

FAMILY OF ARYL, HETEROARYL, O-ARYL AND O-HETEROARYL CARBASUGARS

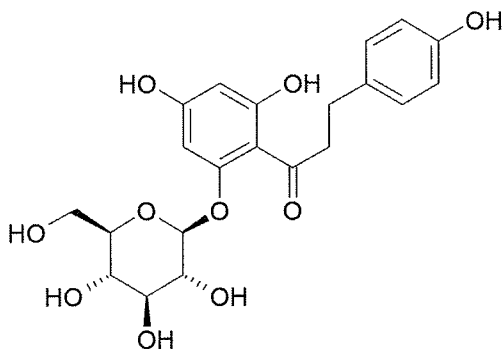
This invention relates to a family of fluorinated aryl, heteroaryl, O-aryl and O-heteroaryl glycoside compounds, the process for their preparation, as well as the application of same in the pharmaceutical or cosmetic fields, in particular for the treatment or prevention of diabetes and obesity, and as depigmenting or lightening agent.

Sugars and the derivatives thereof constitute one of the most common classes of compounds in nature. Based on their chemical structures, they exhibit various physico-chemical properties and can play a key role in a wide variety of biological processes.

In recent years, there has been a growing interest in discovering new glycosides having advantageous properties in terms of improved efficacy, selectivity and stability.

Found among these compounds, in particular, are aryl glycosides or phenol glycosides having applications in the field of cosmetics or in the treatment or prevention of diseases such as diabetes, obesity, cancer, inflammatory diseases, auto-immune diseases, infections, thromboses, and with regard to numerous other therapeutic fields. By their biological properties and their structure, these compounds interest numerous research teams.

Phlorizin may be cited in particular, as a molecule known for its inhibiting activity with regard to sodium-dependent glucose co-transporters (SGLT) (Journal of Clinical Investigation, vol. 79, p. 1510, (1987); *ibid.*, vol. 80, p. 1037 (1987); *ibid.*, vol. 87, p. 561 (1991); J. of Med. Chem., vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578, (2001)).



Phlorizin

Inhibitors of sodium-dependent glucose co-transporters (SGLT), found in particular in the intestines and kidney, are potentially usable for treating diabetes, and more specifically type-II diabetes, but also for hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, syndrome X (also known by the name of metabolic syndrome, J. of Clin. Endocrinol. Metabol., 82, 727-734 (1997)), diabetes-related complications or else atherosclerosis. As a matter of fact, it is known that hyperglycemia participates in the onset and evolution of diabetes and leads to a reduction in the secretion of insulin and a reduction in insulin sensitivity, which results in an increase in the glucose level, thereby exacerbating diabetes. The treatment of hyperglycemia can thus be considered as a mean to treat diabetes.

Such being the case, one of the methods for treating hyperglycemia is to promote the excretion of excess of glucose directly into the urine, e.g., by inhibiting the sodium-dependent glucose co-transporter in the proximal tubules of the kidneys, the effect of which is to inhibit the re-absorption of glucose and to thereby promote the excretion thereof into the urine, leading thus to a reduction in the blood-sugar level.

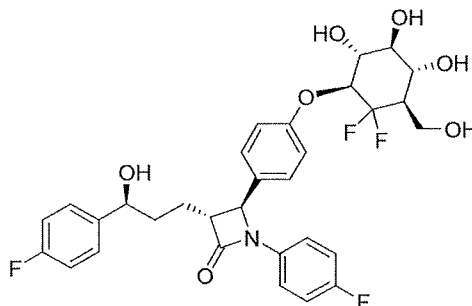
At present, a large number of drugs exist, which can be used for treating diabetes, such as biguanides, sulfonylureas, insulin resistance-improving agents, and inhibitors of α -glycosidases. However, these compounds have numerous side effects, thereby increasing the need for new drugs.

Therefore, the invention provides new compounds, which are useful, in particular, for the treatment or prevention of diabetes and obesity.

These compounds are CF₂-analogues of aryl, heteroaryl, O-aryl, O-heteroaryl glycosides, wherein the intracyclic glycosidic oxygen is replaced by a carbon atom, carrying two fluorine atoms. These compounds will have the distinctive feature of being stable analogues of O-aryl and O-heteroaryl glycosides, when confronted with enzymatic degradation processes, in particular via glycosidase-type enzymes. Moreover, difluorinated carbon is a good mimic of the oxygen atom.

Stable aryl-glycoside analogues, wherein it is the anomeric oxygen which is replaced by a carbon atom carrying two fluorine atoms, are described in the patent application WO 2009/121 939.

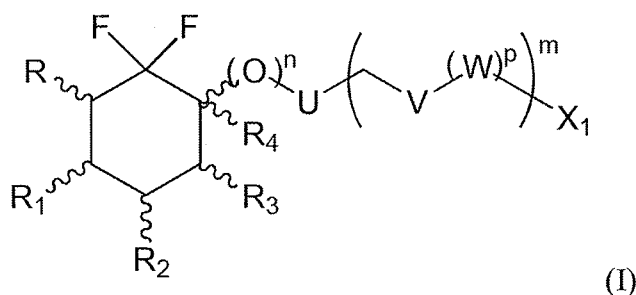
The synthesis of O-aryl glycosides wherein the intracyclic or anomeric oxygen is replaced by a carbon atom, carrying two fluorine atoms is described in the patent applications WO 2005/044 256. The synthesis of the following compound is notably described:



O-aryl and aryl analogues wherein the endocyclic oxygen is replaced by a carbon atom carrying two halogen atoms have also been reported in WO 2009/076 550 but have not been exemplified.

The inventors have thus developed new synthetic approaches enabling access to new aryl, heteroaryl, O-aryl and O-hetero-aryl compounds, useful as SGLT inhibitors, in particular for the treatment or prevention of diabetes and obesity, and useful as Tyrosinase inhibitors, notably for cosmetic applications and especially as depigmenting or lightening agents and also as antioxidants.

Therefore, the present invention relates to a compound having the following formula (I):



(I)

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

wherein:

- n, m and p represent, independently from one another, 0 or 1,

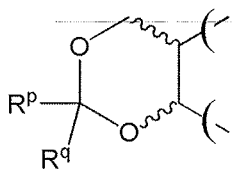
- R represents a hydrogen or a fluorine atom or a CH₃, CH₂F, CH₂OH, CH₂OSiR^aR^bR^c, CH₂OR¹¹, CH₂OCOR¹¹, CH₂OCO₂R¹¹, CH₂OCONR¹²R¹³, CH₂OP(O)(OR¹⁴)₂ or CH₂OSO₃R¹⁴ group,

- R₁ and R₂ represent, independently from one another, a fluorine atom or an OH, OSiR^dR^eR^f, OR¹⁵, OCOR¹⁵, OCO₂R¹⁵ or OCONR¹⁶R¹⁷ group,

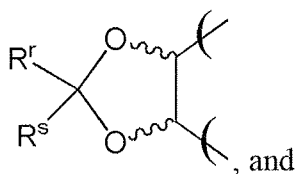
- R₃ represents a hydrogen or fluorine atom or an OH, OSiR^gR^hRⁱ, OR¹⁸, OCOR¹⁸, OCO₂R¹⁸, OCONR¹⁹R²⁰, NR¹⁹R²⁰ or NR¹⁹COR¹⁸ group,

- R₄ represents a hydrogen atom when n = 1, and R₄ represents a hydrogen atom, an halogen atom or an OH, OSiR^jR^kR^l, OR²¹, OCOR²¹, OCO₂R²¹, or OCONR²²R²³ group when n = 0,

or R and R₁, together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



and/or (R₁ and R₂), (R₂ and R₃), and/or (R₃ and R₄), together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



- X₁ represents a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group, and

- U, V and W represent, independently from one another, a phenyl, pyrazolyl, N-(C₁-C₆)alkyl-pyrazolyl, or thienyl ring,

the said ring being optionally substituted with one or more substituents selected from the group consisting of an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ and OSO₃R²⁴ group,

with:

- R^{11} , R^{15} , R^{18} , R^{21} and R^{24} representing, independently from one another, a (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, 5 to 7 ring-membered heterocycloalkyl, aryl, aryl-(C₁-C₆)-alkyl or (C₁-C₆)-alkyl-aryl group, this group being possibly substituted by one or more groups chosen among an halogen atom, an OH, COOH and CHO group,
- R^{12} , R^{13} , R^{16} , R^{17} , R^{19} , R^{20} , R^{22} , R^{23} , R^{25} and R^{26} representing, independently from one another, a hydrogen atom or a (C₁-C₆)-alkyl or aryl-(C₁-C₆)-alkyl group,
- R^{14} representing a hydrogen atom or a (C₁-C₆)-alkyl group,
- R^a to R^o representing, independently from one another, a (C₁-C₆)-alkyl, aryl or aryl-(C₁-C₆)-alkyl group, and
- R^p to R^s representing, independently from one another, a hydrogen atom, a (C₁-C₆)-alkyl group, aryl or aryl-(C₁-C₆)-alkyl group.

In this invention, “pharmaceutically or cosmetically acceptable” is understood to mean what is useful in the preparation of a pharmaceutical or cosmetic composition which is generally safe, non-toxic and neither biologically nor otherwise undesirable and which is acceptable for veterinary and human pharmaceutical use, as well as cosmetic use.

In this invention, “pharmaceutically or cosmetically acceptable salts” of a compound, is understood to designate salts which are pharmaceutically or cosmetically acceptable, as defined herein, and which possess the desired pharmacological activity of the parent compound. Such salts include:

- (1) hydrates and solvates, such as (S)-propylene glycol solvate,
- (2) acid addition salts formed with inorganic acids such as hydrochloric acid, bromhydric acid, sulphuric acid, nitric acid, phosphoric acid or the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphtalenesulfonic acid, propionic acid, salicylic acid, succinic acid, dibenzoyl-L-tartaric acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, trifluoroacetic acid and the like; and

(3) salts formed when an acid proton present in the parent compound is either replaced by a metal ion, e.g., an alkali metal ion (e.g., Na^+ , K^+ or Li^+), an alkaline-earth metal ion (like Ca^{2+} or Mg^{2+}) or an aluminium ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases include aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

In this invention, "tautomer" is understood to designate an isomer obtained by prototropy, i.e. migration of a hydrogen atom and change of localisation of a double bond. The different tautomers of a compound are generally interconvertible and present in equilibrium in solution, in various proportions which can depend on the solvent used, on the temperature or on the pH.

In this invention, "stereoisomers" mean isomers having the same molecular formula and sequence of bonded atoms but which differ in the three-dimensional orientations of their atoms in space. They designate thus E / Z isomers, diastereoisomers and enantiomers. E / Z isomers are compounds having a double bond, the substituents present on this double bond being not on the same side of the double bond. Stereoisomers which are not mirror images of one another are thus designated as "diastereoisomers", and stereoisomers which are non-superimposable mirror images are designated as "enantiomers".

Notably, the sugar moiety of the compounds of the invention can belong to the D or L series, and preferably to the D series.

A carbon atom bound to four non-identical substituents is called a "chiral centre".

An equimolar mixture of two enantiomers is called a racemate mixture.

Within the meaning of this invention, "halogen" is understood to mean an atom of fluorine, bromine, chlorine or iodine.

Within the meaning of this invention, "(C₁-C₆)-alkyl" group is understood to mean a saturated, linear or branched hydrocarbon chain comprising from 1 to 6 carbon atoms, in particular the methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl groups.

Within the meaning of this invention, “(C₂-C₆)-alkenyl” group is understood to mean a linear or branched hydrocarbon chain comprising at least one double bond and comprising from 2 to 6 carbon atoms, e.g., such as an ethenyl (vinyl) or propenyl group.

5 Within the meaning of the invention, “(C₂-C₆)-alkynyl” group is understood to mean a linear or branched hydrocarbon chain comprising at least one triple bond and comprising from 2 to 6 carbon atoms, e.g., such as an ethynyl or propynyl group.

Within the meaning of this invention, “(C₃-C₇)-cycloalkyl” group is understood to mean a saturated hydrocarbon ring comprising from 3 to 7, advantageously from 5 to 7, carbon atoms, in particular the cyclohexyl, cyclopentyl or cycloheptyl group.

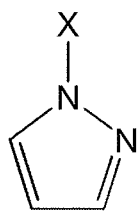
10 Within the meaning of this invention, “5 to 7 ring-membered heterocycloalkyl” group is understood to mean a saturated hydrocarbon ring having 5 to 7 members and containing one or more, advantageously one or two, heteroatoms in place of the carbon atoms, e.g., such as sulphur, nitrogen or oxygen atoms, e.g., such as the tetrahydrofuranyl, piperidiny, pyrrolidinyl, tetrahydropyranyl, 1,3-dioxolanyl group.

15 Within the meaning of this invention, “aryl” group is understood to mean a hydrocarbon aromatic group preferably comprising from 5 to 10 carbon atoms and including one or more fused rings, e.g., such as a phenyl or naphthyl group. This is advantageously phenyl.

20 Within the meaning of this invention, “aryl-(C₁-C₆)-alkyl” group is understood to mean any aryl group as defined above, which is bound to the molecule by means of a (C₁-C₆)-alkyl group as defined above. In particular, a group such as this can be a benzyl group.

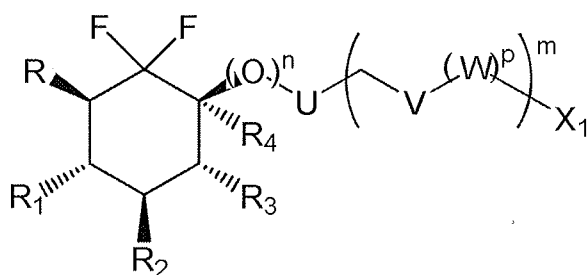
25 Within the meaning of this invention, “(C₁-C₆)-alkyl-aryl” group is understood to mean a (C₁-C₆)-alkyl group as defined above, which is bound to the molecule by means of an aryl group as defined above. In particular, a group such as this can be a methylphenyl group.

Within the meaning of this invention, “N-(C₁-C₆)alkyl-pyrazolyl” group is a group of the following formula, wherein X represents a (C₁-C₆)alkyl group as defined above:

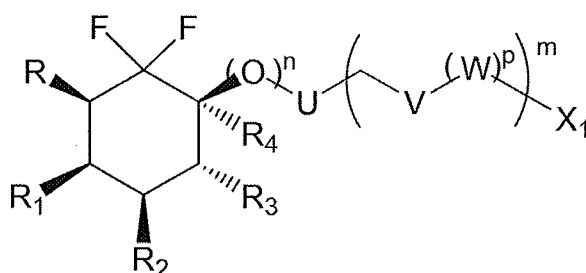


this group being bound to the rest of the molecule by two of the carbon atoms of the pyrazolyl moiety.

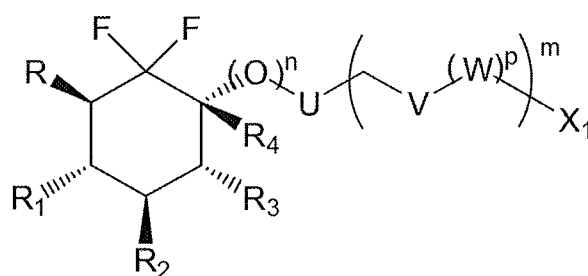
- 5 The compounds of the invention are advantageously based on the following formulas (Ia), (Ib) and (Ic), and in particular (Ia) and (Ic):



(Ia),



(Ib) and



(Ic),

- 10 with R, R₁, R₂, R₃, R₄, X₁, U, V, W, n, m and p as defined above.

- Advantageously, R₁ and R₂ represent, independently from one another, a
 15 fluorine atom or an OH, OSiR^dR^eR^f, OR¹⁵, OCOR¹⁵, OCO₂R¹⁵ or OCONR¹⁶R¹⁷ group
 and R₃ represents a fluorine atom or an OH, OSiR^gR^hRⁱ, OR¹⁸, OCOR¹⁸, OCO₂R¹⁸ or
 OCONR¹⁹R²⁰ group.

More advantageously, R_1 and R_2 represent, independently from one another, an OH, OR^{15} or $OCOR^{15}$ group and R_3 represents an OH, OR^{18} or $OCOR^{18}$ group.

Even more advantageously, R_1 , R_2 and R_3 may be chosen, independently from one another, among an OH, $-O-(C_1-C_6)$ -alkyl, $-O$ -aryl, $-O-(C_1-C_6)$ -alkyl-aryl and
 5 $-OCO-(C_1-C_6)$ -alkyl group.

In particular, R_1 , R_2 and R_3 may be chosen, independently from one another, among an OH, $OSiMe_3$ and benzyloxy (OBn) group, and preferably among OH and OBn.

According to a particular embodiment, R_1 , R_2 and R_3 are identical.

10 According to another particular embodiment, R_1 , R_2 and R_3 are identical and represent each an OH group and R represents a CH_2OH group.

R advantageously represents a hydrogen atom or a CH_3 , CH_2OH , CH_2OR^{11} , $CH_2OSiR^aR^bR^c$, CH_2OCOR^{11} , $CH_2OP(O)(OH)_2$ or CH_2OSO_3H group, and in particular a hydrogen atom or a CH_3 , CH_2OH , CH_2OR^{11} , CH_2OCOR^{11} , $CH_2OP(O)(OH)_2$ or
 15 CH_2OSO_3H group,

with R^a , R^b , R^c and R^{11} as defined above, and with CH_2OR^{11} advantageously representing a $-CH_2O-(C_1-C_6)$ -alkyl, $-CH_2O$ -aryl and $-CH_2O-(C_1-C_6)$ -alkyl-aryl, and CH_2OCOR^{11} group, more advantageously representing a $-CH_2OCO-(C_1-C_6)$ -alkyl group.

Even more advantageously, R represents a CH_2OH , $CH_2OSiR^aR^bR^c$, CH_2OR^{11} or
 20 CH_2OCOR^{11} group, and more advantageously a CH_2OH , CH_2OR^{11} or CH_2OCOR^{11} group, with R^a , R^b , R^c and R^{11} as defined above.

Yet even more advantageously, R represents a CH_2OH , $-CH_2O-(C_1-C_6)$ -alkyl, $-CH_2O$ -aryl, $-CH_2O-(C_1-C_6)$ -alkyl-aryl and $-CH_2OCO-(C_1-C_6)$ -alkyl group.

In particular, R can represent a CH_2OH , CH_2OSiMe_3 or CH_2OBn group, and
 25 preferably a CH_2OH or CH_2OBn group.

In the same way, R_4 may advantageously represent a hydrogen or halogen atom or an OH or OR^{24} group, and in particular a hydrogen atom or an OH or OR^{24} group, with R^{24} as defined above.

Yet even more advantageously, R_4 may represent a hydrogen or halogen atom or
 30 an OH, $-O-(C_1-C_6)$ -alkyl, $-O$ -aryl and $-O-(C_1-C_6)$ -alkyl-aryl group, and in particular, a hydrogen atom or an OH, $-O-(C_1-C_6)$ -alkyl, $-O$ -aryl and $-O-(C_1-C_6)$ -alkyl-aryl group.

In particular, R_4 can represent a hydrogen or halogen (such as Br, Cl, F) atom or an OH group, and advantageously, a hydrogen atom or an OH group, and notably a hydrogen atom.

Preferably, $R_4 = H$ when $n = 1$ and $R_4 = H$ or OH when $n = 0$.

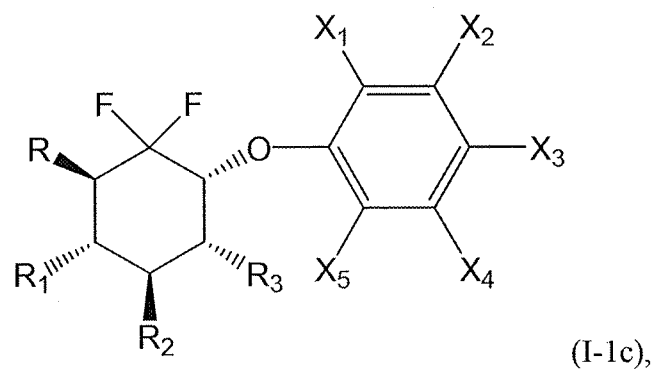
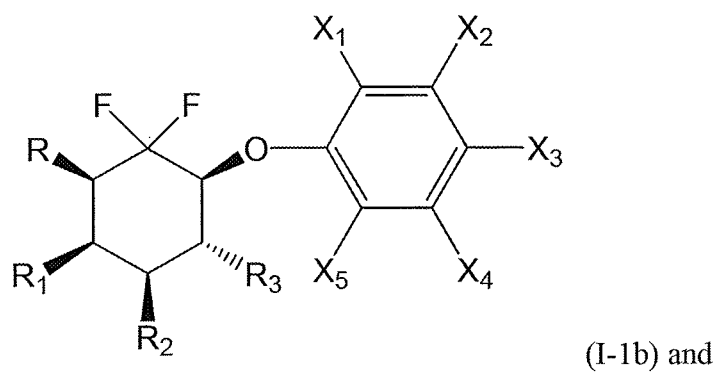
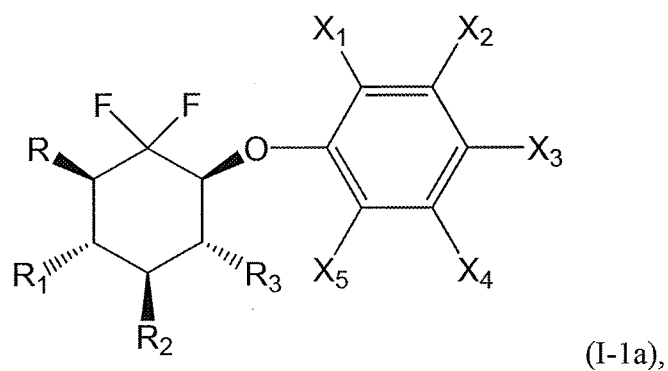
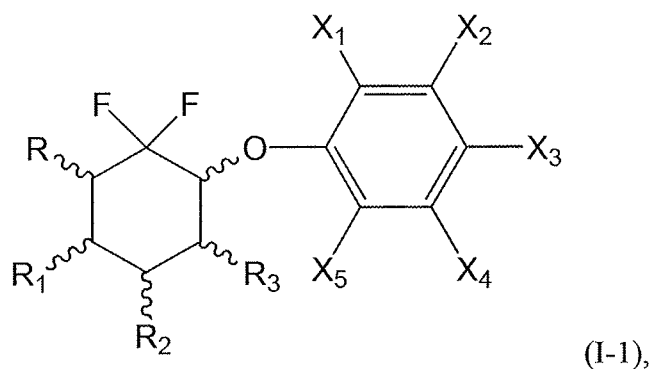
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Advantageously, X_1 is selected from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$ and $CONR^{25}R^{26}$ group; more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$ and CO_2R^{24} group; even more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl and OR^{24} group.

Advantageously, U, V and W represent, independently from one another, a phenyl, pyrazolyl, N-(C₁-C₆)alkyl-pyrazolyl, or thienyl ring, the said ring being optionally substituted with one or more substituents selected from the group consisting of an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$ and $CONR^{25}R^{26}$ group; more advantageously from the group consisting of an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$ and CO_2R^{24} group; even more advantageously from the group consisting of an halogen atom, a OH, (C₁-C₆)-alkyl and OR^{24} group.

(1) In a first embodiment, n is 1.

