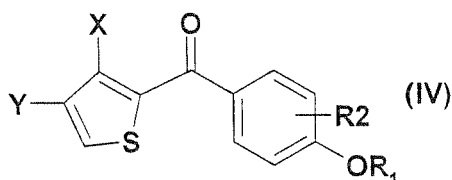
5 being reacted with a compound of the formula (III)



in which

10 R1, R2 and R3 are as defined above under A.1.;

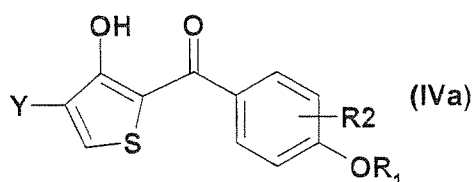
in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV)



15

in which X, Y, R1 and R2 are as defined above; and

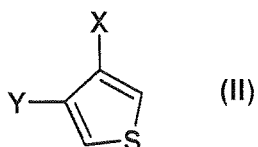
the latter being directly reacted further in the presence of an acid as defined above at
20 from 0 to 200°C to give the compound of the formula (IVa)



in which Y, R1 and R2 are as defined above,

or

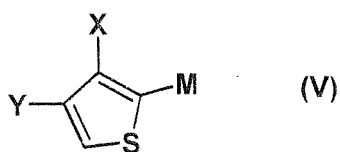
A.3. the thiophene component of the formula (II)



in which X and Y are as defined above,

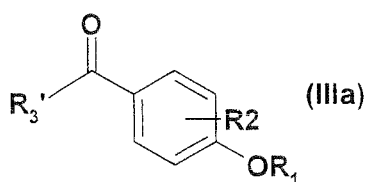
being reacted with one or more organometallic reagents from the series M-(C₁-C₈)-alkyl, MH, M-O-(C₁-C₈)-alkyl or M-N((C₁-C₈)-alkyl)₂ in which M is Li, Na, K, Zn, Mg, Ca,

in apolar solvents at temperatures of from -20 to 45°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,

and the latter being reacted further with a compound of the formula (IIIa)



in which R1 and R2 are as defined above, and

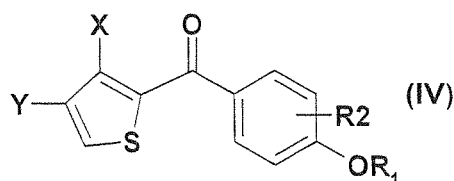
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

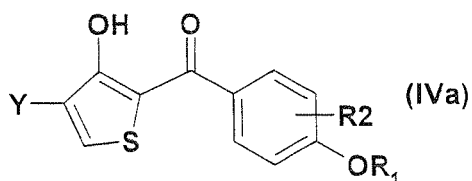
$N((C_6-C_{10})\text{-aryl})-(C_1-C_8)\text{-alkyl}$, $N((C_3-C_8)\text{-cycloalkyl})-(C_3-C_8)\text{-aryl}$, $N((C_6-C_{10})\text{-aryl})_2$, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

5 to give a compound of the formula (IV)



10 in which X, Y, R1 and R2 are as defined above; as described under A.1. at temperatures of from -20°C to $+30^{\circ}\text{C}$;

and subsequently this compound of the formula (IV) being converted in the presence of a Lewis acid into the compound of the formula (IVa)



15

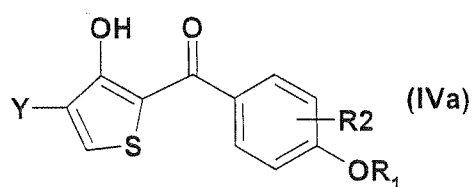
in which Y, R1 and R2 are as defined above, and where appropriate subsequently the compounds of the formula (IVa) being purified by conventional purification methods;

20

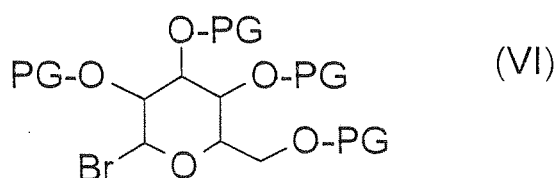
and subsequently

B. Preparation of the acetogluco ketones

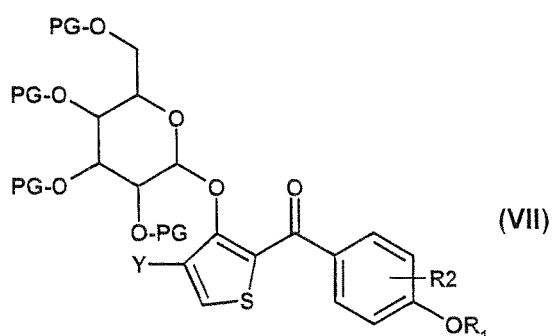
25 the compound of the formula (IVa)



being reacted with from 0.5 to 10 equivalents of a sugar derivative of the formula (VI)



in which PG is an OH protective group, in the presence of from 1 to 15 equivalents of an organic or inorganic base and of from 0.01 to 5 equivalents of a phase-transfer catalyst in a mixture of an organic solvent and water in the ratio of from 10 000:1 to 1:1 at from -20°C to $+80^{\circ}\text{C}$ to give the compound of the formula (VII);



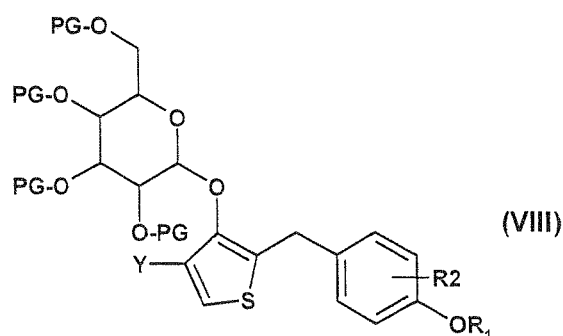
in which PG, Y, R1 and R2 are as defined above;

and subsequently

C. Preparation of the acetoglucomethylenes

the compound of the formula (VII) as described above being reacted in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine,

sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1 to 25 equivalents of one or more further acids at from -100°C to $+100^{\circ}\text{C}$ to give the compound of the formula (VIII)

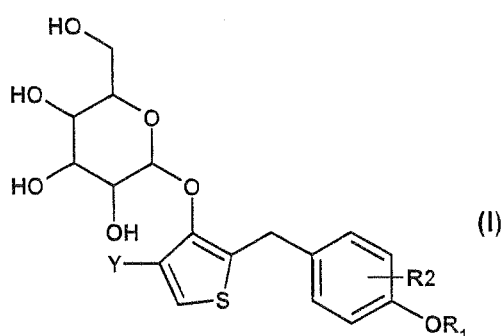


in which PG, Y, R1 and R2 are as defined above;
subsequently

10 D. Preparation of the thiophene-glycoside derivatives

the protective groups being eliminated under basic or acidic conditions, by oxidation or reduction or with fluoride, corresponding to known methods, in the presence of from 0.01 to 25 equivalents of an organic or inorganic base in a suitable solvent at
15 from -50°C to $+150^{\circ}\text{C}$ and subsequently

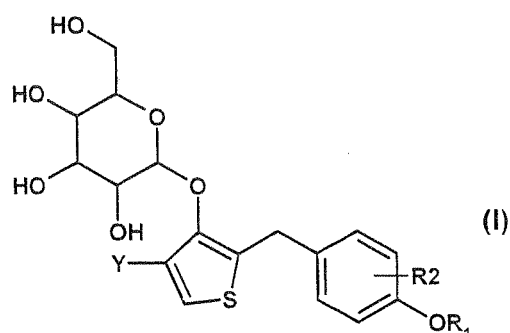
being converted into the compounds of the formula (I)



in which Y, R1 and R2 are as defined above,

and subsequently the compounds of the formula (I) being purified by conventional purification methods.