In a first subclass of this embodiment, $m = 0$ and U is an optionally substituted phenyl. The compounds according to the invention can thus be represented by the following formula (I-1), and more particularly by the following formulas (I-1a), (I-1b) and (I-1c), and in particular (I-1a) and (I-1c):



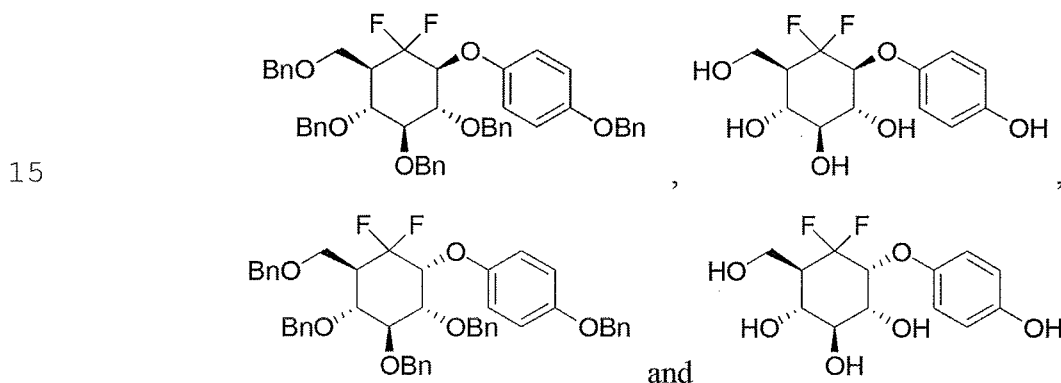
- 5 or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

wherein:

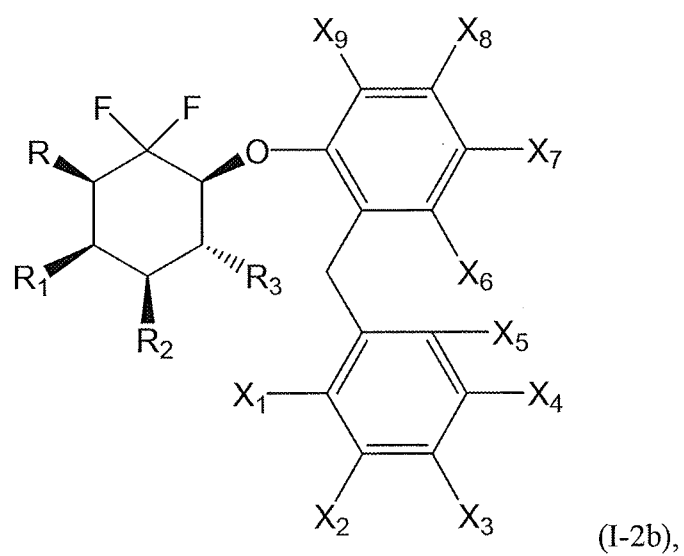
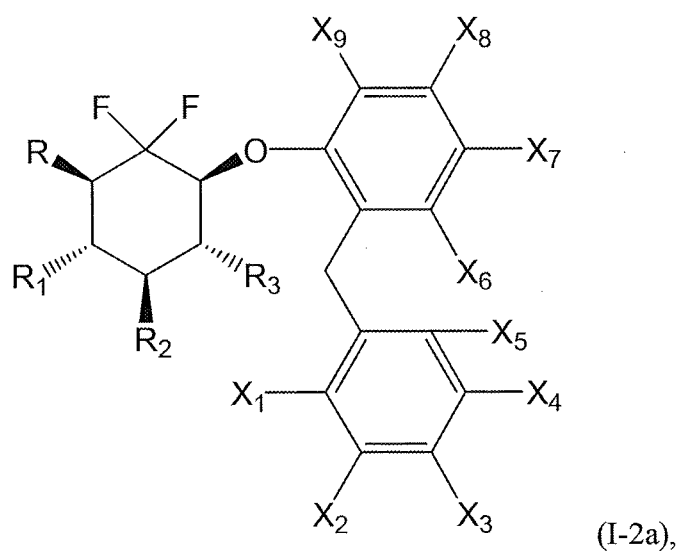
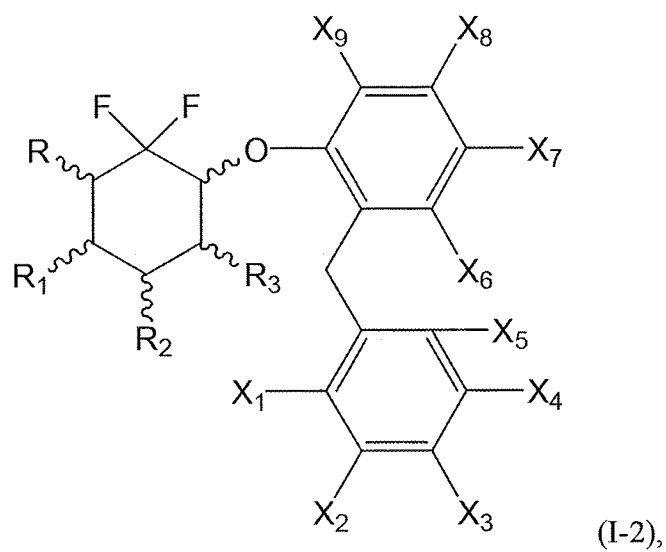
- R, R₁, R₂, and R₃ are as defined above, and

- X_1 , X_2 , X_3 , X_4 and X_5 represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO_2 , SiR^mR^n , (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$, $CONR^{25}R^{26}$, SR^{24} , SO_2R^{24} , CSR^{24} or OSO_3R^{24} group; advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$ and $CONR^{25}R^{26}$ group; more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$ and CO_2R^{24} group; even more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C_1-C_6) -alkyl and OR^{24} group.

Examples within this first subclass include but are not limited to:



In a second subclass of this embodiment, $m = 1$, $p = 0$ and U and V represent, independently from one another, an optionally substituted phenyl. The compounds according to the invention can thus be represented by the following formula (I-2), and more particularly by the following formulas (I-2a) and (I-2b), and in particular (I-2a):

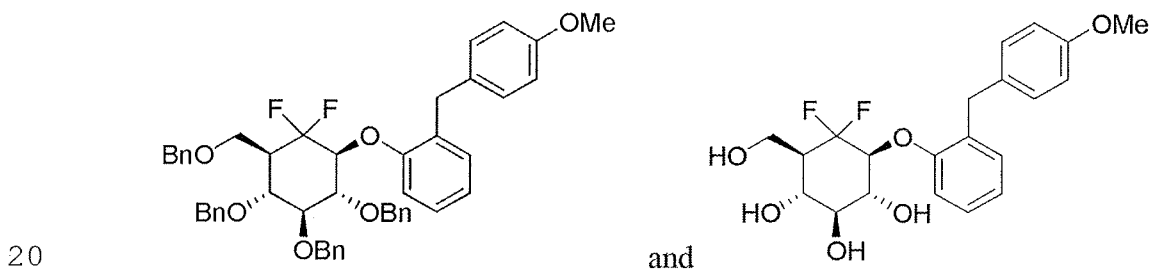


or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

wherein:

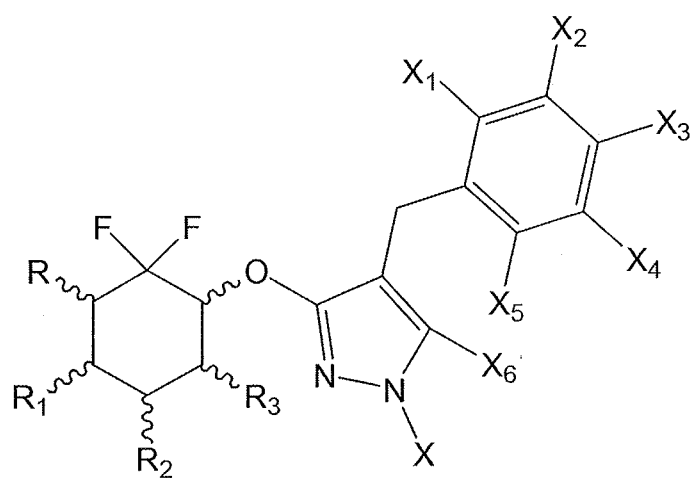
- 5 – R, R₁, R₂, and R₃ are as defined above, and
- X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ and X₉ represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group; advantageously from the group consisting of a hydrogen atom, an
- 10 halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴ and CONR²⁵R²⁶ group; more advantageously from the group consisting of a
- 15 hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴ and CO₂R²⁴ group; even more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl and OR²⁴ group.

Examples within this second subclass include but are not limited to:

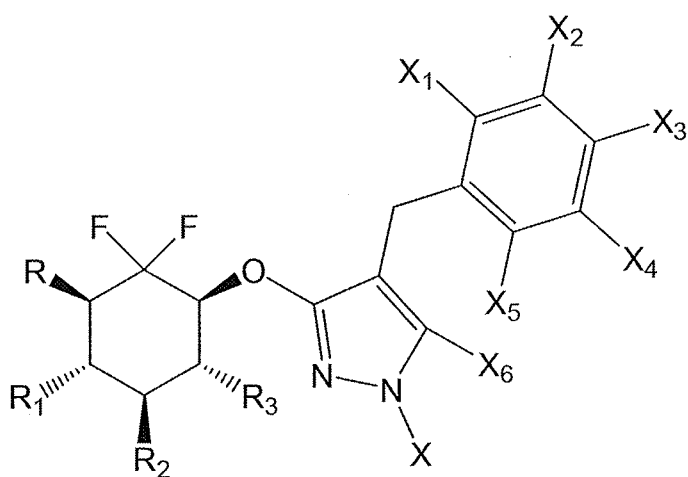


In a third subclass of this embodiment, m = 1, p = 0, U is a pyrazolyl or N-(C₁-C₆)-alkyl-pyrazolyl group and V is an optionally substituted phenyl. The compounds according to the invention can thus be represented by the following formula (I-3), and

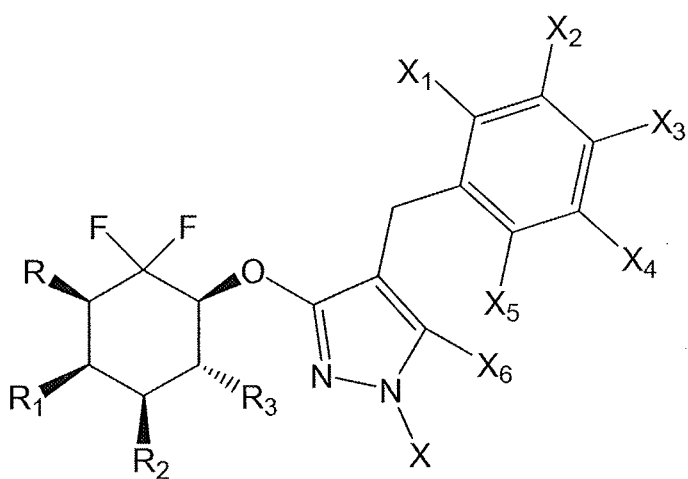
25 more particularly by the following formulas (I-3a) and (I-3b), and in particular (I-3a):



(I-3),



(I-3a),



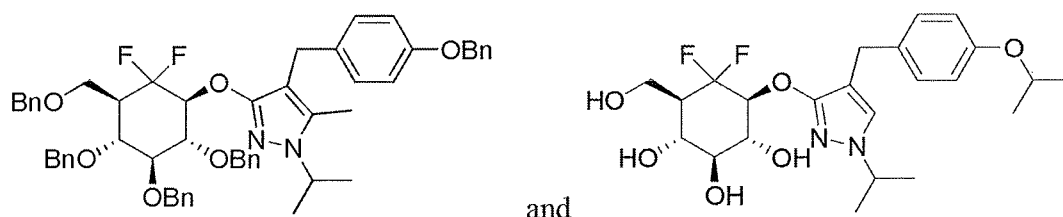
(I-3b),

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

wherein:

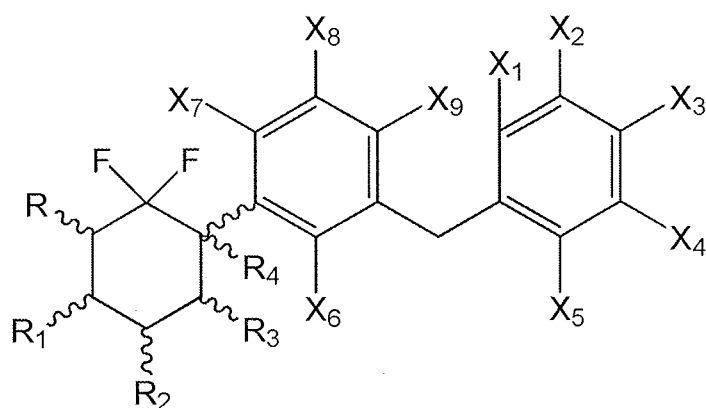
- 5 — R, R₁, R₂, and R₃ are as defined above,
- X₁, X₂, X₃, X₄, X₅ and X₆ represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group;
- 10 advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴ and CONR²⁵R²⁶ group; more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴ and CO₂R²⁴ group;
- 15 even more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl and OR²⁴ group, and
- X represents a hydrogen atom or a (C₁-C₆)-alkyl group.

20 Examples within this third subclass include but are not limited to:

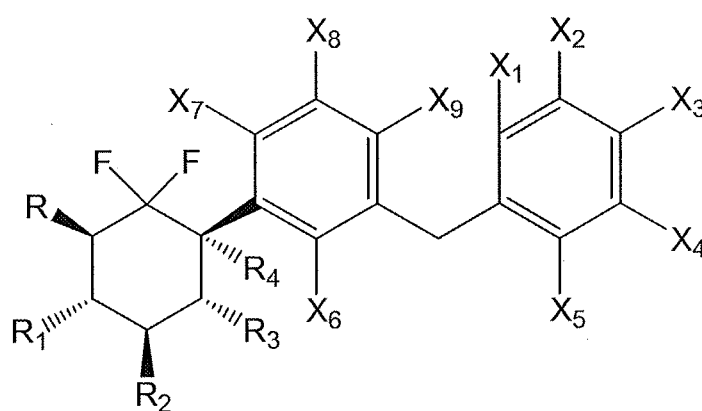


(2) In a second embodiment, n is 0.

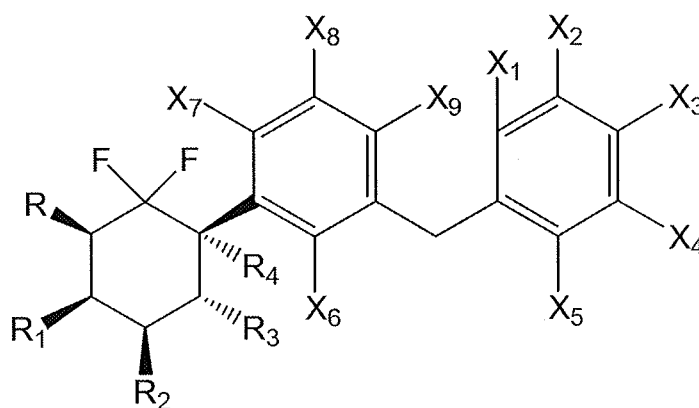
In a first subclass of this embodiment, m = 1, p = 0 and U and V are
 25 independently an optionally substituted phenyl. The compounds according to the invention can thus be represented by the following formula (I-4), and more particularly by the following formulas (I-4a) and (I-4b), and in particular (I-4a):



(I-4),



(I-4a) and



(I-4b),

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer
 5 or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers,
 and particularly a racemate mixture,

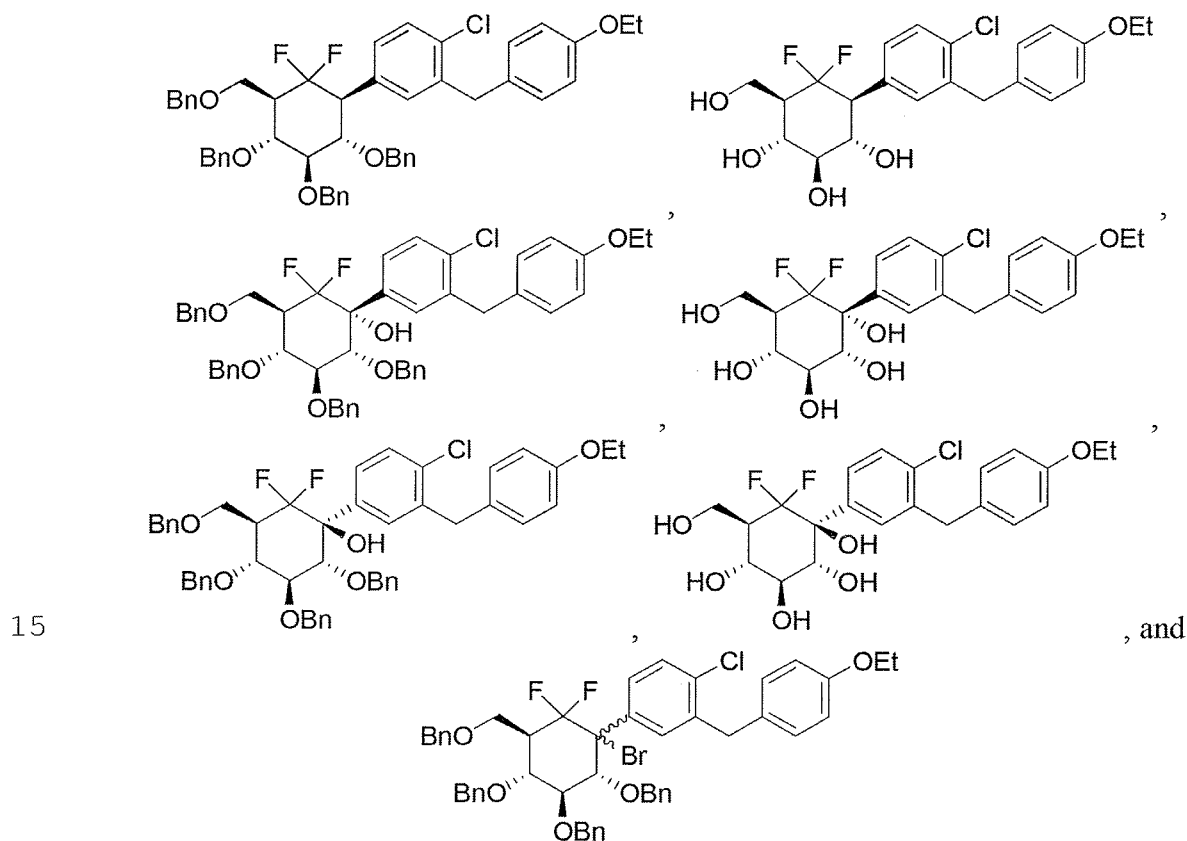
wherein:

- R, R₁, R₂, R₃ and R₄ are as defined above, and
- X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ and X₉ represent, independently from one another,
 10 a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl,
 (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴,

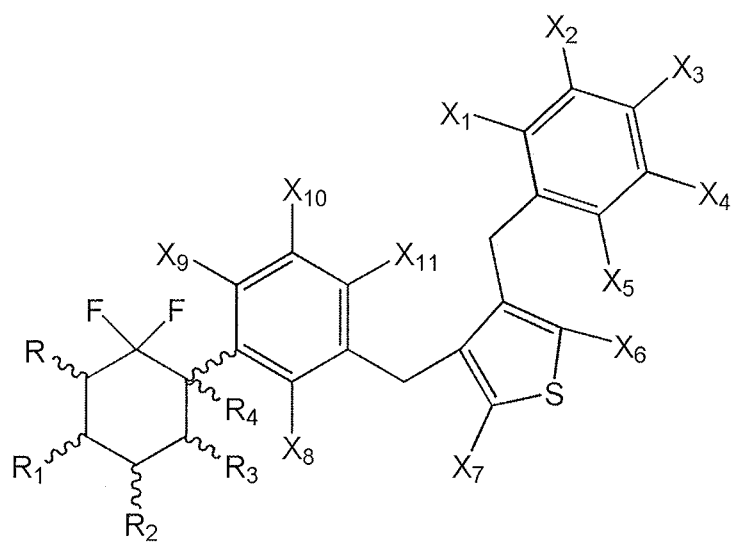
CO_2R^{24} , $\text{NR}^{25}\text{R}^{26}$, $\text{NR}^{25}\text{COR}^{24}$, $\text{CONR}^{25}\text{R}^{26}$, SR^{24} , SO_2R^{24} , CSR^{24} or $\text{OSO}_3\text{R}^{24}$
 group; advantageously from the group consisting of a hydrogen atom, an
 halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-
 cycloalkyl, OR^{24} , COR^{24} , OCOR^{24} , CO_2R^{24} , $\text{NR}^{25}\text{R}^{26}$, $\text{NR}^{25}\text{COR}^{24}$ and
 5 $\text{CONR}^{25}\text{R}^{26}$ group; more advantageously from the group consisting of a
 hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-
 alkynyl, (C₃-C₇)-cycloalkyl, OR^{24} , COR^{24} , OCOR^{24} and CO_2R^{24} group; even
 more advantageously from the group consisting of a hydrogen atom, an halogen
 atom, a OH, (C₁-C₆)-alkyl and OR^{24} group.