- 5 2. A process for preparing compounds of the general formula (I):



in which the meanings are

- 10 Y H, (C₁-C₁₀)-alkyl;
 R₁ (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by
 fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from
 the series O, N, S;
 R₂ H, Cl, Br, I;

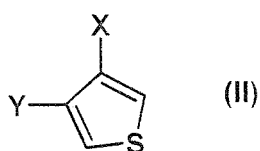
15

which comprises

A. Preparation of the hydroxy ketones

A.2. the thiophene component of the formula (II)

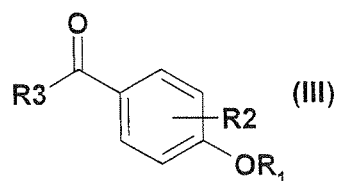
20



in which Y is as defined above, and

- X is O-(C₁-C₈)-alkyl or O-(C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3
 25 heteroatoms from the series O, N, S;

being reacted with a compound of the formula (III)

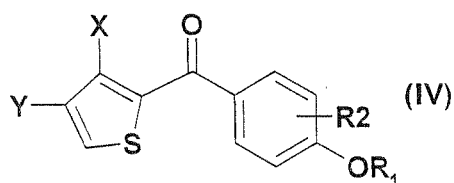


in which

- 5 R1 and R2 are as defined above, and
R3 is Cl, Br, I;

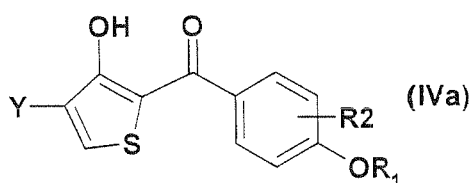
in the presence of from 0.1 to 10 equivalents of one or more acids in a suitable solvent at from -50 to $+150^{\circ}\text{C}$ to give a compound of the formula (IV),

10



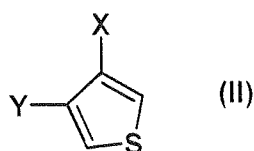
in which X, Y, R1 and R2 are as defined above; and

- 15 the latter being directly converted further in the presence of an acid as defined above at from 0 to 200°C into the compound of the formula (IVa)



- 20 in which Y, R1 and R2 are as defined above,
or

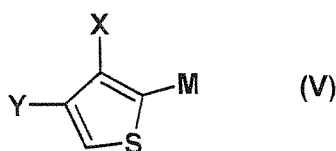
A.3. the thiophene component of the formula (II)



in which X and Y are as defined above,

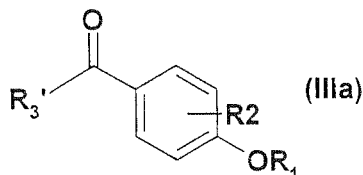
being reacted with one or more organometallic reagents from the series M-(C₁-C₈)-alkyl, MH, M-O-(C₁-C₈)-alkyl or M-N((C₁-C₈)-alkyl)₂ in which M is Li, Na, K, Zn, Mg, Ca,

in apolar solvents at temperatures of from -20 to 45°C to give the reactive intermediate of the formula (V)



in which X, Y and M are as defined above,

and the latter being reacted further with a compound of the formula (IIIa)



in which R1 and R2 are as defined above, and

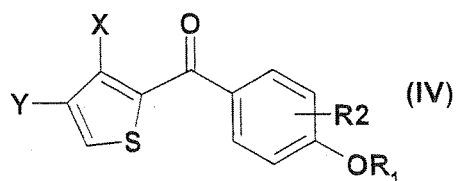
R3' is Cl, Br, I,

NH-(C₁-C₈)-alkyl, NH-O-(C₁-C₈)-alkyl, N((C₁-C₈)-alkyl)₂, N-(C₁-C₈)-alkyl-O-(C₁-C₈)-alkyl,

N(C₃-C₈)-cycloalkyl, where the alkyl ring may comprise one or more heteroatoms from the series N, O, S,

N((C₆-C₁₀)-aryl)-(C₁-C₈)-alkyl, N((C₃-C₈)-cycloalkyl)-(C₃-C₈)-aryl, N((C₆-C₁₀)-aryl)₂, where the aromatic systems and the cyclic alkanes may comprise one or more heteroatoms from the series N, O, S,

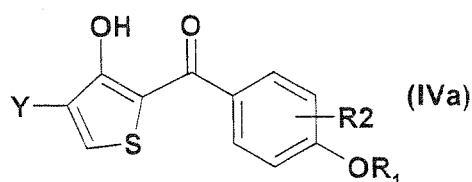
to give a compound of the formula (IV)



in which X, Y, R1 and R2 are as defined above; as described under A.2. at

5 temperatures of from -20°C to $+30^{\circ}\text{C}$;

and subsequently this compound of the formula (IV) being converted in the presence of a Lewis acid into the compound of the formula (IVa)

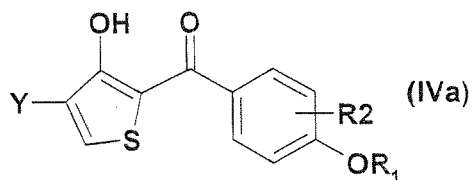


in which Y, R1 and R2 are as defined above, and where appropriate subsequently the compounds of the formula (IVa) being purified by conventional purification methods;

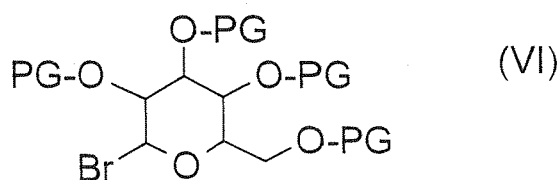
and subsequently

B. Preparation of the acetogluco ketones

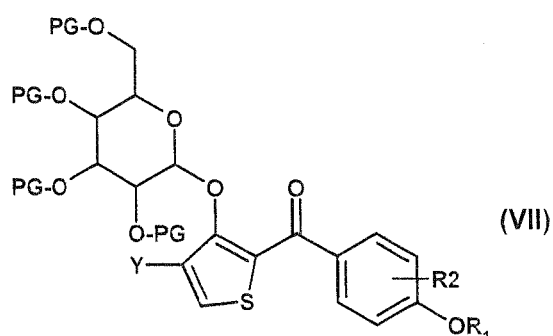
the compound of the formula (IVa)



being reacted with from 0.5 to 10 equivalents of a sugar derivative of the formula (VI)



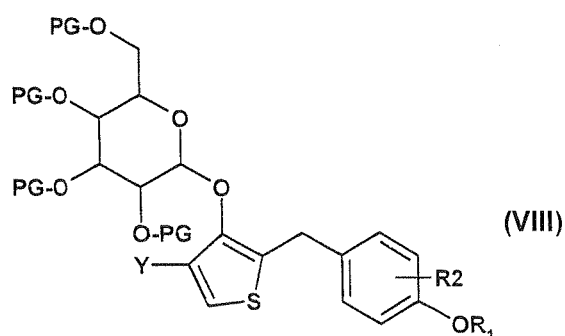
in which PG is an OH protective group, in the presence of from 1 to 15 equivalents of an organic or inorganic base and of from 0.01 to 5 equivalents of a phase-transfer catalyst in a mixture of an organic solvent and water in the ratio of from 10 000:1 to 1:1 at from -20°C to $+80^{\circ}\text{C}$ to give the compound of the formula (VII);



in which PG, Y, R1 and R2 are as defined above;
and subsequently

C. Preparation of the acetoglucomethylenes

the compound of the formula (VII) as described above being reacted in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1 to 25 equivalents of one or more further acids at from -100°C to $+100^{\circ}\text{C}$ to give the compound of the formula (VIII)