10

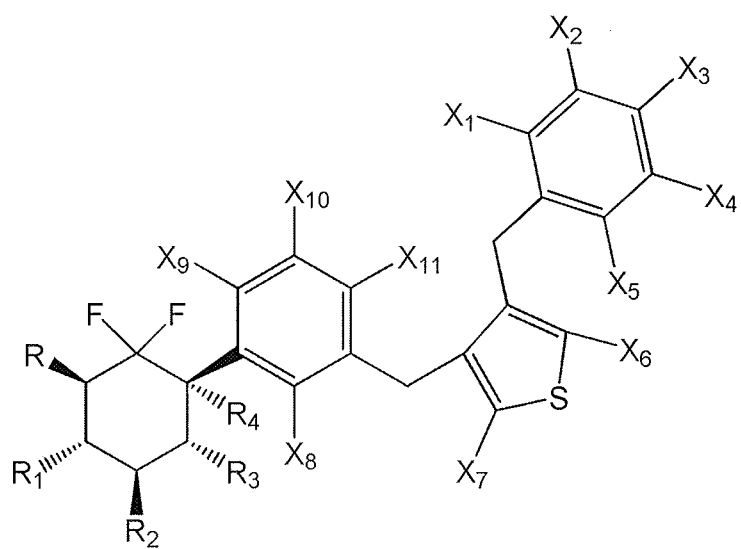
Examples within this first subclass include but are not limited to:



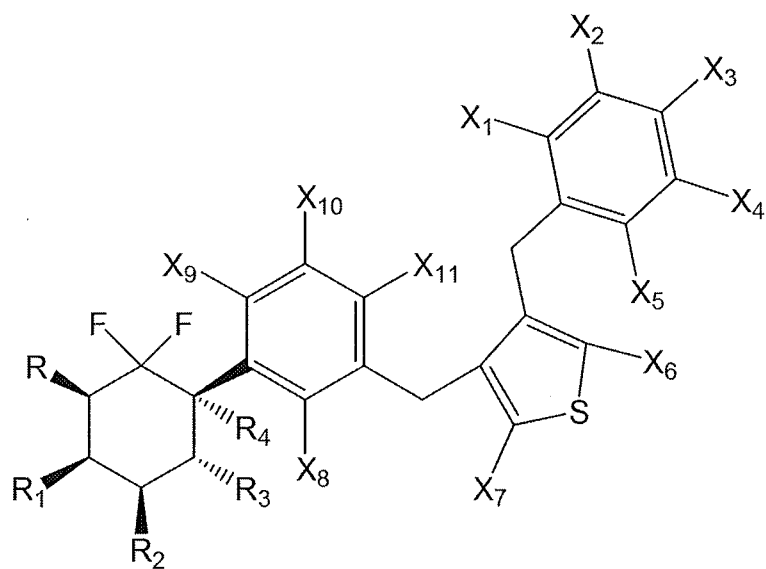
In a second subclass of this embodiment, $m = 1$, $p = 1$, U and W are
 independently an optionally substituted phenyl and V is an optionally substituted thienyl.
 20 The compounds according to the invention can thus be represented by the following
 formula (I-5), and more particularly by the following formulas (I-5a) and (I-5b), and in
 particular (I-5a):



(I-5),



(I-5a),



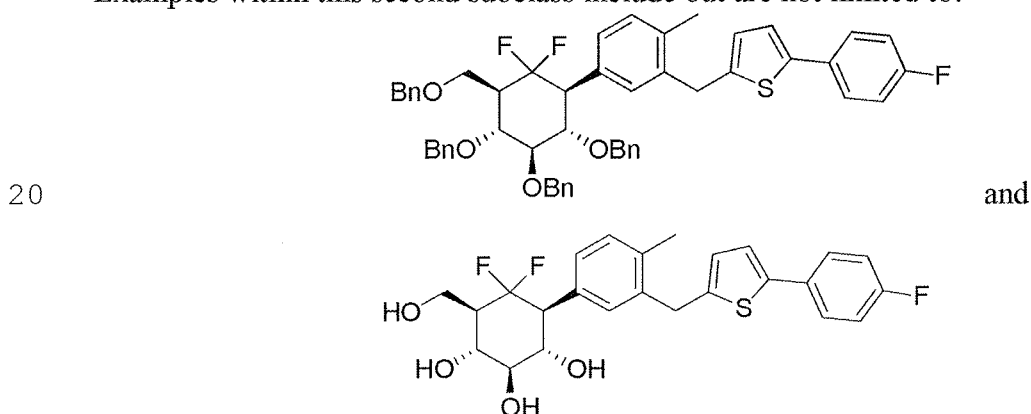
(I-5b),

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

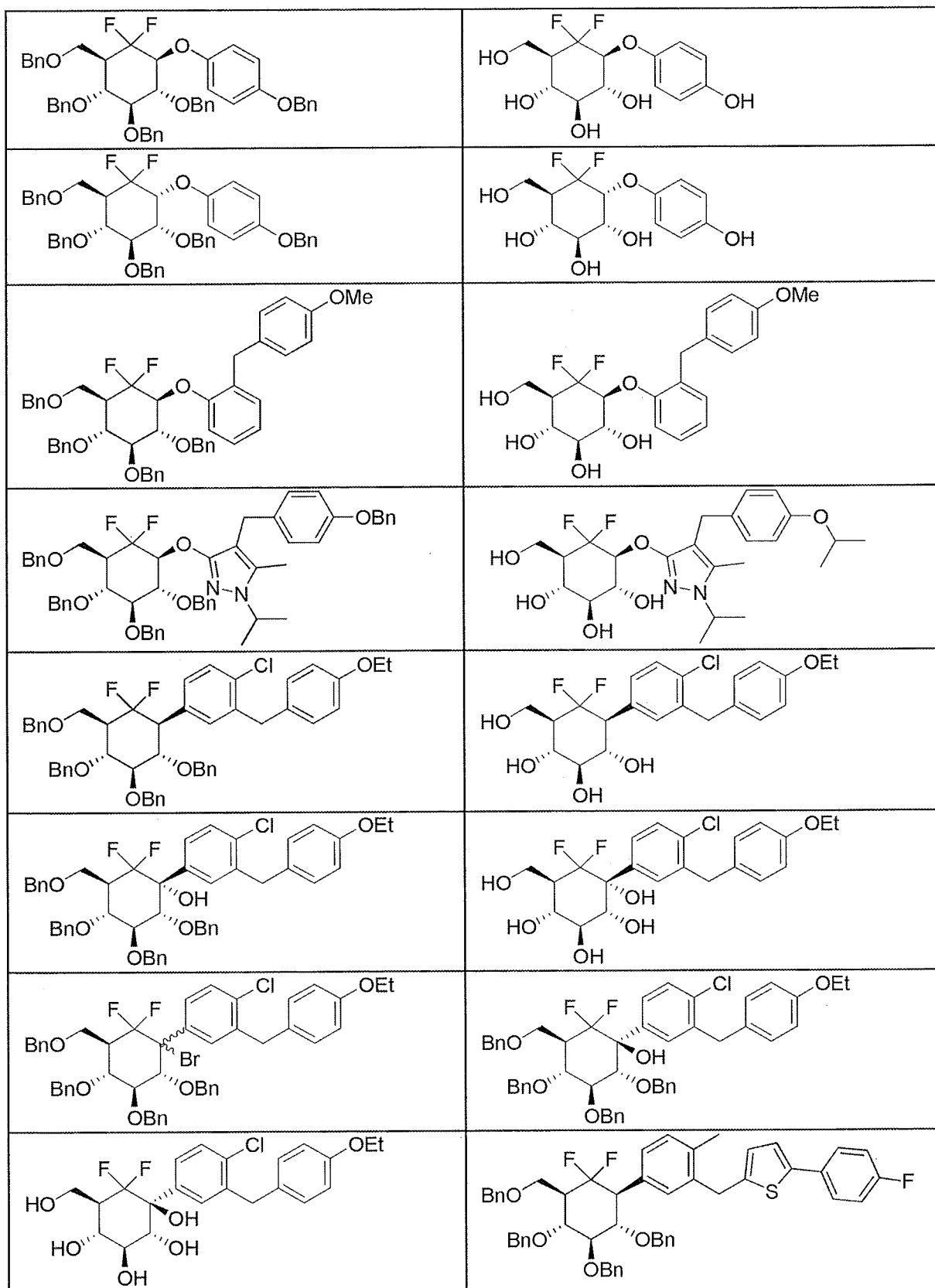
wherein:

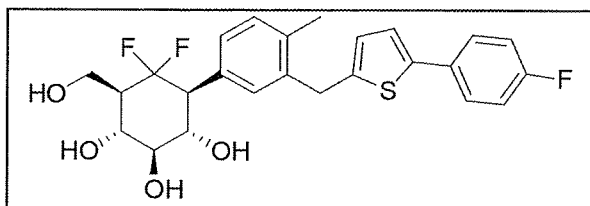
- 5 — R, R₁, R₂, R₃ and R₄ are as defined above, and
- X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀ and X₁₁ represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or
- 10 OSO₃R²⁴ group; advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴ and CONR²⁵R²⁶ group; more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-
- 15 alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴ and CO₂R²⁴ group; even more advantageously from the group consisting of a hydrogen atom, an halogen atom, a OH, (C₁-C₆)-alkyl and OR²⁴ group.

Examples within this second subclass include but are not limited to:



Compounds according to the invention can thus be selected from the following compounds:





Another object of this invention is a compound as defined above, for use as a drug, in particular as an inhibitor of the sodium-dependent glucose co-transporter, such as SGLT1, SGLT2 and SGLT3.

5 Within the meaning of this invention, “inhibitor of the sodium-dependent glucose co-transporter” is understood to mean a compound capable of inhibiting partially or totally the sodium-dependent glucose co-transporter.

More particularly, the compounds of the invention may be used for treating or preventing diabetes, and more particularly type-II diabetes, diabetes-related
10 complications, such as arteritis of the lower extremities, cardiac infarction, renal insufficiency, neuropathy or blindness, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, X syndrome and arteriosclerosis. The compounds of the invention are used in particular for treating or preventing diabetes.

The compounds of the invention may likewise be used as an anti-cancer, anti-
15 infective, anti-viral, anti-thrombotic or anti-inflammatory drug.

The invention likewise relates to a compound of the invention for its use in the treatment or prevention of diabetes, and more particularly type-II diabetes, diabetes-related complications, such as arteritis of the lower extremities, cardiac infarction, renal
20 insufficiency, neuropathy or blindness, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, X syndrome and arteriosclerosis, as well as for its use as an anti-cancer, anti-infective, anti-viral, anti-thrombotic or anti-inflammatory drug, and in particular in the treatment or prevention of diabetes.

The invention likewise relates to the use of a compound of the invention for the manufacture of a drug intended for the treatment or prevention of diabetes, and more
25 particularly type-II diabetes, diabetes-related complications, such as arteritis of the lower extremities, cardiac infarction, renal insufficiency, neuropathy or blindness, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, X syndrome and arteriosclerosis, as well as for the manufacture of an anti-cancer, anti-infective, anti-

viral, anti-thrombotic or anti-inflammatory drug, and in particular for the treatment or prevention of diabetes.

The invention likewise relates to a method for the treatment or prevention of diabetes, and more particularly type-II diabetes, diabetes-related complications, such as arteritis of the lower extremities, cardiac infarction, renal insufficiency, neuropathy or blindness, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, X syndrome and arteriosclerosis, as well as for an anti-cancer, anti-infective, anti-viral, anti-thrombotic or anti-inflammatory treatment, and in particular in for the treatment or prevention of diabetes, including the administration of an effective amount of at least one compound of the invention to a patient in need thereof.

Silylated compounds of the present invention, as well as compounds with $R = CH_2OBn$, $R_1 = OBn$, $R_2 = OBn$ and/or $R_3 = OBn$, will not be preferred for their use as medicament.

The compounds useful as a drug, and notably in the treatment or prevention of diabete, are more particularly the compounds of formula (Ia) or (Ib), and in particular (Ia); notably the compounds of formula (I-2) to (I-5), such as (I-2a) to (I-5a) and (I-2b) to (I-5b), and in particular (I-2a) to (I-5a).

Another object of this invention is the cosmetic use of a compound of the invention as defined above, for lightening, bleaching, depigmenting the skin, removing blemishes from the skin, particularly age spots and freckles, or preventing pigmentation of the skin, or as antioxidant, via topical application in particular.

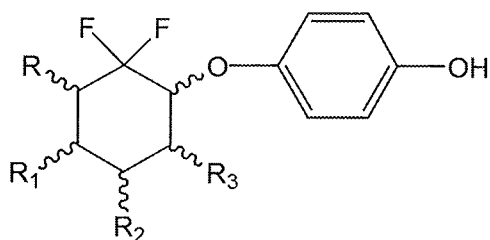
The present invention relates thus to a method for lightening, bleaching, depigmenting the skin, removing blemishes from the skin, particularly age spots and freckles, or preventing pigmentation of the skin, comprising the topical application of at least one compound of the invention.

Silylated compounds of the present invention, as well as compounds with $R = CH_2OBn$, $R_1 = OBn$, $R_2 = OBn$ and/or $R_3 = OBn$, will not be preferred for their cosmetic use.

The compounds useful in the cosmetic field, in particular as depigmenting or lightening agents, are more particularly the compounds of formula (Ia), (Ib) or (Ic), and

in particular (Ic); notably the compounds of formula (I-1), such as (I-1a), (I-1b) and (I-1c), and more particularly (I-1c).

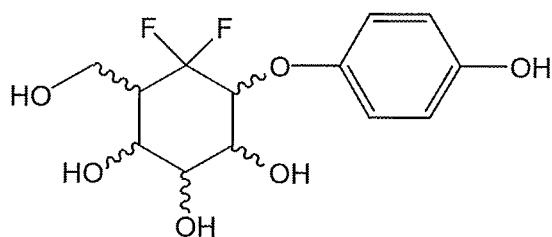
In particular, compounds with depigmenting activity are tyrosinase inhibitors. They are in particular compounds of the following formula:



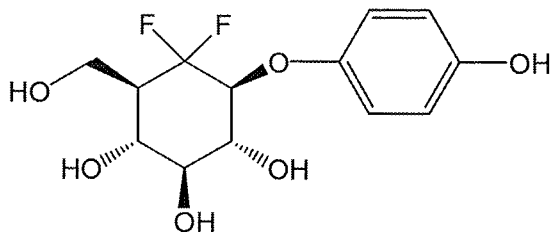
5

, and preferably a compound of the following

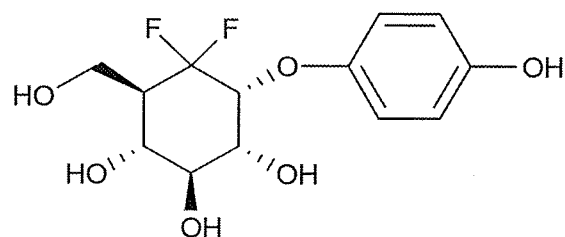
formula:



, such as:



and



10

Another object of this invention is a pharmaceutical or cosmetic composition including at least one compound of the invention as defined above and at least one pharmaceutically or cosmetically acceptable vehicle.

The compounds according to the invention can be administered orally, sublingually, parenterally, subcutaneously, intramuscularly, intravenously, transdermally, locally or rectally.

15

In the pharmaceutical compounds of this invention, for oral, sublingual, parenteral, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active ingredient can be administered in unit forms of administration, mixed together with conventional pharmaceutical carriers, for animals or human beings.

- 5 Suitable unit forms of administration include oral forms such as tablets, gel capsules, powders, granules and oral solutions or suspensions, sublingual or buccal forms of administration, parenteral, subcutaneous, intramuscular, intravenous, intranasal or intraocular forms of administration and rectal forms of administration.

10 When a solid composition is prepared in the form of tablets, the principal active ingredient is mixed with a pharmaceutical vehicle such as gelatine, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose or other suitable materials or else treated in such a way that they have an extended or delayed activity and continuously release a predetermined amount of active principle.

15 A gel capsule preparation is obtained by mixing the active ingredient with a diluent and by pouring the mixture obtained into soft or hard capsules.

A preparation in the form of a syrup or elixir can contain the active ingredient in conjunction with a sweetening agent, antiseptic, as well as a flavour-producing agent and appropriate colouring agent.

20 Powders or granules dispersible in water can contain the active ingredient mixed together with dispersing agents, wetting agents, or suspending agents, as well as with taste correctors or sweetening agents.

For rectal administration, suppositories are used, which are prepared with binding agents melting at rectal temperature, e.g., cocoa butter or polyethylene glycols.

25 For parenteral, intranasal or intraocular administration, aqueous suspensions are used, isotonic saline solutions or sterile and injectable solutions, which contain pharmacologically compatible dispersing agents and/or wetting agents.

The active principle can also be formulated as microcapsules, possibly with one or more additive carriers.

30 The compounds of the invention can be used at doses of between 0.01 mg and 1000 mg per day, given in a single dose once a day or administered in several doses throughout the day, e.g., twice daily in equal doses. The daily dose administered is advantageously between 0.1 mg and 100 mg, even more advantageously between

2.5 mg and 50 mg. It may be necessary to use doses exceeding these ranges, of which those skilled in the art will themselves be aware.

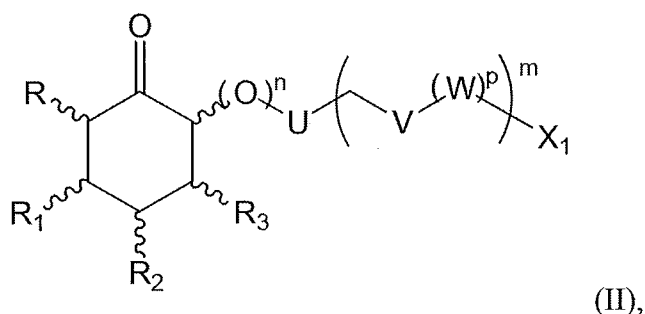
In one particular embodiment of the invention, the pharmaceutical or cosmetic composition can also be formulated for topical administration. It may be introduced in forms commonly known for this type of administration, i.e., in particular, lotions, foams, gels, dispersions, sprays, shampoos, serums, masks, body milks or creams, for example, with excipients enabling, in particular, penetration of the skin so as to improve the properties and accessibility of the active principle. Besides the composition according to the invention, these compositions generally further contain a physiologically acceptable medium, which generally contains water or a solvent, e.g., alcohols, ethers or glycols. They can also contain surface-active agents, preservatives, stabilizers, emulsifiers, thickeners, other active principles producing a complementary or possibly synergic effect, trace elements, essential oils, perfumes, colouring agents, collagen, chemical or mineral filters, hydrating agents or thermal waters.

In one particular embodiment, the pharmaceutical composition of the invention may include at least one other active principle, in addition to the compound of the invention.

Examples of active principles that can be cited are antidiabetic agents, such as sulfonylurea-type compounds which are hypoglycemic sulfamides which increase insulin secretion like, e.g., chlorpropamide, tolbutamide, tolazamide, glipizide, gliclazide, glibenclamide, gliquidone and glimepiride, biguanides which reduce the hepatic glyconeogenesis and the insulin resistance like metformine, thiazolidinediones (also called glitazones) which increase the sensibility to insulin like rosiglitazone, pioglitazone and ciglitazone, alpha-glucosidases inhibitors which slow down the intestinal absorption of carbohydrates like acarbose, miglitol and voglibose, meglitinides (also called glitinides) which increase insulin pancreatic secretion like repaglinide and nateglinide, incretin mimics like exenatide or dipeptidylpeptidase-4 (DPP4) inhibitors like sitagliptin, vildagliptin and insulin, or antilipidic agents, such as statins which reduce cholesterol by inhibiting the enzyme HMG-CoA reductase like atorvastatin and cerivastatin, fibrates like bezafibrate, gemfibrozil and fenofibrate, or ezetimibe.

The present invention concerns also processes for preparing a compound according to the invention.

The present invention concerns thus a process for preparing a compound of formula (I) according to the invention for which $R_4 = H$ comprising the fluorination of a compound of the following formula (II):



wherein R , R_1 , R_2 , R_3 , X_1 , U , V , W , n , m and p are as defined above.

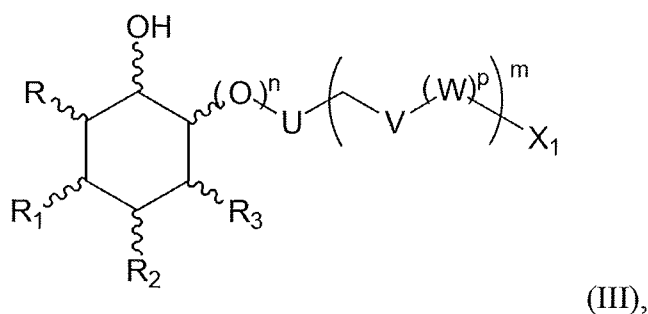
The fluorination will be carried out in the presence of a fluorinating agent, such as DAST (diethylaminosulphurtrifluoride).

If necessary additional steps of protection, deprotection, substitution, etc. can be carried out, these steps being well known to the person skilled in the art.

The compound of formula (I) obtained can be recovered by separation from the reaction medium by methods well known to the person skilled in the art, such as by extraction, evaporation of the solvent or by precipitation or crystallisation (followed by filtration).

The compound can be also purified if necessary by methods well known to the person skilled in the art, such as by recrystallisation, by distillation, by chromatography on a column of silica gel or by high performance liquid chromatography (HPLC).

The compound of formula (II) can be prepared by oxidation of a compound of the following formula (III):

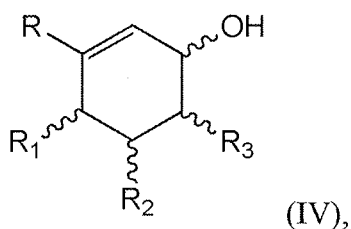


wherein R, R₁, R₂, R₃, X₁, U, V, W, n, m and p are as defined above.

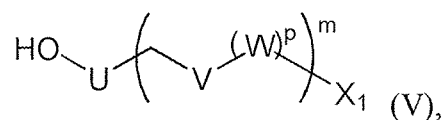
The oxidation will be carried out in the presence of an oxidant according to procedures well known to the person skilled in the art. The oxidant can be for example Dess-Martin periodinane, PCC (Pyridinium chlorochromate), etc.

When n = 1, the process for preparing the compound of formula (III) can comprise the following successive steps:

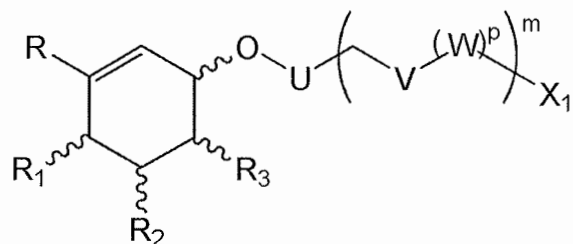
(a1) coupling between a compound of the following formula (IV):



wherein R, R₁, R₂ and R₃ are as defined above,
and a compound of the following formula (V):



wherein X₁, U, V, W, m and p are as defined above,
to give a compound of the following formula (VI):



(VI),

wherein R, R₁, R₂, R₃, X₁, U, V, W, m and p are as defined above, and

- (b1) hydroboration-oxidation reaction of the compound of formula (VI) obtained in previous step (a1) to give a compound of formula (III) with n = 1.

5

Step (a1) can be carried out in the conditions of the Mitsunobu reaction well known to the person skilled in the art, notably using DEAD (diethyl azo dicarboxylate), DIAD (diisopropyl azo dicarboxylate) or ADDP (azodicarboxylic acid dipiperidine) as coupling agent and PPh₃ or P(nBu)₃ as phosphine.

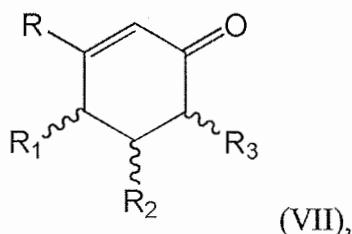
10

Step (b1) can be carried out in conditions well known to the person skilled in the art, notably by reaction with a borane such as BH₃, and in particular BH₃.THF or BH₃.Me₂S, in a solvent such as THF, followed by the addition of hydrogen peroxide in the presence of a base such as sodium hydroxide.

15

When n = 0, the process for preparing the compound of formula (III) can comprise the following successive steps:

- (a2) coupling between a compound of the following formula (VII):

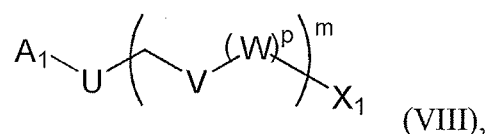


(VII),

wherein R, R₁, R₂ and R₃ are as defined above,

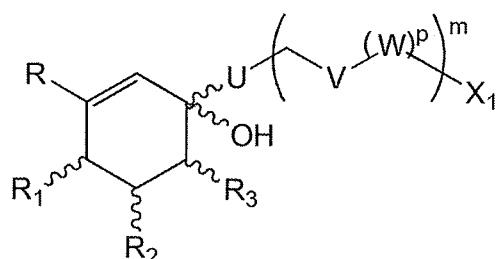
20

and a compound of the following formula (VIII):



wherein X_1 , U , V , W , m and p are as defined above and A_1 represents $-\text{Li}$ or $-\text{Mg-Hal}$, Hal being a halogen atom,

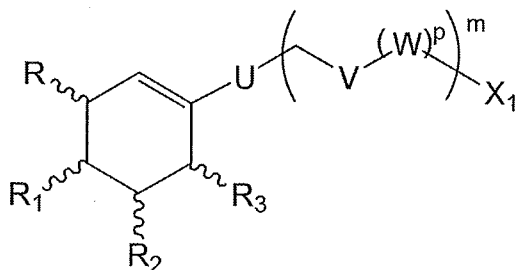
to give a compound of the following formula (IX):



(IX),

wherein R , R_1 , R_2 , R_3 , X_1 , U , V , W , m and p are as defined above,

- (b2) reduction of the compound of formula (IX) obtained in previous step (a2) to give a compound of the following formula (X):



(X),

wherein R , R_1 , R_2 , R_3 , X_1 , U , V , W , m and p are as defined above, and

- (c2) hydroboration-oxidation reaction of the compound of formula (X) obtained in previous step (b2) to give a compound of formula (III) with $n = 0$.

Step (a2) can be carried out through the reaction of compound of formula (VIII) obtained from the halogenated derivative by reaction with magnesium to form the Grignard reagent or by halogen exchange using a lithium base such as *n*-butyllithium to form the corresponding lithiated compound, with compound of formula (VII), in a solvent such as THF.

Such compound of formula (VII) is obtained in conditions well known to the person skilled in the art, and notably according to a process described in EP0240175 or *Carbohydrate Research* **2010**, 345, 1056-1060.