in which PG, Y, R1 and R2 are as defined above;

subsequently

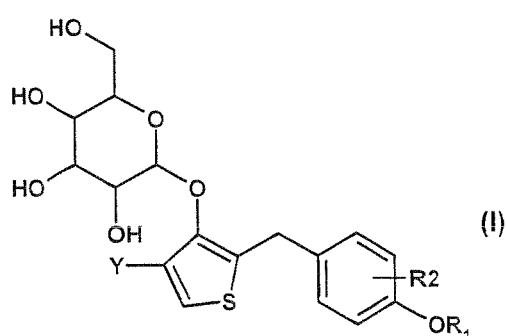
5

D. Preparation of the thiophene-glycoside derivatives

the protective groups being eliminated under basic or acidic conditions, by oxidation
or reduction or with fluoride, corresponding to known methods, in the presence of
10 from 0.01 to 25 equivalents of an organic or inorganic base in a suitable solvent at
from -50°C to $+150^{\circ}\text{C}$ and subsequently

being converted into the compounds of the formula (I)

15



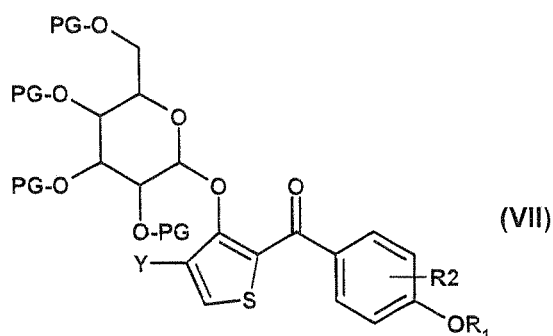
in which Y, R1 and R2 are as defined above,

20 and subsequently the compounds of the formula (I) being purified by conventional
purification methods.

3. The process for preparing the compounds of the formula (I) as claimed in claim 1 or 2, wherein the activator in step C. Preparation of the acetoglucomethylenes is iodine.

5

4. A process for preparing the intermediate compounds of the formula (VIII), which comprises
a compound of the formula (VII),



10

in which

PG is an OH protective group;

Y is H, (C₁-C₁₀)-alkyl;

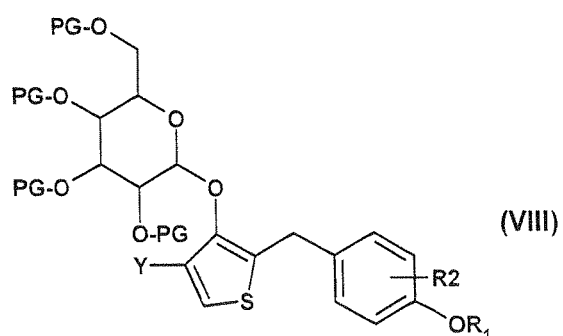
15 R1 is (C₁-C₈)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; (C₅-C₁₀)-aryl, where aryl may also comprise 1 to 3 heteroatoms from the series O, N, S;

R2 H, Cl, Br, I;

being reacted

20

in an organic suitable solvent with from 1 to 15 equivalents of one or more hydride donors and from 0.1 to 5 equivalents of one or more activators selected from the group of lithium chloride, bromine, sodium bromide or potassium bromide, iodine, sodium iodide or potassium iodide, sodium triiodide or potassium triiodide and from 1
25 to 25 equivalents of one or more further acids at from -100°C to +100°C to give the compound of the formula (VIII)



in which PG, Y, R1 and R2 are as defined above.

5

5. The process for preparing the intermediate compounds of the formula (VIII) as claimed in claim 4, wherein the activator is iodine.

10 6. The process for preparing the compounds of the formula (I) as claimed in claim 1 to 3, in which the meanings are

Y H;

R1 (C₁-C₄)-alkyl, where one, more than one or all hydrogen(s) may be replaced by fluorine; and

15 R2 H.