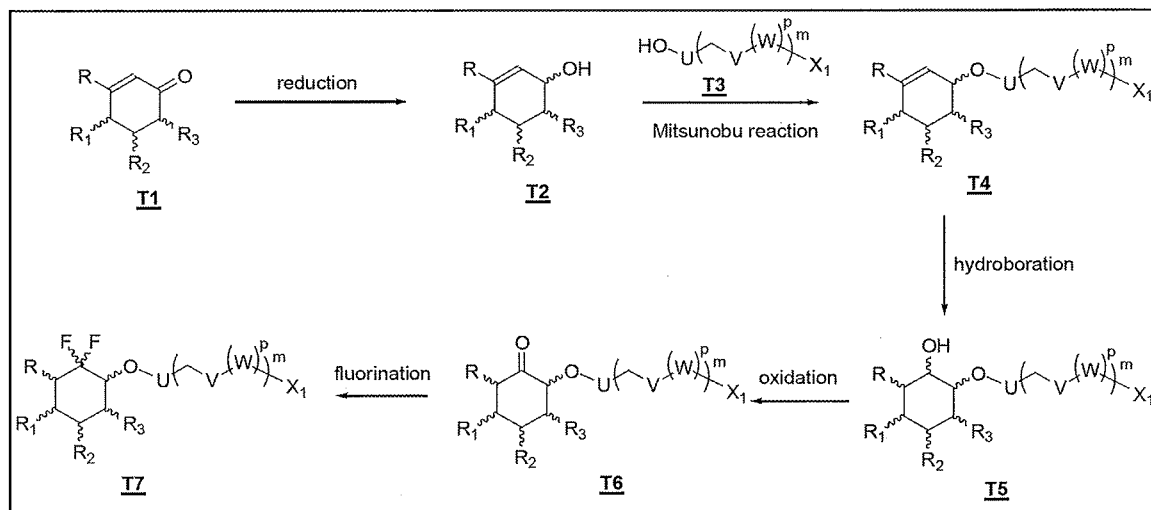
- 5 The compound of formula (VIII) can be obtained from the halogenated derivative by reaction with magnesium to form the Grignard reagent or by halogen exchange using a lithium base such as n-butyllithium to form the corresponding lithiated compound.

Step (b2) can be carried out in the presence of a reducing agent such as Et_3SiH and a Lewis acid such as $\text{BH}_3\cdot\text{Et}_2\text{O}$.

Step (c2) corresponds to previous step (b1).

The process to prepare compounds according to the invention with $\text{R}_4 = \text{H}$ will be better detailed below and in the following experimental part.

Scheme A: Synthetic pathway for compounds of the first embodiment (wherein $n=1$)



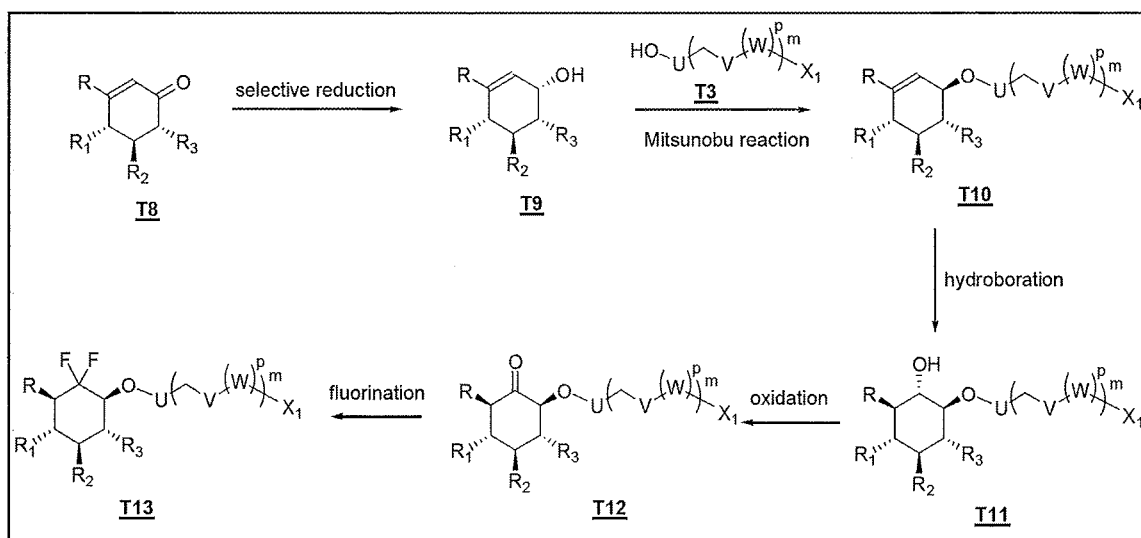
- (a) In a first step cyclohexenone **T1** undergoes a reduction involving standard conditions such as NaBH_4 , $\text{NaBH}_4/\text{CeCl}_3$, LiAlH_4 or L-selectride.
- (b) A Mitsunobu-coupling reaction between compound **T2** and alcohol **T3** then occurs under standard conditions using DEAD, DIAD or ADDP as coupling agent and PPh_3 or P(nBu)_3 as phosphine.

(c) Hydroboration of compound **T4** using $\text{BH}_3\cdot\text{THF}$ or $\text{BH}_3\cdot\text{Me}_2\text{S}$ leads to compound **T5**.

(d) The alcohol function of compound **T5** is oxidized into a ketone according to typical procedures involving PCC, Dess-Martin periodinane yielding compound **T6**.

(e) Compound **T6** can be fluorinated using fluorinating agent such as DAST to afford the difluorocarbasugar **T7**. In a last step, protective groups can be removed according to typical procedures described in Protective groups (*Protective groups in organic synthesis*, T. W. Greene).

More particularly:



(a) In a first step cyclohexenone **T8** undergoes a regioselective reduction involving lithium tri-sec-butylborohydride as described in *Can. J. Chem* **2004**, 82, 1361-1364.

(b) A Mitsunobu-coupling reaction between compound **T9** and alcohol **T3** then occurs under standard conditions using DEAD, DIAD or ADDP as coupling agent and PPh_3 or $\text{P}(\text{nBu})_3$ as phosphine.

(c) Hydroboration of compound **T10** using $\text{BH}_3\cdot\text{THF}$ or $\text{BH}_3\cdot\text{Me}_2\text{S}$ leads to compound **T11**.

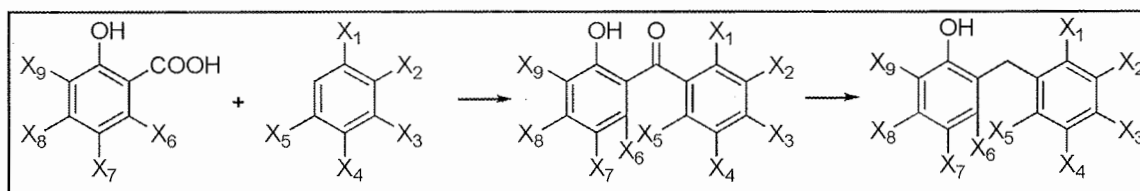
(d) The alcohol function of compound **T11** is oxidized into a ketone according to typical procedures involving PCC, Dess-Martin periodinane yielding compound **T12**.

(e) Compound **T12** can be fluorinated using fluorinating agent such as DAST to afford the difluorocarbasugar **T13**. In a last step, protective groups can be removed according to typical procedures described *Protective groups in organic synthesis*, T. W. Greene.

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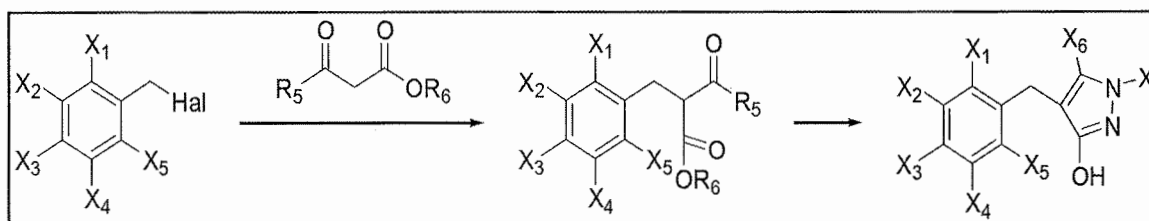
Cyclohexenone **T8** was prepared according to EP0240175 or Cumpstey, I. *Carbohydrate Research* **2010**, 345, 1056-1060, applying the synthesis to the glucose series from the commercially available 2,3,4,6-O-benzyl-D-glucopyranose.

10 Compound **T3** can be either commercially available (*first subclass*) or synthesized according to:



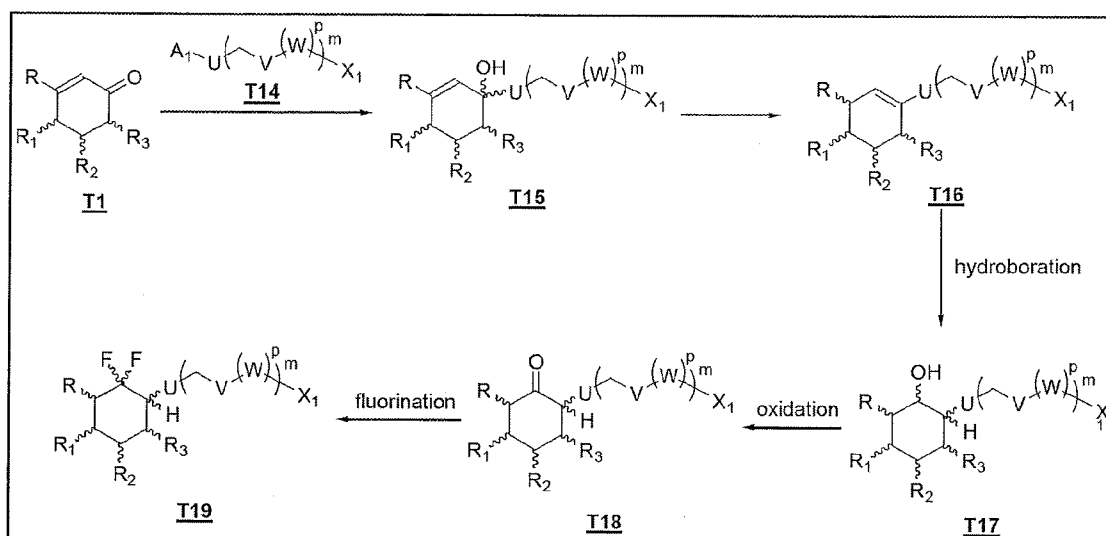
(*second subclass*)

15 Or



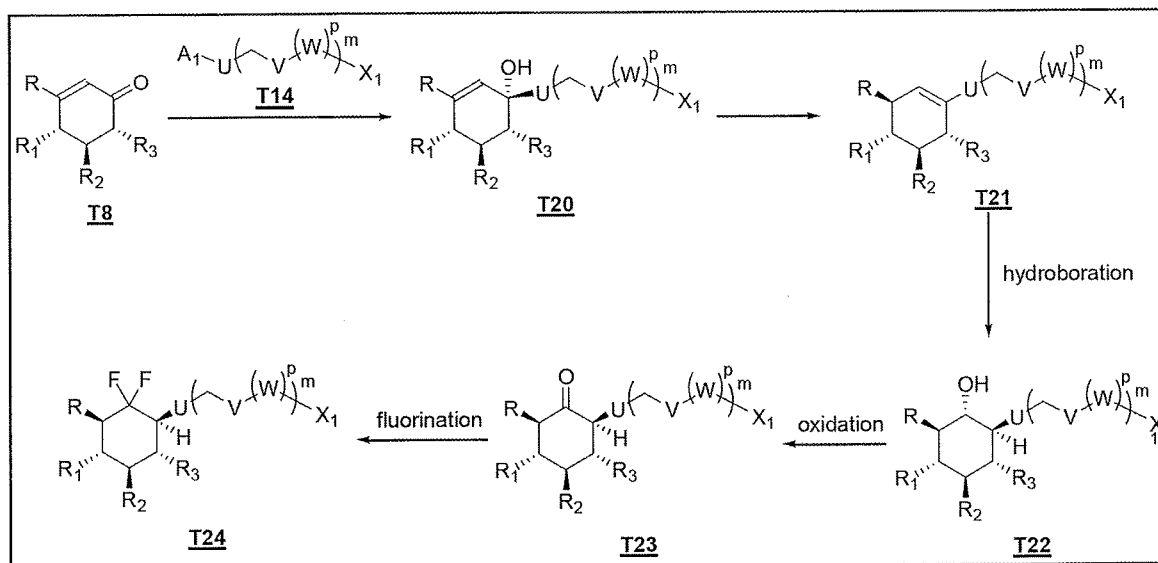
(R₅ and R₆ representing a (C₁-C₆)alkyl group) (*third subclass*)

20 **Scheme B:** Synthetic pathway for compounds of the second embodiment (wherein n=0 and R₄=H)



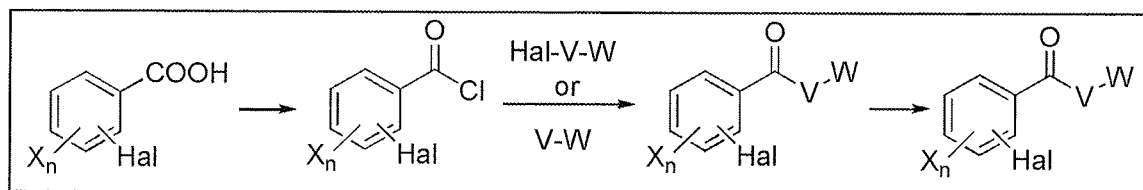
- (a) In a first step, a Grignard reagent or a lithiated compound **T14**, prepared from the corresponding halogenated compound according to a typical procedure, is added onto cyclohexenone **T1**.
- (b) In the next step of the synthesis, compound **T15** is treated with a reducing agent such as Et_3SiH in the presence of a Lewis acid such as $BF_3 \cdot Et_2O$, yielding compound **T16**.
- (c) Hydroboration of compound **T16** using $BH_3 \cdot THF$ or $BH_3 \cdot Me_2S$ leads to compound **T17**.
- (d) The alcohol function of compound **T17** is oxidized into a ketone according to typical procedures involving PCC, Dess-Martin periodinane yielding compound **T18**.
- (e) Compound **T18** can be fluorinated using fluorinating agent such as DAST to afford the difluorocarb sugar **T19**. In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

And more particularly:

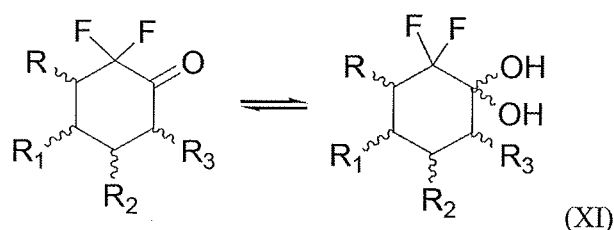


- (a) In a first step, a Grignard reagent or a lithiated compound **T14**, prepared from the corresponding halogenated compound according to a typical procedure, is added onto cyclohexenone **T8**.
- (b) In the next step of the synthesis, compound **T20** is treated with a reducing agent such as Et_3SiH in the presence of a Lewis acid such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, yielding compound **T21**.
- (c) Hydroboration of compound **T21** using $\text{BH}_3 \cdot \text{THF}$ or $\text{BH}_3 \cdot \text{Me}_2\text{S}$ leads to compound **T22**.
- (d) The alcohol function of compound **T22** is oxidized into a ketone according to typical procedures involving PCC, Dess-Martin periodinane yielding compound **T23**.
- (e) Compound **T23** can be fluorinated using fluorinating agent such as DAST to afford the difluorocarbasugar **T24**. In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

Halogenated compound giving access to compound **T14** can be synthesized according to the following scheme:



The present invention concerns also a process for preparing a compound of the formula (I) according to the invention for which $n = 0$ and $R_4 \neq H$ comprising the coupling of a compound of formula (VIII) as defined above and a compound of the following formula (XI)



wherein R , R_1 , R_2 , and R_3 are as defined above,

to give a compound of formula (I) for which $n = 0$ and $R_4 = OH$,

followed optionally by the substitution of the OH function to give a compound of formula (I) for which $n = 0$ and $R_4 = \text{halogen}$, $OSiR^iR^kR^l$, OR^{21} , $OCOR^{21}$, OCO_2R^{21} , or $OCONR^{22}R^{23}$.

These steps of coupling and substitution can be carried out in conditions well known to the person skilled in the art.

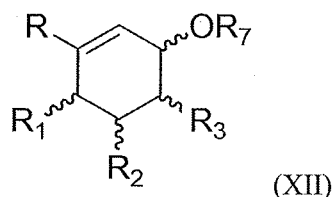
If necessary additional steps of protection, deprotection, substitution, etc. can be carried out, these steps being well known to the person skilled in the art.

The compound of formula (I) obtained can be recovered by separation from the reaction medium by methods well known to the person skilled in the art, such as by extraction, evaporation of the solvent or by precipitation or crystallisation (followed by filtration).

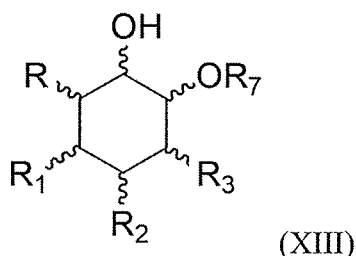
The compound can be also purified if necessary by methods well known to the person skilled in the art, such as by recrystallisation, by distillation, by chromatography on a column of silica gel or by high performance liquid chromatography (HPLC).

The process for preparing the compound of formula (XI) can comprise the following successive steps:

- (a3) hydroboration-oxidation reaction of the compound of formula (XII)

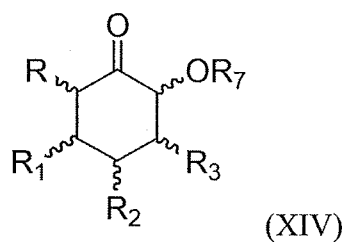


wherein R, R₁, R₂, and R₃ are as defined above and R₇=SiR^{a1}R^{b1}R^{c1} or CH₂OCH₃ (methoxymethyl - MOM), with R^{a1}, R^{b1} and R^{c1} each representing independently a (C₁-C₆)-alkyl, aryl or aryl-(C₁-C₆)-alkyl group, to give a compound of the following formula (XIII)



wherein R, R₁, R₂, and R₃ are as defined above and R₇=SiR^{a1}R^{b1}R^{c1} or CH₂OCH₃ (methoxymethyl - MOM),

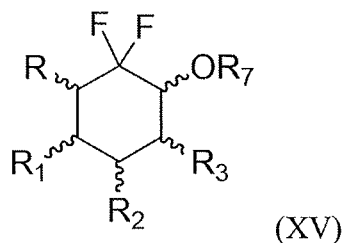
- (b3) oxidation of the compound of formula (XIII) obtained in previous step (a3) to give a compound of the following formula (XIV)



wherein R, R₁, R₂, and R₃ are as defined above and R₇=SiR^{a1}R^{b1}R^{c1} or CH₂OCH₃ (methoxymethyl - MOM),

- (c3) when R₇=SiR^{a1}R^{b1}R^{c1}, deprotection of the compound of formula (XIV) obtained in previous step (b3) to give a compound of formula (XIV) with R₇=H,
- (d3) when R₇=H, protection of the compound of formula (XIV) with R₇=H obtained in previous step (c3) to give a compound of formula (XIV) with R₇=COR₈ with R₈ representing a (C₁-C₆)-alkyl, aryl or aryl-(C₁-C₆)-alkyl group,

- (e3) fluorination of the compound of formula (XIV) with $R_7 = \text{COR}_8$ or CH_2OCH_3 obtained in previous step (d3) or (b3) to give a compound of the following formula (XV)



- 5 wherein R, R_1 , R_2 , and R_3 are as defined above and $R_7 = \text{COR}_8$ or CH_2OCH_3 ,
- (f3) deprotection of the compound of formula (XV) with $R_7 = \text{COR}_8$ or CH_2OCH_3 obtained in previous step (e3) to give a compound of formula (XV) with $R_7 = \text{H}$, and
- (g3) oxidation of the compound of formula (XV) with $R_7 = \text{H}$ obtained in previous
- 10 step (f3) to give a compound of formula (XI).

Step (a3) corresponds to previous step (b1). Compound of formula (XII) can be prepared from compound of formula (IV) by a protection step, well known to the person skilled in the art.

- 15 Steps (b3) and (g3) can be carried out in the presence of an oxidant such as Dess-Martin periodinane, PCC (Pyridinium chlorochromate), etc.

Steps (c3) and (d3) are optional and required only when $R_7 = \text{SiR}^{\text{a1}}\text{R}^{\text{b1}}\text{R}^{\text{c1}}$ in the starting material of formula (XII).

- Step (c3), (d3) and (f3) can be carried out in conditions well known to the
- 20 person skilled in the art.

Step (e3) can be carried out in the presence of a fluorinating agent, such as DAST (diethylaminosulphurtrifluoride).

- The present invention concerns also a process for preparing a compound of formula (I)
- 25 according to the invention for which $R_4 = \text{H}$ comprising the following steps:

- (a4) bromination of a compound of formula (I) with $R_4 = \text{OH}$ to give a compound of formula (I) with $R_4 = \text{Br}$, and

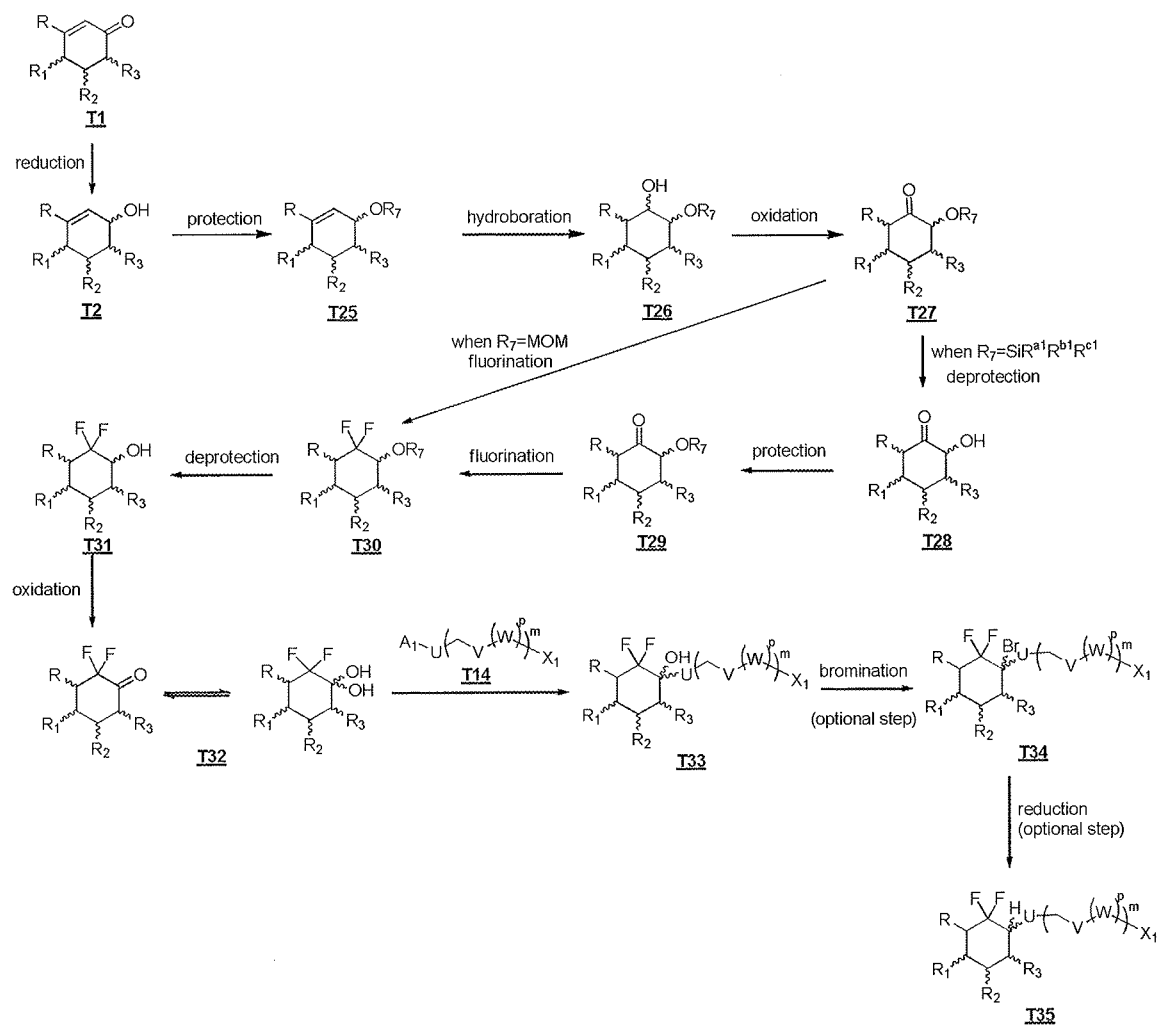
- (b4) reduction of the compound of formula (I) with $R_4 = \text{Br}$ obtained in previous step (a4) to give a compound of formula (I) with $R_4 = \text{H}$.

Step (a4) can be carried out in the presence of a brominating agent such as SOBr_2 . The reaction is advantageously carried out also in the presence of a base such as pyridine. The starting material can be prepared according to the process described above to prepare compounds of formula (I) with $R_4 \neq \text{H}$.

Step (b4) can be carried out in the presence of a hydride such as Bu_3SnH .

The process to prepare compounds according to the invention with $n = 0$ and $R_4 = \text{OH}$ or H will be better detailed below and in the following experimental part.

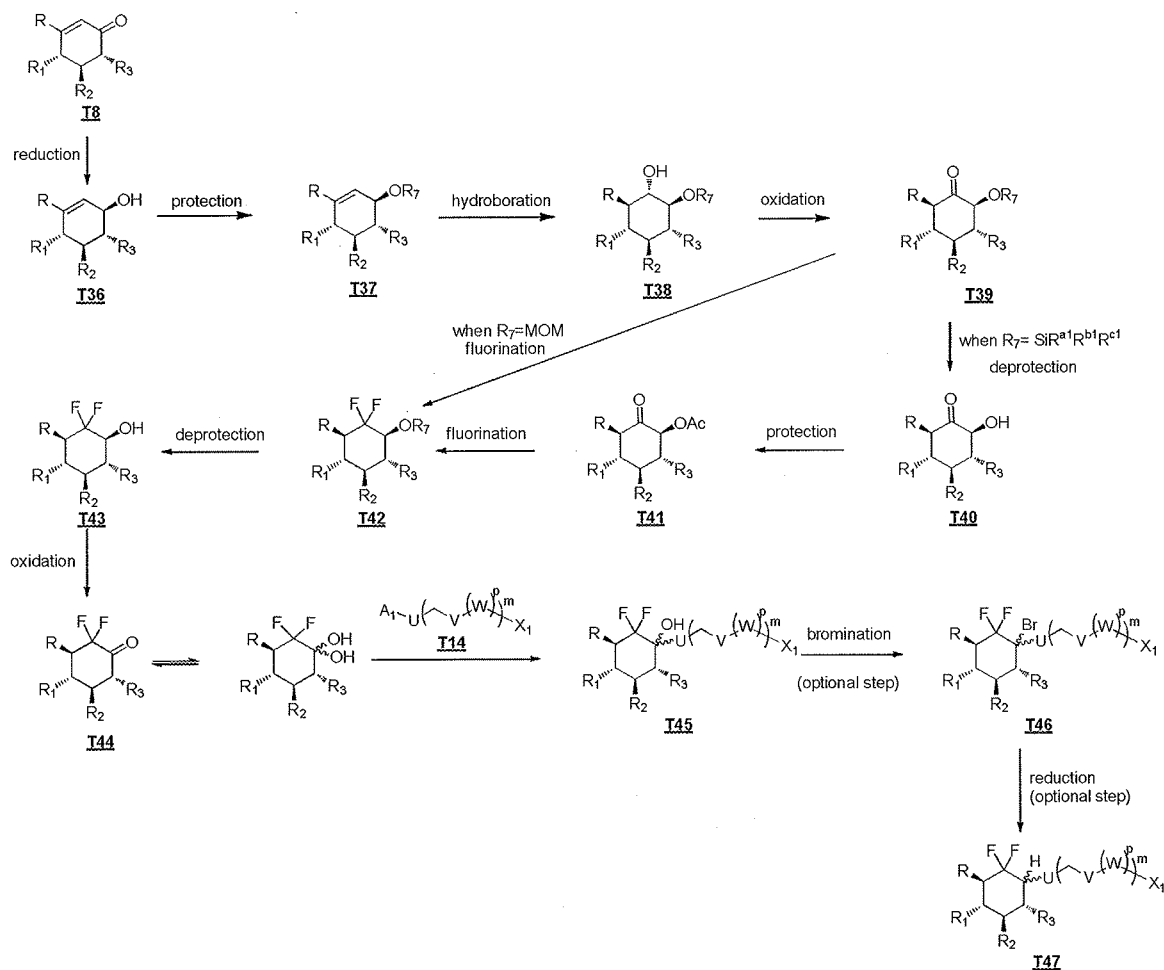
Scheme C: Synthesis of compounds with $n=0$ and $R_4=\text{OH}$ or H



- (a) In a first step cyclohexenone **T1** undergoes a reduction involving standard conditions such as NaBH₄, NaBH₄/CeCl₃, LiAlH₄ or L-selectride.
- (b) Alcohol **T2** is then protected in the form of a silyl ether, according to well known procedures described in *Protective groups in organic synthesis*, T. W. Greene, to give compound **T25**.
- (c) Hydroboration of compound **T25** using BH₃.Me₂S or BH₃.THF leads to compound **T26**.
- (d) Compound **T26** is then oxidized into the corresponding ketone **T27** according to typical procedures involving PCC, Dess-Martin periodinane, etc.
- (e) When **T27** bears a R₇ which is a silylated protective group, this silylated protective group of compound **T27** is then removed under acidic conditions using typical procedures described in *Protective groups in organic synthesis*, T. W. Greene, to afford alcohol **T28**.
- (f) This alcohol **T28** is protected into an ester according to well known procedures described in *Protective groups in organic synthesis*, T. W. Greene, to give compound **T29**.
- (g) Compound **T27** (when R₇ = MOM) or **T29** is fluorinated using a fluorinated reagent such as DAST to afford the fluorinated compound **T30**.
- (h) The ether or ester protective group (OR₇) of compound **T30** is removed under typical conditions described in *Protective groups in organic synthesis*, T. W. Greene, to afford alcohol **T31**.
- (i) This alcohol **T31** is then oxidized using Dess-Martin periodinane to afford compound **T32**.
- (j) A Grignard reagent or lithiated compound **T14**, prepared from the corresponding halogenated compound according to a typical procedure, is added onto compound **T32** to afford **T33**.
- (k) Compound **T33** is brominated according to typical procedures including the use of SOBr₂ followed by the addition of pyridine to afford compound **T34**.
- (l) Compound **T34** is then reduced in the presence of a hydride such as Bu₃SnH.
- (m) In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

It should be noted that steps (k) and (l) are carried out only for the preparation of a compound of formula (I) with $R_4 = H$.

And more particularly:



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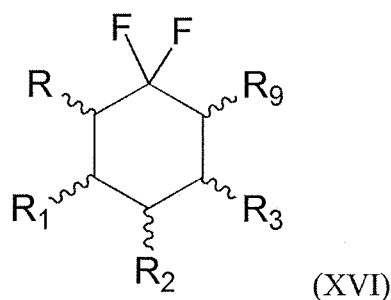
- (a) In a first step cyclohexenone **T8** undergoes a selective reduction involving $NaBH_4/CeCl_3$, in THF and MeOH.
- (b) Alcohol **T36** is then protected using imidazole and TBDMSCl to give compound **T37** with $R_7 = TBDMS$; or dimethoxymethane and P_2O_5 to give compound **T37** with $R_7 = CH_2OCH_3$.
- (c) Hydroboration of compound **T37** using $BH_3 \cdot Me_2S$ leads to compound **T38**.
- (d) Compound **T38** is then oxidized into the corresponding ketone **T39** according to typical procedures involving PCC, Dess-Martin periodinane, etc.

10

- (e) When R_7 =TBDMS, this silylated protective group of compound **T39** is then removed under acidic conditions such as HCl 12N in methanol and dichloromethane to afford alcohol **T40**.
- (f) This alcohol **T40** is protected into an acetate using Ac_2O , pyridine and a catalytic amount of DMAP (Dimethylaminopyridine) to give compound **T41**.
- (g) Compound **T41** or compound **T39** with $R_7=CH_2OCH_3$ is fluorinated using DAST in dichloromethane to afford the fluorinated compound **T42**.
- (h) When $R_7 = Ac$, the acetate protecting group of compound **T42** is removed using sodium methanolate in methanol to afford alcohol **T43**.
- (i) When $R_7 = CH_2OCH_3$, the MOM protective group of **T42** is removed using TFA in dichloromethane to afford alcohol **T43**.
- (j) This alcohol **T43** is then oxidized using Dess-Martin periodinane to afford compound **T44**.
- (k) A Grignard reagent or a lithiated compound **T14**, prepared from the corresponding halogenated compound according to a typical procedure, is added onto compound **T44** to give compound **T45**.
- (l) Compound **T45** is brominated with $SOBr_2$ in dichloromethane followed by the addition of pyridine to afford compound **T46**.
- (m) Compound **T46** is then reduced in the presence of Bu_3SnH in toluene to give compound **T47**.
- (n) In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

It should be noted that steps (k) and (l) are carried out only for the preparation of a compound of formula (I) with $R_4 = H$.

The present invention concerns also a process for preparing a compound of formula (I) according to the invention for which $R_4 = H$ and $n=1$ comprising a coupling reaction between a compound of the following formula (XVI):



wherein R, R₁, R₂, and R₃ are as defined above and R₉ represents a leaving group, with a compound of formula (V) as defined above.

5 The term “leaving group” as used in the present invention refers to a chemical group which can be easily replaced with a nucleophile during a nucleophile substitution reaction, the nucleophile being in the present case an alcohol, i.e. a molecule carrying a group OH. Such a leaving group can be in particular a halogen atom or a sulfonate. The sulfonate is in particular a group –OSO₂-R₁₀ with R₁₀ representing a (C1-C6alkyl),
 10 aryl, aryl-(C1-C6)-alkyl or (C1-C6)-alkyl-aryl group. The sulfonate can be in a mesylate (CH₃-S(O)₂O-), a triflate (CF₃-S(O)₂O-) or a tosylate (p-Me-C₆H₄-S(O)₂O-).

This reaction can be carried out in conditions well known to the person skilled in the art, notably in the presence of a base such as NaH, K₂CO₃, or MeONa.

15 If necessary, additional steps of protection, deprotection, substitution, etc. can be carried out, these steps being well known to the person skilled in the art.

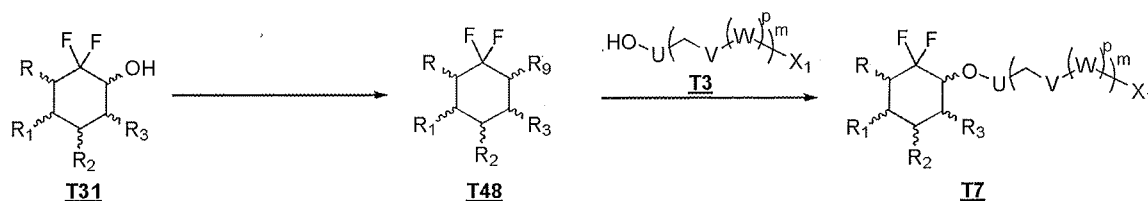
The compound of formula (I) obtained can be recovered by separation from the reaction medium by methods well known to the person skilled in the art, such as by extraction, evaporation of the solvent or by precipitation or crystallisation (followed by
 20 filtration).

The compound can be also purified if necessary by methods well known to the person skilled in the art, such as by recrystallisation, by distillation, by chromatography on a column of silica gel or by high performance liquid chromatography (HPLC).

25 The compound of formula (XVI) can be prepared from a compound of formula (XV) wherein R₇=H according to procedures well known to the person skilled in the art. For example, when the leaving group is a halogen atom, the reaction can be carried out in the presence of a halogenating agent. When the leaving group is a sulfonate, the

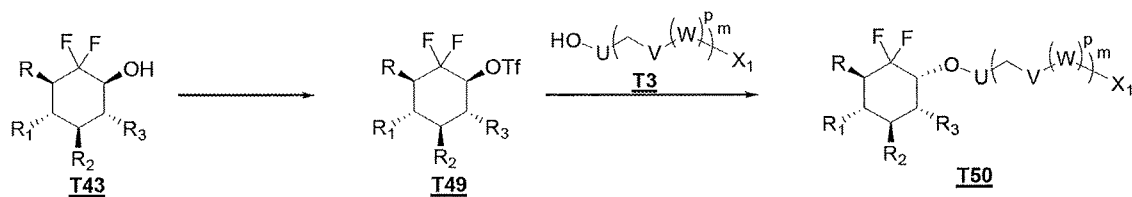
reaction can be carried out in the presence of the corresponding sulfonic acid and a base such as pyridine.

The process to prepare compounds according to the invention with $n = 1$ and $R_4 = H$ will be better detailed below and in the following experimental part.



- (a) In a first step, the alcohol group of **T31** is converted into a leaving group such as a halogen or a mesyl, tosyl or trifluoromethanesulfonyl group according to procedures well known of the person skilled in the art.
- (b) **T48** is then substituted by the alcoholate generated from **T3** by the use of a base such as NaH, K_2CO_3 , or MeONa, to afford **T7**.
- (c) In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

And more particularly:



- (a) In a first step, the alcohol group of **T43** is converted into its corresponding trifluoromethanesulfonyl group in the presence of trifluoromethanesulfonyl anhydride and pyridine to afford compound **T49**.
- (b) **T49** is then substituted by the alcoholate generated from **T3** by the use of NaH to give **T50**. The reaction is performed in dimethylformamide.
- (c) In a last step, protective groups can be removed according to typical procedures described in *Protective groups in organic synthesis*, T. W. Greene.

The invention will be better understood upon reading the following examples and figures, these examples serving solely to illustrate the invention.

FIGURES

5 Figure 1 represents urinary glucose excretion for compound **16** and for compound **50** between 0 and 8 hours following oral administration (3 mg/kg po).

Figure 2 represents urinary glucose excretion for compound **16** and for compound **50** between 16 and 28 hours following oral administration (3 mg/kg po).

10 Figure 3 represents oral glucose tolerance test for compound **16** at 1, 3 and 10 mg/kg po.

Figure 4 represents oral glucose tolerance test for compound **16** 18 hours post oral administration of compound **16** (3 mg/kg po).

Figure 5 represents urinary glucose excretion for compound **16** and for compound **50** between 16 and 28 hours following oral administration (3 mg/kg po).

15 Figure 6 represents urinary glucose excretion for compound **16** and for compound 9 of WO2009/1076550 between 16 and 28 hours following oral administration (3 mg/kg po).

Figure 7 represents the HPLC spectrum of compound **21**.

Figure 8 represents the HPLC spectrum of compound **26**.

20 Figure 9 represents the HPLC spectrum of compound **26** after 4h of incubation at 37°C in the presence of β -glucosidase.

Figure 10 represents the HPLC spectrum of Sergliflozin-A.

Figure 11 represents the HPLC spectrum of Sergliflozin-A after 4h of incubation at 37°C in the presence β -glucosidase.

25

EXAMPLES

1. Preparation of the compounds of the invention

The abbreviations encountered are defined as follows:

30 Ac acetyl
 ADDP azodicarboxylic acid dipiperidine
 Bn benzyl

	cat.	Catalytic
	DAST	diethylaminosulphurtrifluoride
	DCM	dichloromethane
	de	diastereomeric excess
5	DMAP	4-Dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	eq.	equivalent
	ESI	electrospray ionisation
10	g	gram
	Hz	Hertz
	mg	milligram
	MHz	megahertz
	min.	minute
15	mL	milliliter
	mmol	millimole
	mM	millimolar
	μ mol	micromole
	nmol	nanomole
20	NMR	Nuclear Magnetic Resonance
	po	per os
	PEG	Polyethylene glycol
	QS	Quantum Satis
	Rf	rate of flow
25	rt	room temperature
	TFAA	trifluoroacetic anhydride
	THF	tetrahydrofuran
	TLC	Thin layer Chromatography
	TMS	trimethylsilyl
30	TBDMS	Tert-butyldimethylsilyl

The features of the devices used to conduct analyses of all of the compounds described in this application are indicated herein below:

The ^{19}F NMR spectra were recorded on BRUKER DPX 300 spectrometer. The internal reference used is fluorotrichloromethane CFCl_3 . Chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants (J) in Hertz (Hz).

The following abbreviations were used:

s for singlet, bs for broad singlet, d for doublet, t for triplet, qdt for quartet, m for multiplet or massive, dd for doublet of doublet, etc.

The mass spectra were obtained on a spectrophotometer Waters LCT Premier XE coupled to a LC Waters Acquity.

GC-MS spectra were performed on a Micromass Autospec 8kV, equipped with a GC HP 6890, Capillar column WCOT, HP 5MS, 30m, DI:0.25mm, at 50°C (0.5mn), from 50 to 280°C at 10°C/mn, and 280°C for 5mn, with IE:70eV.

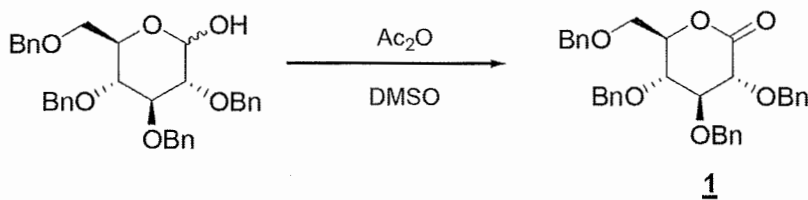
Automated column chromatography was performed on Biotage SP4 instruments using Biotage® SNAP cartridges. Follow-up is ensured via thin-layer chromatography (TLC) with Kieselgel 60F-254-0.25-mm plates. The ratio of the migration distance of a compound on a given support to the migration distance of an eluent is called the retardation factor (Rf).

Exemplary compound preparations according to the invention will be described hereinbelow, for non-limiting, illustrative purposes.

Synthesis of compound 1

$\text{C}_{34}\text{H}_{34}\text{O}_6$ $M = 538.63 \text{ g.mol}^{-1}$

Mass: (ESI^+): 561.2 ($M + \text{Na}$)

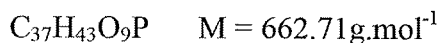


Acetic anhydride (420mL) was added to a round bottom flask under inert atmosphere containing 2,3,4,6-tetra-O-benzyl-D-glucopyranose (100g ; 185mmol) in DMSO (640mL). The mixture was stirred overnight at room temperature before being cooled to 0°C. A large volume of water was added and stirring was stopped so that the reaction

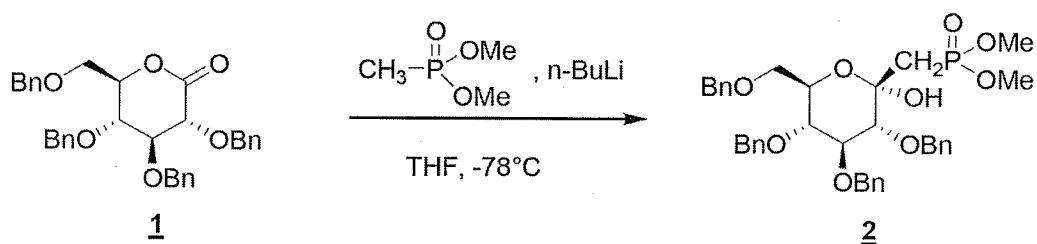
mixture was allowed to settle for 3h (the crude lactone lies at the bottom of the flask). The supernatant was removed and the crude mixture was diluted with Et₂O and washed 3 times with water, neutralised with saturated aqueous solution of NaHCO₃ and washed again twice with water. The organic layer was then dried over magnesium sulphate, filtered and concentrated. The crude mixture was purified by silica gel chromatography (cyclohexane / ethyl acetate 8:2; R_f = 0.61) to afford the desired lactone **1** as a colourless oil with 80% yield.

Synthesis of compound **2**

10



Mass: (ESI⁺): 685.33 [M+Na]⁺; 1346.80 [2M+Na]⁺

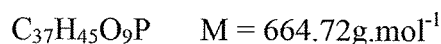


Under inert atmosphere, *n*-butyllithium (1.6M solution in hexanes, 168mL, 0.27mol, 2.9eq) was added dropwise to a solution of dimethyl methyl-phosphonate (42mL, 0.39mol, 4.2eq) in THF (390mL) cooled to -78°C. The mixture was stirred for 30 minutes at this temperature before a solution of lactone **1** (50g, 93mmol, 1eq) in tetrahydrofuran (230mL) was added dropwise at the same temperature. The mixture was stirred for 30 minutes before being allowed to warm to 0°C with stirring.

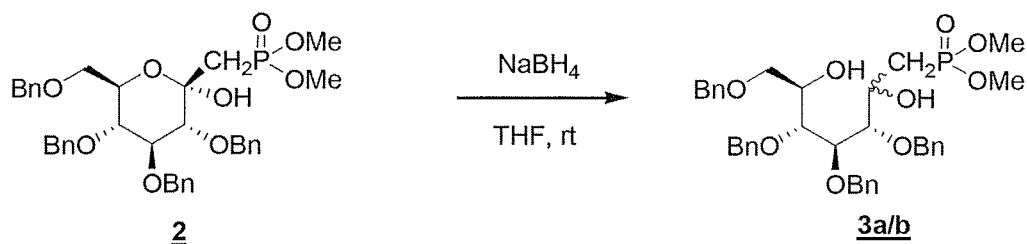
The reaction mixture was poured into an ice-cooled mixture of 10% saturated ammonium chloride aqueous solution (100mL) and ethyl acetate (300mL). The organic layer was separated, washed with water, dried over sodium sulphate, filtered and then concentrated under reduced pressure to afford quantitatively 3,4,5,7-tetra-O-benzyl -1-deoxy-1-(dimethoxyphosphoryl)-D-gluco-2-heptulopyranose **2** (63g) as a slightly yellowish oil which gives white crystals overtime.

25

Synthesis of compounds **3a/b**

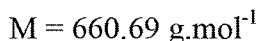
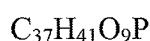


Mass: (ESI⁺): 665.13 (M + H); 687.27 (M + Na); 696.73 (M + MeOH)

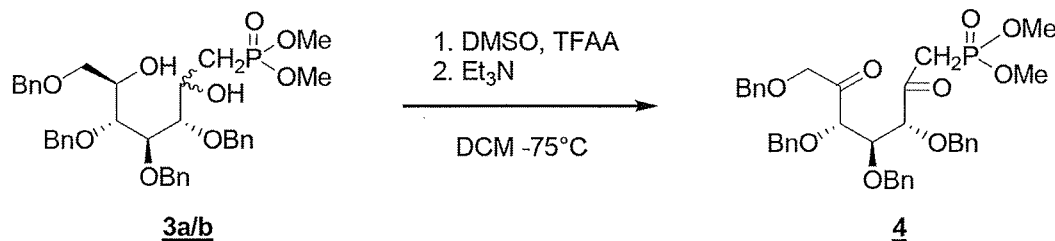


To a solution of **2** (69.5g, 105mmol, 1eq) in tetrahydrofuran (600mL) was added by portion sodium borohydride (7.44g, 210mmol, 2eq). The mixture was stirred overnight at room temperature prior to be concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic layer was washed with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude compound **3** (mixture of diastereomers **a** and **b**, 70.5g, 100%) was engaged in the next step without further purification.

10 Synthesis of compound 4



Mass: (ESI⁺): 661.00 (M + H); 683.20 (M + Na); 1343.0 (2M + Na)⁺

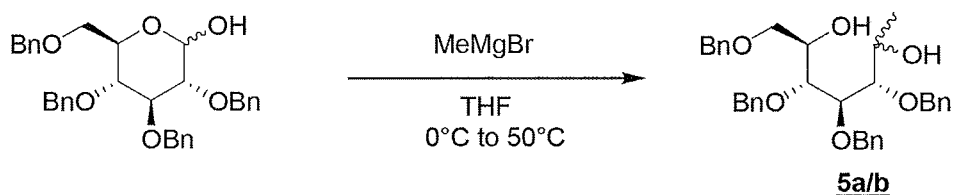


A solution of trifluoroacetic anhydride (27.1mL, 0.19mol, 4eq) in dichloromethane (130mL), cooled to 0°C was added dropwise under inert atmosphere to a solution of dimethylsulfoxide (20.8mL, 0.29mol, 6eq) in dichloromethane (260mL) prepared at ambient temperature before being cooled to -75°C. The mixture was stirred for 45 minutes at -75°C, before a solution of **3** (32.43g, 48.8mmol, 1eq) in dichloromethane (260mL) cooled to -75°C was added. The mixture was stirred for 1.5h at the same temperature. Triethylamine (54.2mL, 0.39mmol, 8eq) was added dropwise to the reaction mixture which was then allowed to warm to 0°C with stirring. A 2N hydrochloric acid aqueous solution was added to the reaction mixture. The organic layer was separated, washed with a saturated sodium hydrogenocarbonate solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude

compound **4** (36.3g, 100%), obtained in the form of a yellowish oil was engaged in the next step without further purification.

Synthesis of compounds **5a/b**

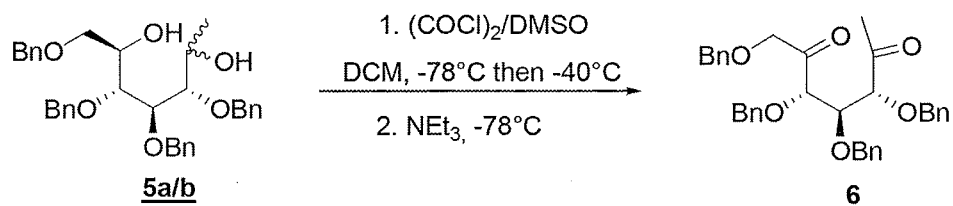
5 $C_{35}H_{40}O_6$ $M = 556.69 \text{ g.mol}^{-1}$
Mass: (ESI⁺): 557.20 (M + H); 1135.07 (2M + Na)



2,3,4,6-tetra-O-benzyl-D-glucopyranose (50g, 92.7mmol, 1eq) was dissolved in THF (645mL) and cooled to 0°. Methylmagnesium bromide (185mL of a 1.4M solution in THF/toluene, 259.4mmol, 2.8eq) was added dropwise under inert atmosphere and the reaction mixture was stirred for 10min at 0°C and 3h30 at 50°C. TLC (cyclohexane-ethyl acetate, 7:3) showed complete conversion of starting material into two products (R_fa=0.17 and R_fb=0.25). The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulphate, filtered and concentrated to afford quantitatively the desired crude diol **5** (as a mixture of diastereomers **a** and **b**) in the form of yellow oil. This compound was engaged in the following step without further purification.

20 Synthesis of compound **6**

$C_{35}H_{36}O_6$ $M = 552.66 \text{ g.mol}^{-1}$
Mass: (ESI⁺): 575.40 (M + Na); 575.40 (M + K); 1127.07 (2M + Na); 1142.93 (2M + K)⁺.



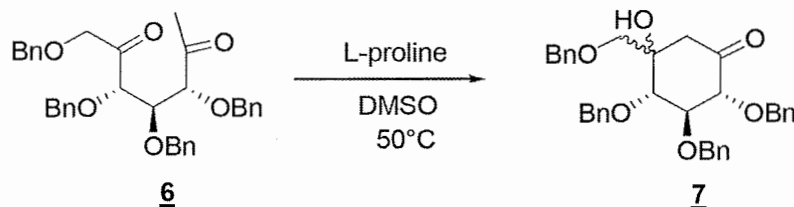
25 A solution of dimethylsulfoxide (14mL, 0.20mol, 9eq) in dichloromethane (50mL) was added dropwise to a solution of oxalyl chloride (12.5mL, 0.13mol, 6eq) in

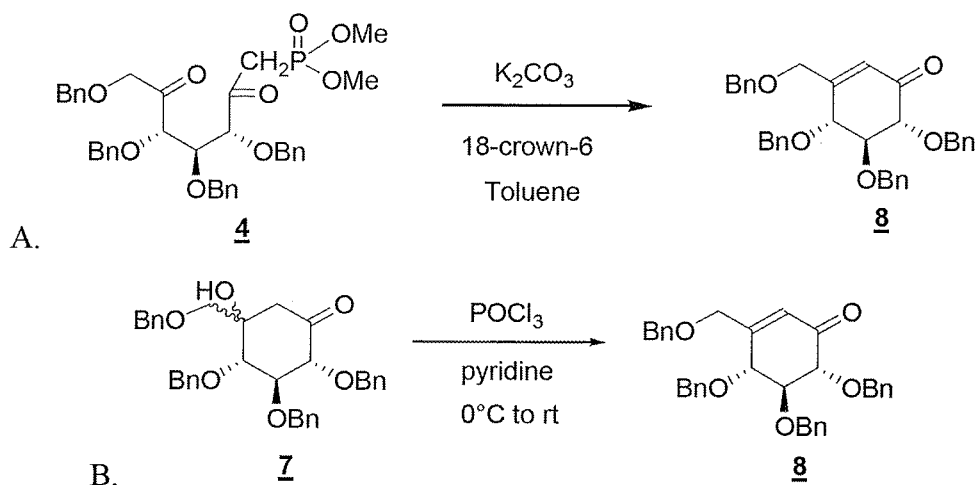
dichloromethane (50mL) cooled to -78°C , under inert atmosphere. The mixture was stirred at -78°C for 30min before a solution of diol 5 (12.2g, 21.9mmol, 1eq) in dichloromethane (50mL) was added dropwise. After 45min, a precipitate appeared and the reaction mixture was warmed to -40°C and stirred for an additional 30min. The mixture was then re-cooled to -78°C and triethylamine (55mL, 0.39mol, 18eq) was added dropwise. After 15min, the cooling bath was removed and the reaction mixture was allowed to reach room temperature. A large amount of precipitate had formed. After a further 2h, toluene (400mL) was added and the precipitate was removed by filtration. The residue was washed with toluene and the filtrate was concentrated and purified by silica gel chromatography (cyclohexane / ethyl acetate 97:3 to 70:30) to afford diketone 6 (9.92g, 76% yield) as an orange oil.

Synthesis of compound 7



Mass: (ESI⁺): 570.27 (M + H₂O); 575.33 (M + Na)

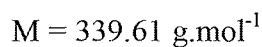
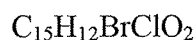
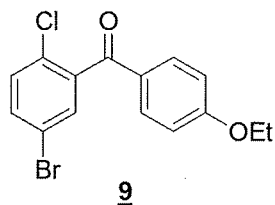


**Procedure A:**

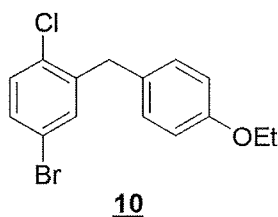
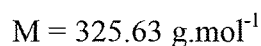
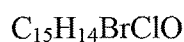
To a solution of 4 (10.5g, 15.89mmol, 1eq) in toluene (400mL) were added 18-crown-6 (168mg, 0.64mmol, 0.04eq) and potassium carbonate (6.69g, 48.5mmol, 3.05eq.). The mixture was stirred overnight at room temperature, and then the remaining insoluble material was filtered off and washed with toluene. The filtrate and the washings were combined, washed with 2N hydrochloric acid aqueous solution followed by saturated sodium hydrogencarbonate aqueous solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified on silica gel chromatography (cyclohexane/ethyl acetate 98:2 to 80:20) to afford cyclohexenone 8 (4.07g; 48% yield) as yellowish oil.

Procedure B:

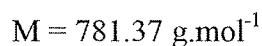
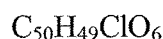
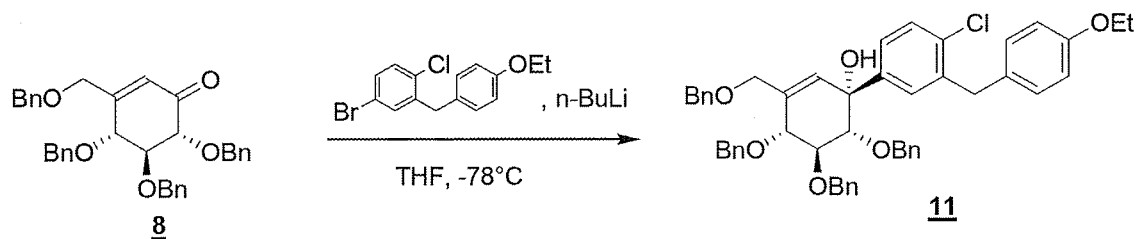
A solution of 7 (3.27g, 5.92mmol, 1eq) in pyridine (14mL) was cooled to 0°C before POCl₃ (2.75mL, 29.6mmol, 5eq) was added dropwise. The mixture was stirred at this temperature for 10 min before the cooling bath was removed. The reaction mixture was stirred overnight at room temperature before being re-cooled to 0°C. POCl₃ (2.75mL, 29.6mmol, 5eq) was added once again trying to complete the reaction. The mixture was stirred for an additional 20h at room temperature before being diluted with Et₂O (20mL) and poured onto crushed ice. 1M HCl aqueous solution (100mL) was added, and the mixture was extracted with Et₂O (200mL & 100mL). The combined organic extracts were washed with brine (100mL), dried over sodium sulphate, filtered and concentrated before being purified on silica gel chromatography (cyclohexane / ethyl acetate 98:2 to 80:20) to afford compound 8 (1.46g, 46% yield) as an orange oil.

Synthesis of compound 9Mass: (GC-MS): 338-340

- 5 The synthesis of this product is described in *J. Med. Chem.* **2008**, *51*, 1145–1149.

Synthesis of compound 10

- 10 The synthesis of this product is described in *J. Med. Chem.* **2008**, *51*, 1145–1149.

Synthesis of compound 11Mass: (ESI⁺): 798.20 (M + H₂O)

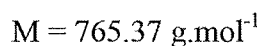
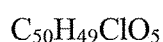
15

- Under inert atmosphere, Mg powder (265mg, 10.9mmol, 2.4eq) was charged into a three necked flask, followed by addition of a portion of 1/3 of a solution of the 4-bromo-1-chloro-2-(4-ethylbenzyl)benzene (2.95g, 9.1mmol; 2eq) in dry THF (25mL) and 1,2-dibromoethane (10 mol % of Mg; 85mg; 0.45mmol). The mixture was heated to
- 20 reflux. After the reaction was initiated (exothermic and consuming of Mg), the

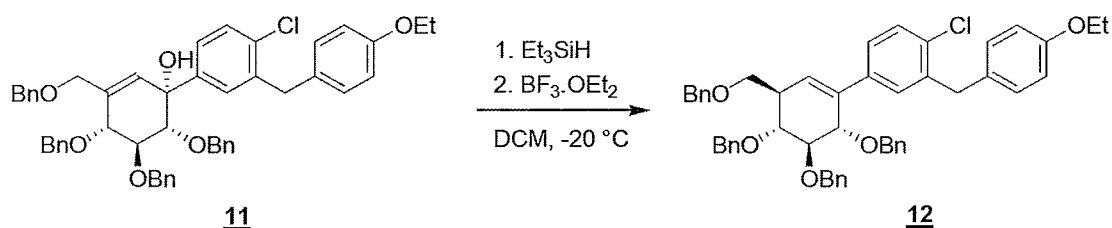
remaining solution of 2-(4-ethylbenzyl)-4-bromo-1-chlorobenzene in dry THF was added dropwise. The mixture was then allowed to react for another one hour under gentle reflux until most of the Mg was consumed.

The above Grignard reagent was added dropwise into the solution of cyclohexenone **8** (2.42g, 4.53mmol, 1eq) in dry THF (25mL) under inert atmosphere at room temperature (about 25°C), then allowed to react for 3h. A saturated aqueous solution of ammonium chloride was added into the mixture to quench the reaction. The mixture was extracted with Et₂O, washed with brine, dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 80:20) to afford the target compound **11** as a yellow oil (3.01g, 86%).

Synthesis of compound **12**



Mass: (ESI⁺): 782.13 (M + H₂O)

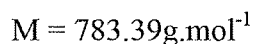
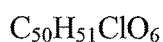


15

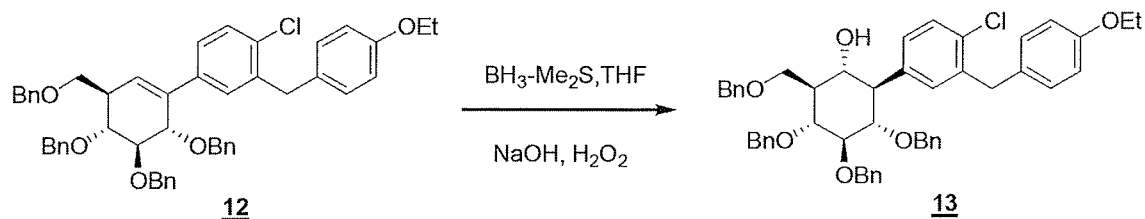
Triethylsilane (0.210mL, 1.30mmol, 3eq) and boron-trifluoride etherate (48% BF₃, 0.110mL, 0.866mmol, 2eq) were successively added into a solution of alcohol **11** (338mg, 0.433mmol, 1eq) in dichloromethane (5mL) under inert atmosphere at -20°C. After stirring for 2.5h, a saturated aqueous solution of sodium chloride was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (10mL×3) and the organic layer was washed with brine, dried over Na₂SO₄, filtrated and concentrated. The residue was purified on silica gel chromatography (cyclohexane/ethyl acetate 9.8:0.2 to 8:2) to afford the target compound **12** as a white powder (278 mg, 0.363mmol, 84%).

20

25 Synthesis of compound **13**



Mass: (ESI⁺): 800 (M + H₂O); 1581 (2M + H₂O)



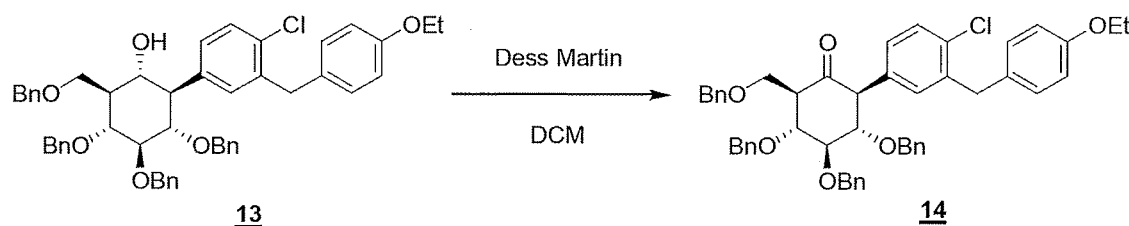
Under inert atmosphere, borane-dimethyl sulfide complex (2M in THF, 16.7mL, 33mmol, 10.5eq) was added to a solution of **12** (2.41g; 3.15mmol, 1eq) in dry THF (100mL) cooled to 0°C. The reaction mixture was then refluxed for 1h, cooled to 0°C and treated carefully with sodium hydroxide (3M in H₂O, 10.5mL, 31.5mmol, 10eq), followed by hydrogen peroxide (30% in H₂O, 3.2mL, 31.5mmol, 10eq) at room temperature (above 30°C). The mixture was allowed to react overnight at room temperature (~25°C) before a saturated aqueous solution of ammonium chloride was added to quench the reaction. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 97:3 to 73:27) to afford the desired compound **13** (1.05g; 43%) as a yellowish oil.

15 Synthesis of compound 14

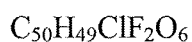
$\text{C}_{50}\text{H}_{49}\text{ClO}_6$

$M = 781.37\text{g}\cdot\text{mol}^{-1}$

Mass: (ESI⁺): 798 (M + H₂O); 1471; 1579 (2M + H₂O)



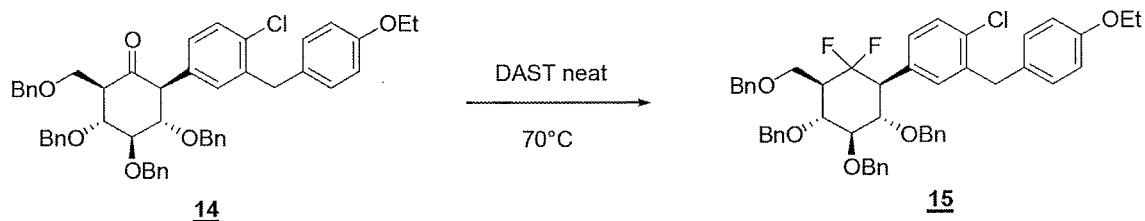
Dess-Martin periodinane (81mg; 1.91mmol; 1.5eq) was added portion wise to a solution of alcohol **13** (1.0g; 1.28mmol, 1eq) in anhydrous dichloromethane (20mL) at 0°C. The reaction was then stirred overnight at room temperature before being quenched with 1N aqueous solution of sodium hydroxide. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane / ethyl acetate 98:2 to 82:18), to afford the target ketone **14** (783mg, 79% yield) as a colorless oil.

Synthesis of compound 15

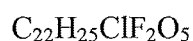
$$M = 803.37 \text{ g} \cdot \text{mol}^{-1}$$

^{19}F NMR (CDCl_3 , 282.5 MHz): -100.3 (d, $J=254\text{Hz}$, 1F, CFF); -113.3 (td, $J_1=254\text{Hz}$, $J_2=29\text{Hz}$, 1F, CFF).

5 Mass: (ESI^+): 820.00 ($\text{M}+\text{H}_2\text{O}$)



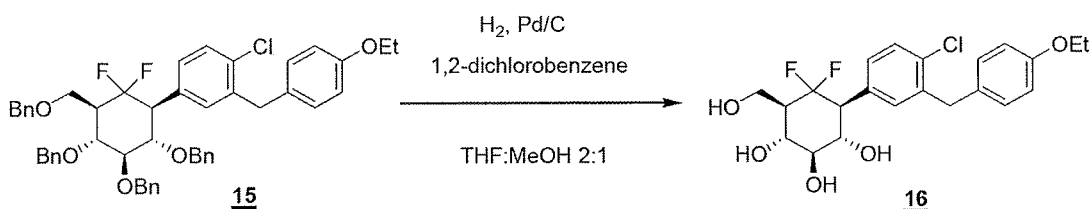
A solution of ketone **14** (421mg, 0.539mmol, 1eq) in DAST (2mL, 16.3mmol, 30eq.) was stirred under inert atmosphere at 70°C for 12h. The mixture was then cooled to room temperature and dichloromethane was added. The solution was poured on a mixture of water, ice and solid NaHCO_3 . Agitation was maintained for 30min while reaching room temperature. The aqueous layer was extracted with dichloromethane and the organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified on silica gel chromatography (cyclohexane/ethyl acetate 98:2 to 80:20) to afford the desired compound **15** as a yellowish oil (182mg, 42% yield).

Synthesis of compound 16

$$M = 442.88 \text{ g} \cdot \text{mol}^{-1}$$

^{19}F NMR (MeOD , 282.5 MHz): -96.7 (d, $J=254\text{Hz}$, 1F, CFF); -112.2 (td, $J_1=254\text{Hz}$, $J_2=28\text{Hz}$, 1F, CFF).

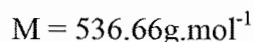
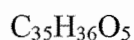
20 Mass: (ESI^+): 465.3 ($\text{M}+\text{Na}$)



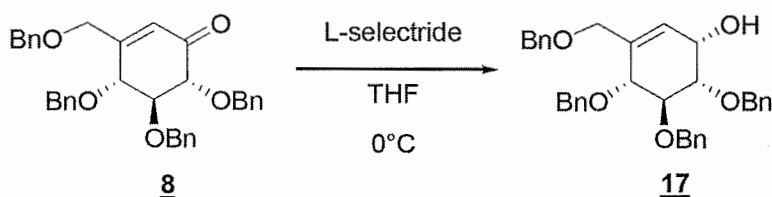
o-Dichlorobenzene (0.320mL, 2.82mol, 10eq) followed by Pd/C 10% (0.342g, 0.32mol, 1.1eq) were added to a solution of **15** (228mg, 0.28mmol, 1eq) in a mixture of THF and MeOH (2:1, v/v, 160mL). The reaction was placed under hydrogen atmosphere and

stirred at room temperature for 2h. The reaction mixture was filtered and concentrated before being purified on silica gel chromatography (dichloromethane/methanol 100:1 to 90:10) to afford compound **16** (105mg, 83% yield).

5 Synthesis of compound 17



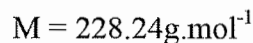
Mass: (ESI⁺): 554.13 (M + H₂O); 1095 (2M + Na)



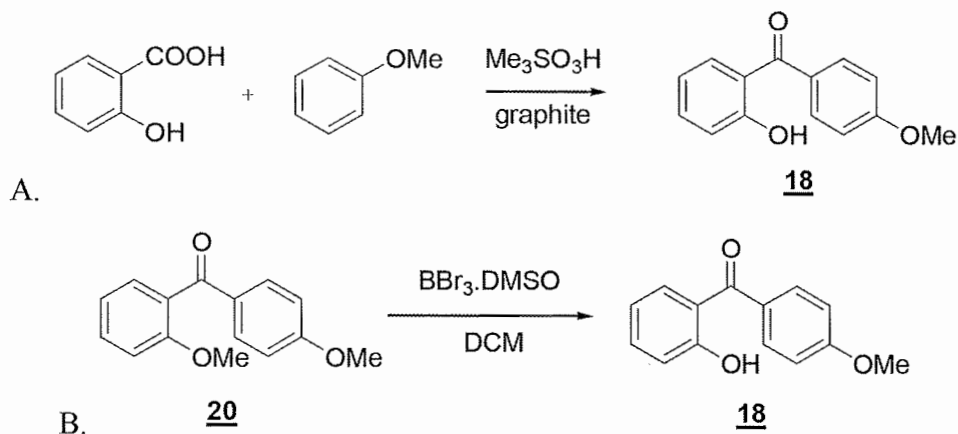
A 1M solution of L-selectride in THF (0.84mL, 0.84mmol, 1.5eq), was added dropwise to a stirred and cooled (0°C) solution of cyclohexenone **8** (0.300g, 0.56mmol, 1eq) in THF (14mL) under inert atmosphere. The mixture was stirred for 18h allowing it to warm up to room temperature gradually. A saturated aqueous solution of ammonium chloride was then added and the resultant mixture was stirred for an additional 15 min. Water was added and the aqueous solution was then extracted with ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated to afford quantitatively the desired compound **17** (350mg) as a yellow oil.

Synthesis of compound 18

20



Mass: (GC-MS): 228 (M)



Procedure A.

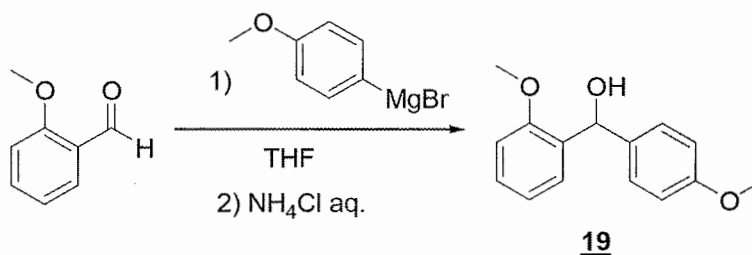
2-Hydroxybenzoic acid (13.8g, 0.1mol, 1eq) and anisole (10.9mL, 0.1mol, 1eq) were added to a mixture of graphite (9.6g, 0.8mol, 8eq) and methanesulfonic acid (25mL, 0.4mol, 4eq) heated to 80°C. The reaction mixture was stirred at this temperature for 12h before being cooled to room temperature. The mixture was then extracted twice with chloroform and the combined organic layers were washed with a saturated aqueous solution of NaHCO₃, dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane / ethyl acetate 70:30) to afford compound **18** (4g 17% yield) as an orange oil.

Procedure B.

BBr₃.DMSO (10.8g, 34.42mmol, 1.1eq) was added portion wise to a solution of **20** (7.58g, 31.29mmol, 1eq) in dichloromethane (150mL) cooled to 0°C. The reaction was stirred at 0°C for 3h before being poured onto a mixture of water and ice. After 10min stirring, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulphate, filtered and concentrated to afford compound **18** (6.78g) as a purple oil.

Synthesis of compound 19

Mass: (ESI⁺): 227.1 (M + H - H₂O)



A solution of 4-methoxyphenylmagnesium bromide (0.5M in THF, 300mL, 0.150mol, 1.1eq) was added drop wise under inert atmosphere to a solution of 2-methoxybenzaldehyde (18.75g, 0.137mol, 1eq) in THF (188mL) cooled to 0°C. The resulting mixture was stirred at room temperature overnight before being poured onto a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with ethyl

acetate and the combined organic layers were dried over sodium sulphate, filtered and concentrated to afford compound **19** (37.5g) as a brown oil.

Synthesis of compound **20**

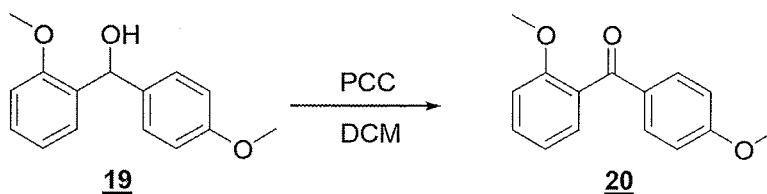
5



$$M = 242.27 \text{ g} \cdot \text{mol}^{-1}$$

Mass: (GC-MS): 51; 64; 77; 92; 107; 121; 128; 135; 139; 181; 197; 211; 225;

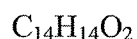
242



Pyridinium chlorochromate (34.3g, 159mmol, 2eq) was added to a solution of alcohol **19** (19.4g, 79.4mmol, 1eq) in dichloromethane (210mL) containing molecular sieves. The reaction mixture was stirred overnight at room temperature, filtered to remove PCC residues and molecular sieves and concentrated. The crude residue was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 85:15) to afford ketone **20** (12.6g, 38% yield) as a yellowish solid.

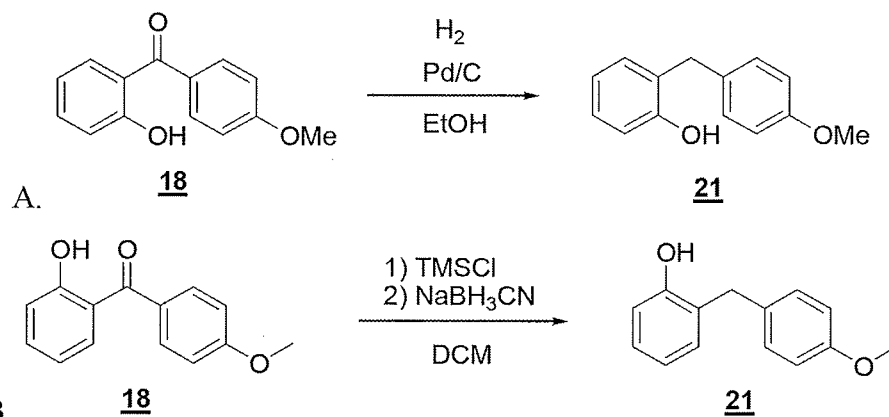
15

Synthesis of compound **21**



$$M = 214.26 \text{ g} \cdot \text{mol}^{-1}$$

Mass: (GC-MS): 214



20

Procedure A.

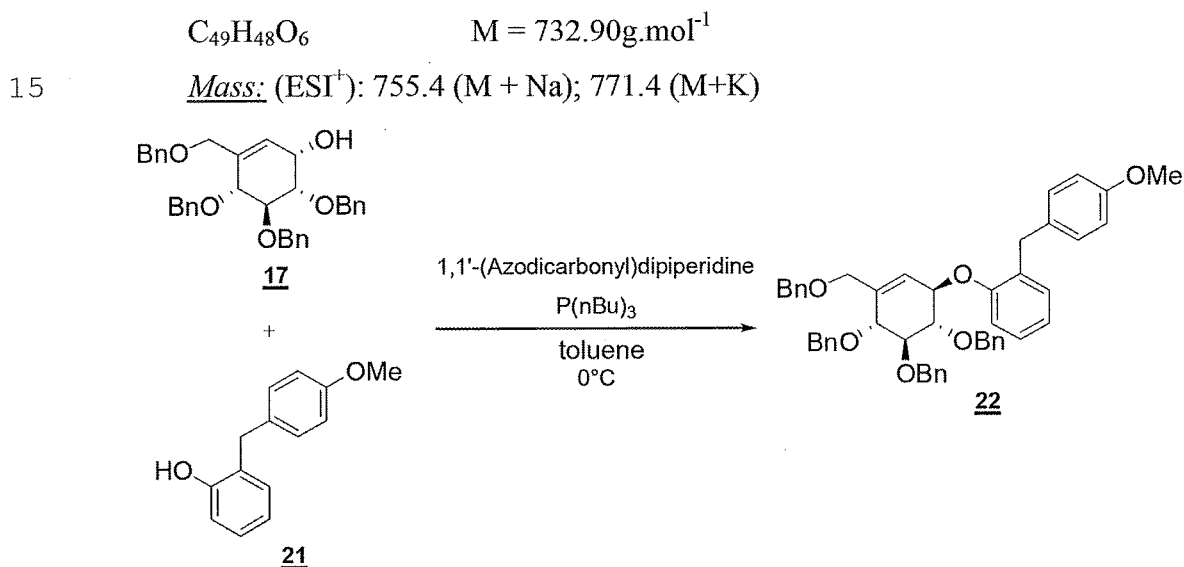
10% Pd/C was added to a solution of **18** (1.5g, 6.6mmol, 1eq) in ethanol. The solution was stirred under hydrogen atmosphere under 30bars until completion of the reaction.

Palladium particles were removed by filtration and the solution was concentrated to afford compound **21** (1.32g, 93% yield) as a white powder.

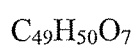
Procedure B.

A solution of **18** (8.1g, 35.5mmol, 1eq) in acetonitrile (130mL) under inert atmosphere was cooled to 0°C. TMSCl (20.7mL, 163.3mmol, 4.6eq) followed by NaBH₃CN (10.5g, 1667mmol, 4.7eq) were slowly added (exothermic reaction). The resultant yellow suspension was stirred at room temperature for 2h before being poured onto water. Dichloromethane was then added and the organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude residue was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 83:17) to afford the target compound **21** (80% yield) as a yellowish solid.

Synthesis of compound **22**

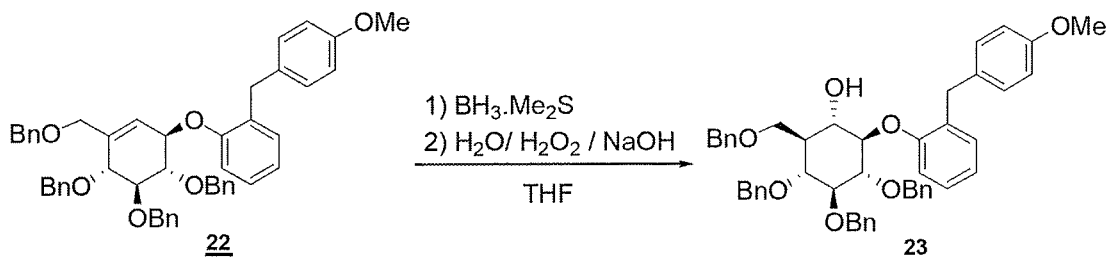


To a solution of **17** (50mg, 0.093mmol, 1eq) in toluene (0.30mL) cooled to 0°C under inert atmosphere were successively added **21** (30mg, 0.140mmol, 1.5eq), tributylphosphine (0.35mL, 0.140mmol, 1.5eq) and 1,1'-(azodicarbonyl)dipiperidine (35mg, 0.140mmol, 1.5eq). The reaction mixture was stirred at 0°C for 30min. A dense precipitate appeared and the mixture was dissolved with dichloromethane and concentrated under reduced pressure to give a white residue which was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 80:20) to afford the target compound **22** (63mg, 93% yield) as colorless oil.

Synthesis of compound 23

$$M = 750.92 \text{ g} \cdot \text{mol}^{-1}$$

Mass: (ESI⁺): 773.8 (M + Na); 789.7 (M + K)



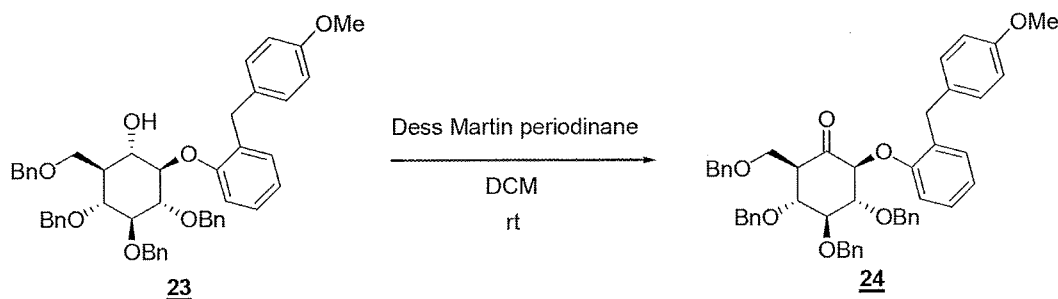
- 5 To a cooled solution (0°C) of **22** (62mg, 0.085mmol, 1eq) in anhydrous THF (0.837mL) was added BH₃·Me₂S (2M solution in THF, 0.169mL, 0.338mmol, 4eq). The resultant solution was stirred overnight at room temperature before being cooled again to 0°C. Water (0.107mL, 23.6mmol, 70eq), hydrogen peroxide (30% aqueous solution, 0.258mL, 10.1mmol, 30eq) and sodium hydroxide (2M aqueous solution, 0.338mL, 2.7mmol, 8eq) were then successively added and the mixture was stirred at room temperature for 3h. Water and ethyl acetate were added and the organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated. The crude compound was then purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 75:25) to afford alcohol **23** (34mg, 53% yield) as a white solid.

15

Synthesis of compound 24

$$M = 748.90 \text{ g} \cdot \text{mol}^{-1}$$

Mass: (ESI⁺): 771.7 (M + Na); 787.7 (M + K)

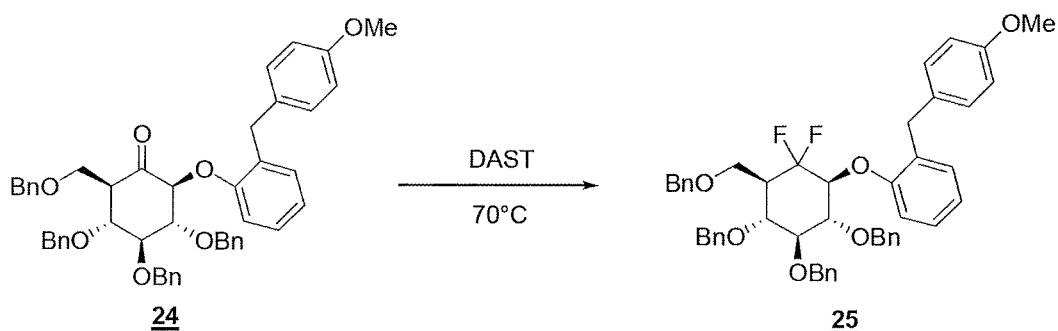


- 20 Dess Martin periodinane (29mg, 0.068mmol, 1.5eq) was added to a solution of alcohol **23** (34mg, 0.045mmol, 1eq) in dichloromethane (0.680mL) cooled to 0°C. The resulting mixture was stirred at room temperature for 3h before a solution of sodium hydroxide (1N aqueous solution) and dichloromethane were added to the mixture. The organic

layer was separated, dried over sodium sulphate, filtered and concentrated to afford the desired ketone **24** (36mg, 70% yield) as a white solid.

Synthesis of compound **25**

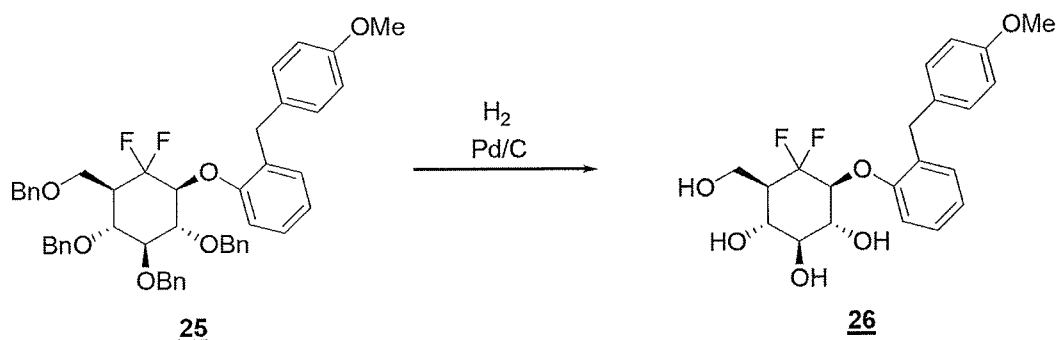
- 5 $C_{49}H_{48}F_2O_6$ $M = 770.90 g \cdot mol^{-1}$
 ^{19}F NMR ($CDCl_3$, 282.5MHz): -109.3 (d, $J=252Hz$, 1F, CFF); -120.3 (ddd, $J_1=252Hz$, $J_2=30Hz$, $J_3=19Hz$, 1F, CFF).
 Mass: (ESI⁺): 773.4 (M - HF); 793.5 (M + Na)



- 10 DAST (0.72mL, 4.96mmol, 20eq) was added to a solution of ketone **24** (183mg, 0.244mmol, 1eq) in dichloromethane (0.720mL) under inert atmosphere and the reaction mixture was stirred overnight at room temperature. The solution was cooled to room temperature before being poured in water. Dichloromethane was added and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried over sodium sulphate, filtered and concentrated. The crude product was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 90:10) followed by preparative HPLC (Kromasil C18, acetonitrile / water 89:11) to afford compound **25** in 32% yield as a white solid.

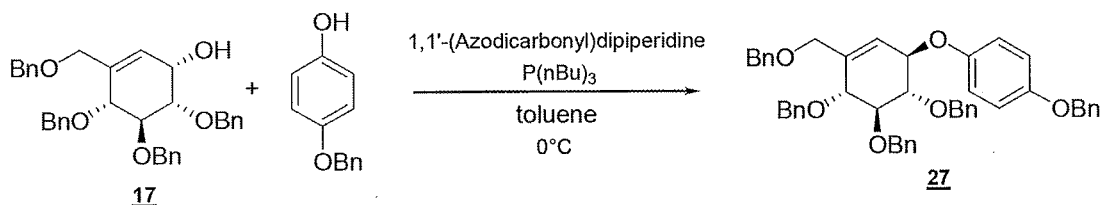
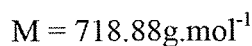
20 Synthesis of compound **26**

- $C_{21}H_{24}F_2O_6$ $M = 410.41 g \cdot mol^{-1}$
 ^{19}F NMR ($MeOD$, 282.5MHz): -109.6 (d, $J=251Hz$, 1F, CFF); -122.4 (ddd, $J_1=251Hz$, $J_2=28Hz$, $J_3=20Hz$, 1F, CFF).
 Mass: (ESI): 445.2 (M+Cl)



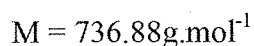
Compound **25** (48mg, 0.06mmol, 1eq) was dissolved in a mixture of THF (6.3mL) and methanol (6.3mL). 10% Pd/C (48mg, 0.04mmol, 0.7eq) followed by 2 drops of 12N aqueous solution of hydrochloric acid were added. The mixture was then stirred for 1h under hydrogen atmosphere at room temperature before being filtered and concentrated. The crude mixture was purified on silica gel chromatography (dichloromethane/methanol 100:0 to 90:10) to afford the target compound **26** (42mg, 67% yield) as a white solid.

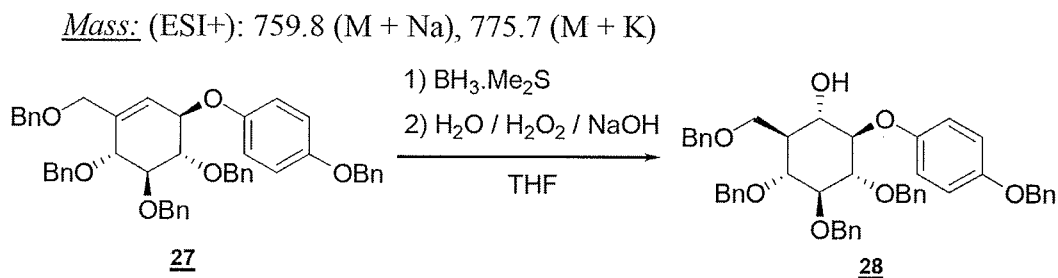
10 Synthesis of compound 27



A solution of **17** (30mg, 0.056mmol, 1eq) in toluene (0.180mL) was cooled to 0°C under an inert atmosphere and 4-(benzyloxy)phenol (17mg, 0.085mmol, 1.5eq), tributylphosphine (0.42mL, 0.168mmol, 3eq) and 1,1'-(azodicarbonyl)dipiperidine (42mg, 0.167mmol, 3eq) were successively added. The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with dichloromethane and concentrated under reduced pressure to yield a white residue which was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 80:20) to afford compound **27** (30mg, 75% yield) as colorless oil.

Synthesis of compound 28



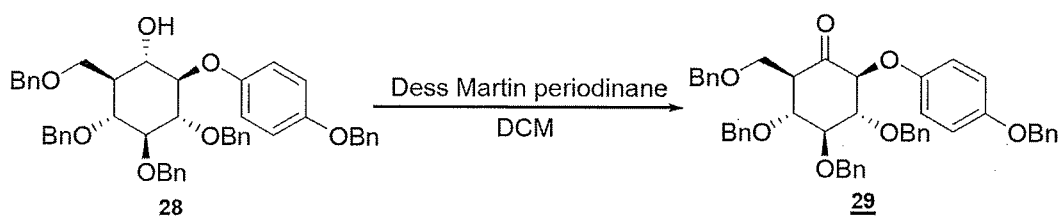


BH₃.Me₂S (3.48mL, 6.96mmol, 2eq) was added, under inert atmosphere, to a solution of **27** (1.00g, 1.39mmol, 1eq) in dry tetrahydrofuran (15mL) cooled to 0°C. This mixture was stirred overnight at room temperature. Water (1.75mL, 97.4mmol, 70eq) was then added at 0°C, followed by a 30% aqueous solution of H₂O₂ (4.73mL, 41.7mmol, 30eq) and 1M aqueous solution of sodium hydroxide (11.1mL, 11.1mmol, 8eq). The resultant mixture was stirred at room temperature for 3 hours. A large amount of water was then added, followed by extraction with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated. The crude mixture was purified by silica gel chromatography (cyclohexane / ethyl acetate 95:5 to 60:40) to afford **28** (791mg, 78% yield) as a yellowish oil.

Synthesis of compound **29**

28 $C_{48}H_{46}O_7$ $M = 734.87g.mol^{-1}$

Mass: (ESI⁺): 757.8 (M + Na), 773.7 (M + K)



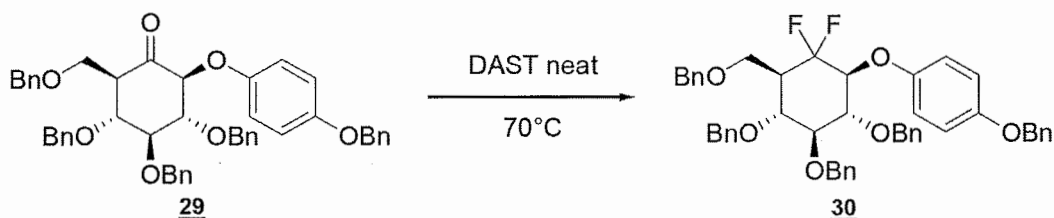
Dess-Martin periodinane (17mg, 0.041mmol, 1.5eq) was added to a solution of alcohol **28** (682mg, 1.61mmol, 1eq) in dry dichloromethane (20mL) at room temperature. The reaction was stirred overnight at room temperature before being diluted with dichloromethane and quenched with a 1M aqueous solution of sodium hydroxide. After extraction with dichloromethane, the organic layer was dried over MgSO₄, filtered and concentrated to afford crude ketone **29** (730mg, 91% yield) as a yellowish oil.

Synthesis of compound **30**

29 $C_{48}H_{46}O_7$ $M = 756.87g.mol^{-1}$

^{19}F NMR (CDCl_3 , 282.5 MHz): -120.6 (ddd, 1F, $J_1=251\text{Hz}$, $J_2=28\text{Hz}$, $J_3=20\text{Hz}$, CFF);
-108.7 (d, 1F, $J=251\text{Hz}$, CFF)

Mass: (ESI $^+$): 779.3 $[\text{M}+\text{Na}]^+$; 795.3 $[\text{M}+\text{K}]^+$



- 5 A solution of ketone 29 (15mg, 2.04 μmol , 1eq) in DAST (0.130mL, 0.276mmol, 130eq) was stirred overnight under inert atmosphere at 70°C. The crude mixture was then diluted with dichloromethane and quenched carefully with H₂O. The organic layer was washed with a saturated aqueous solution of NaHCO₃, dried over MgSO₄, filtered and concentrated. The crude mixture was purified by preparative TLC (cyclohexane / ethyl
10 acetate 85:15) to afford compound 30 as a yellowish oil.

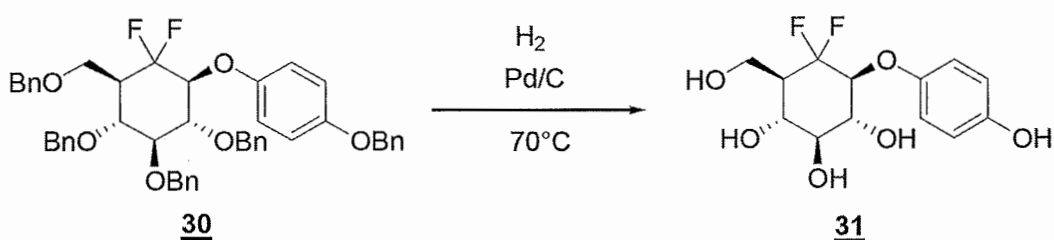
Synthesis of compound 31

$\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_6$

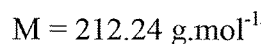
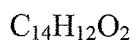
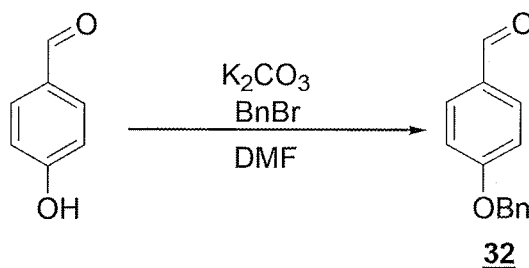
$M = 306.26\text{g}\cdot\text{mol}^{-1}$

- 15 ^{19}F NMR (MeOD, 282.5 MHz): -109.2 (d, $J=253\text{Hz}$, 1F, CFF); -123.0 (ddd, $J_1=253\text{Hz}$, $J_2=29\text{Hz}$, $J_3=20\text{Hz}$, 1F, CFF).

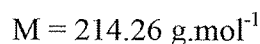
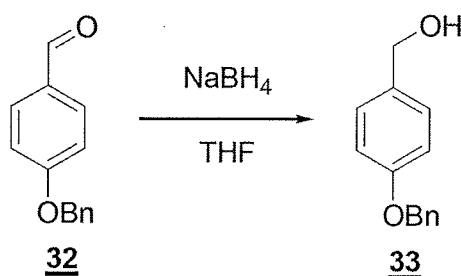
Mass: (ESI $^-$): 341.0 $[\text{M}+\text{Cl}]^-$



- Compound 30 (191mg, 0.252mmol, 1eq) was dissolved in a THF- ethanol (4:1, v/v, 120 mL) under inert atmosphere. 10% Pd/C (191mg, 0.17mmol, 0.7eq) and 9 drops of
20 12N aqueous solution of hydrochloric acid were added to the mixture which was degassed 5 times with H₂. The resultant black suspension was stirred under an atmosphere of H₂ at room temperature for 45min. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified on silica gel chromatography (dichloromethane/Methanol 100:0 to 90:10) to afford the target
25 compound 31 in 73% yield as a colorless oil.

Synthesis of compound 32Mass: (Cl^+): 213 ($M + H$)

- 5 4-Hydroxybenzaldehyde (4g, 32.8mmol, 1eq) and potassium carbonate (4.75g, 34.4mmol, 1.05eq) were dissolved in dry DMF (30mL). Benzyl bromide (4.1mL, 34.4mmol, 1.05eq) was slowly added. The resultant mixture was stirred overnight under inert atmosphere at room temperature. Iced water was added to the reaction mixture to quench the reaction and which was then diluted with a large amount of water. The
- 10 mixture was filtered and the residue was washed with water and dissolved in ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give quantitatively crude aldehyde 32 as a yellowish oil which slowly crystallizes overtime.

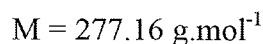
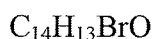
15 Synthesis of compound 33Mass: (GC-MS): 91; 197; 214 (M).

- A solution of aldehyde 32 (6.5g, 30.6mmol, 1eq) in dry tetrahydrofuran (25mL) was
- 20 added dropwise to a suspension of $NaBH_4$ (1.51g, 39.8mmol, 1.3eq) in anhydrous tetrahydrofuran (25mL). The resultant mixture was stirred 72 hours under inert atmosphere at room temperature before being quenched with iced water, diluted with diethyl ether, acidified with an aqueous solution of HCl 4N, and extracted with diethyl ether. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$,

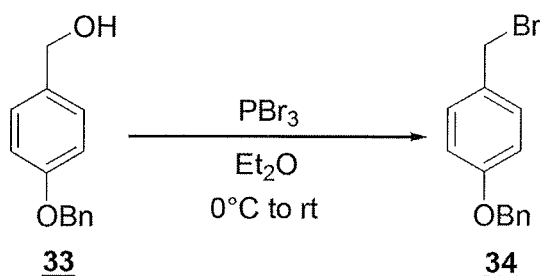
dried over MgSO_4 , filtered and concentrated to give crude alcohol **33** (97% yield) as a white amorphous solid.

Synthesis of compound **34**

5



Mass: (CI⁺): 107; 197, 277 (M + H)

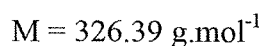
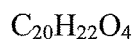


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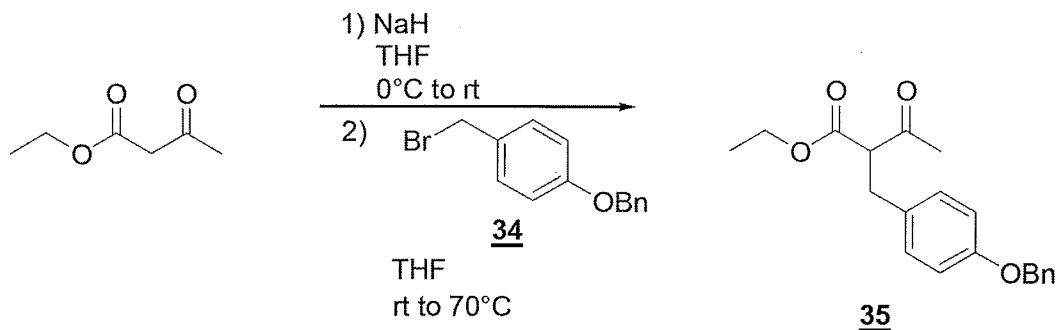
To an ice-cold suspension of crude alcohol **33** (6g, 28.0mmol, 2.4eq.) in diethyl ether (50mL), was added PBr_3 (1.1mL, 11.67mmol, 1eq) at a rate such that the temperature did not exceed 8°C . The resultant mixture was stirred 2 hours under inert atmosphere at room temperature. The reaction mixture was then cooled in an ice-bath, quenched with iced water and diluted with diethyl ether and ethyl acetate. The organic layer was washed with an aqueous saturated solution of NaHCO_3 , dried over MgSO_4 , filtered and concentrated to give crude compound **34** (99% yield) as a white amorphous solid.

15

Synthesis of compound **35**



Mass: (ESI⁺): 349.1 (M + Na); 365.1 (M + K)

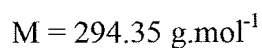


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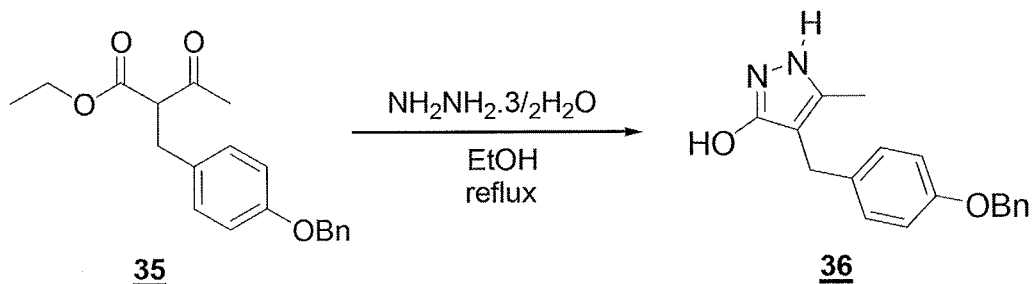
To a suspension of NaH 95% (0.61g, 25.26mmol, 1eq) in dry THF (30mL) under inert atmosphere, was added a solution ethylacetoacetate (3.5mL, 27.79mmol, 1.1eq) in dry THF (10mL). The resultant mixture was stirred 30 minutes at room temperature before adding dropwise a solution of **34** (7g, 25.26mmol, 1eq) in THF (13mL). The mixture

was then stirred overnight at 70°C and cooled to room temperature prior to be concentrated. The residue was taken up with Et₂O (60mL), washed with H₂O and brine, dried over MgSO₄, filtered and concentrated. The resultant crude mixture was purified on silica gel column (99/1 to 85/15 Cyclohexane/Ethyl Acetate) to afford compound **35** (77% yield) as a yellowish oil.

Synthesis of compound **36**



Mass: (ESI⁺): 317.1 (M + Na); 333.1 (M + K)

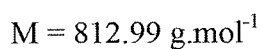
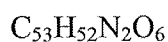


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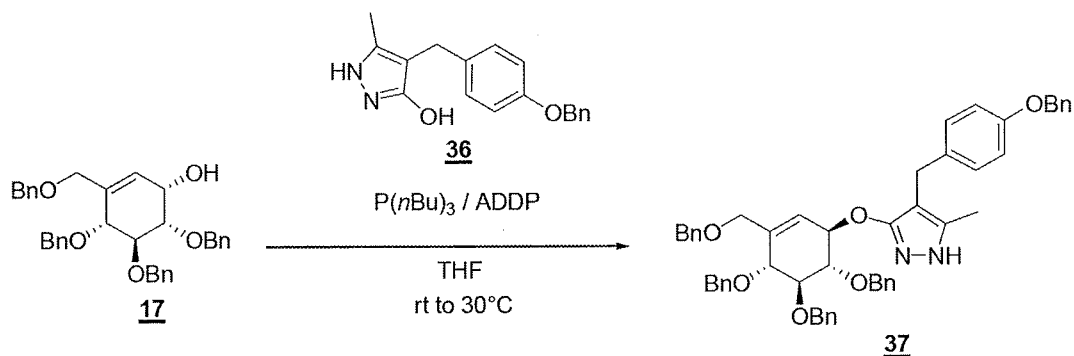
To a solution of **35** (6.5g, 19.91mmol, 1eq) in ethanol (50mL) was added hydrazine hydrate 55% (1.25mL, 22.10mmol, 1.1eq) at room temperature. The resultant mixture was refluxed 3 hours at room temperature. The reaction media was then cooled in an ice bath and filtered. The precipitate was washed with cold ethanol to afford compound **36** (77% yield) as a white solid.

15

Synthesis of compound **37**



Mass: (ESI⁺): 813.5 (M + H); 835 (M + Na); 851.4 (M + K).

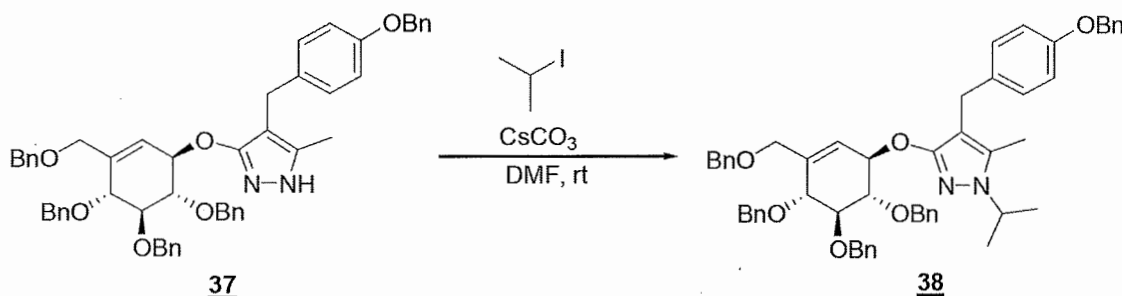
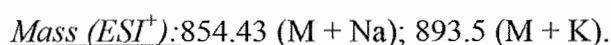
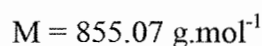


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Compound **36** (328mg, 1.11mmol, 1.5eq) was added to a solution of **17** (400mg, 0.75mmol, 1eq) in dry THF (6.4mL) under inert atmosphere followed by tri-*n*-

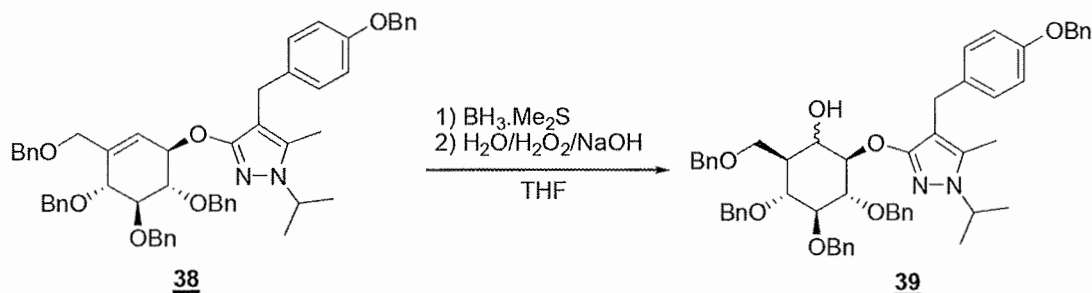
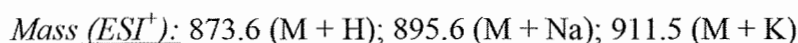
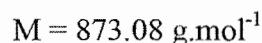
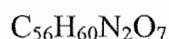
butylphosphine (198mg, 0.98mmol, 1.3eq) and azodicarboxylic acid dipiperidine (376mg, 1.49mmol, 2.0eq). The resultant yellow suspension was stirred at 30°C overnight. The solvent was removed and the crude mixture was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 60:40) to afford compound **37** (262mg, 43% yield) as a yellowish oil.

Synthesis of compound **38**



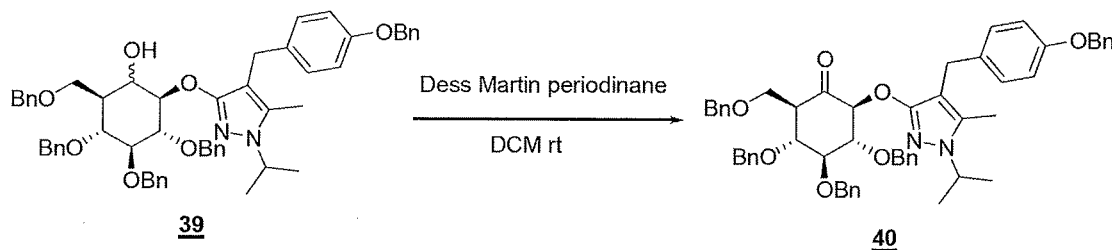
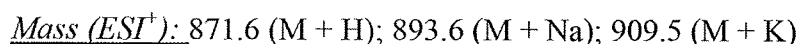
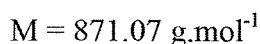
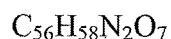
Cesium carbonate (4.1g, 12.5mmol, 15eq) followed by isopropyl iodide (0.99g, 5.83mmol, 7eq) were added to a solution of **37** (0.68g, 0.83mmol, 1eq) in DMF under inert atmosphere. The resultant suspension was stirred at room temperature for 3h. The mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated. The crude yellow oil was purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 77:23) to afford the desired compound **38** (549mg, 77% yield) as a yellowish oil.

Synthesis of compound **39**



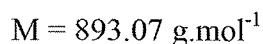
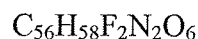
A solution of 9-BBN (0.5M in THF, 0.585mL, 0.29mmol, 10eq) was added to a solution of **38** (25mg, 0.03mmol, 1eq) in dry THF, under inert atmosphere. The colorless solution was refluxed overnight before being cooled to 0°C. Water (0.047mL), aqueous solution of hydrogen peroxide (30% w/w, 0.100mL) and 2N aqueous solution of sodium hydroxide (0.117mL) were successively added. The resultant white suspension was stirred for an additional 3h. The mixture was then diluted with ethyl acetate and poured onto water. The organic phase was then dried over magnesium sulphate, filtered and concentrated to afford a yellowish oil. Purification over silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 80:20) yielded alcohol **39** (2mg, 8% yield).

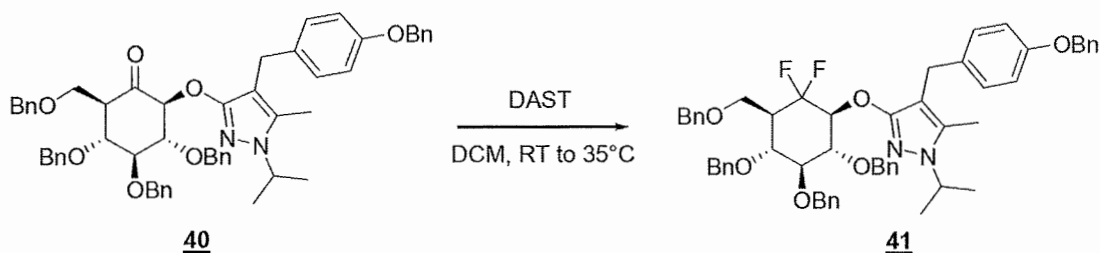
Synthesis of compound **40**



Dess-Martin periodinane (9mg, 0.021mmol, 1.5eq) was added to a solution of **39** (12mg, 0.014mmol, 1eq) in dry dichloromethane under inert atmosphere. The reaction mixture was stirred at room temperature for 2h before being diluted with dichloromethane and 1N aqueous sodium hydroxide. The aqueous layer was then extracted with dichloromethane and the resultant organic layer was dried over sodium sulphate, filtered and concentrated. The crude yellow oil was then purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 72:28) to afford ketone **40** (8mg, 67% yield) as a yellowish oil.

Synthesis of compound **41**





DAST (0.05mL, 0.410mmol, 45eq) was added to a solution of **40** (8mg, 0.009mmol, 1eq) in dry dichloromethane (0.05mL) under inert atmosphere. The reaction mixture was stirred at room temperature overnight and 3h at 35°C. The reaction mixture was allowed to reach room temperature before being diluted with dichloromethane and poured into water. The organic layer was then washed with a saturated aqueous solution of NaHCO₃, dried over magnesium sulphate, filtered and concentrated to afford crude compound **41** as an orange residue.

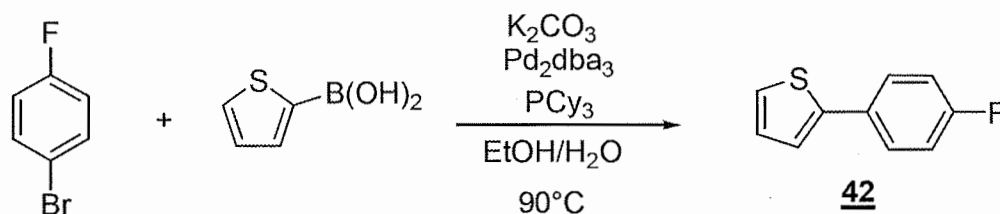
10 Synthesis of compound 42

C₁₀H₇FS

M = 178.23 g.mol⁻¹

¹⁹F NMR (CDCl₃, 282.5MHz): -109.8 (m, 1F, Ar-F).

Mass (GC-MS): 133 (41%); 178 (100%)



Into a freshly degassed mixture of EtOH (69mL) and H₂O (9mL) was added Pd₂dba₃ (534mg, 0.58mmol, 0.025eq), PCy₃ (660mg, 2.35mmol, 0.1eq), 2-thiophene boronic acid (3.00g, 23.4mmol, 1eq), K₂CO₃ (6.48g, 46.9mmol, 2eq), and 4-bromofluorobenzene (5.17mL, 47.0mmol, 2eq). The resultant mixture was stirred overnight at 90°C and then allowed to reach room temperature. MgSO₄ was added to quench water and the mixture was filtered on a pad of Celite using ethyl acetate. The filtrate was concentrated and purified on silica gel chromatography (cyclohexane/ ethyl acetate 100:0 to 95:5) to afford compound **42** (3.84g, 92% yield) as a white solid.

Synthesis of compound 43

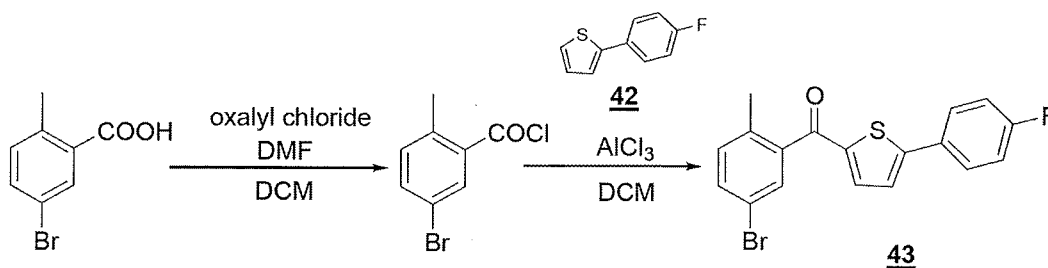
25

C₁₈H₁₂BrFOS

M = 375.25 g.mol⁻¹

^{19}F NMR (CDCl_3 , 282.5MHz): -111.3 (m, 1F, Ar-F).

Mass (GC-MS): 375.0 (97%); 376.0 (28%); 377.0 (100%); 416.0 (23%); 418.0 (23%)



5 5-Bromo-2-methylbenzoic acid (725mg, 3.37mmol, 1eq) was suspended in dry dichloromethane (9.7mL). Oxalyl chloride (0.32mL, 3.74mmol, 1.1eq) and N,N-dimethylformamide (0.013mL, 0.17mmol, 0.05eq) were then added at room temperature and the mixture was stirred for 6 hours. The solvent was then evaporated to give 5-bromo-2-methylbenzoyl chloride as yellow oil. This crude product was dissolved
 10 in dry dichloromethane (19.3mL), AlCl_3 (49.5mg, 3.71mmol, 1.1eq) and **42** (600mg, 3.37mmol, 1eq) were then added at 0°C (internal temperature). The resultant mixture was stirred at this temperature for 30 minutes and then at room temperature overnight. The reaction mixture was poured into ice and water, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were
 15 gathered, dried over MgSO_4 , filtered and concentrated. The residue was taken up with n-hexane to form a precipitate which was collected by filtration, washed with n-hexane and dried to afford compound **43** (69% yield) as yellowish crystals.

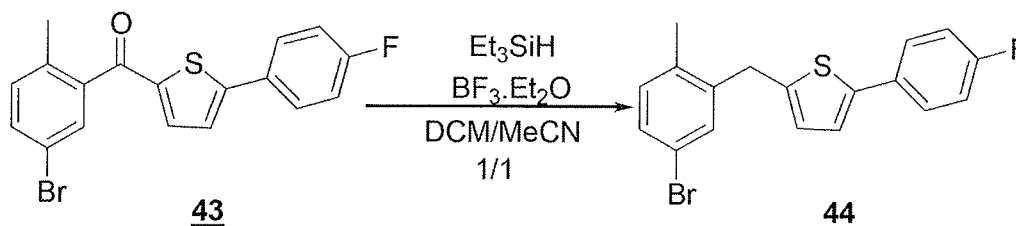
Synthesis of compound **44**

20

 $\text{C}_{18}\text{H}_{14}\text{BrFS}$
 $M = 361.27 \text{ g}\cdot\text{mol}^{-1}$

^{19}F NMR (CDCl_3 , 282.5MHz): -115.0 (m, 1F, Ar-F).

Mass (ESI⁺): 133 (29%); 177 (49%); 182 (55%); 184 (70%); 191 (72%); 281 (39%); 360 (95%); 362 (100%)



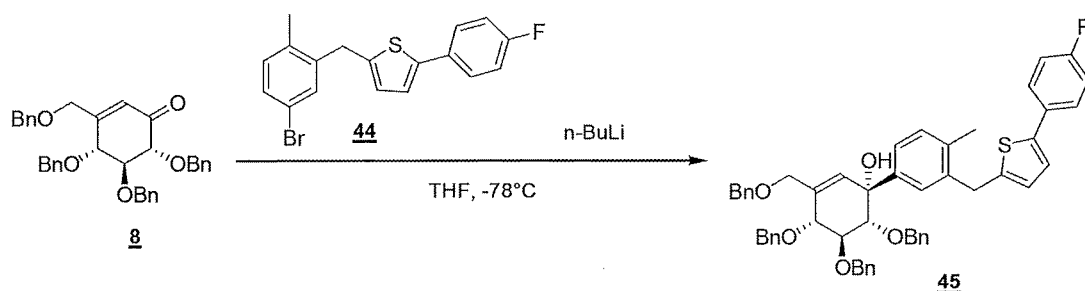
Et₃SiH (0.99mL, 6.18mmol, 2.9eq) was added at room temperature to a solution of ketone **43** (800mg, 2.13mmol, 1eq) in anhydrous dichloromethane-acetonitrile (1:1, v/v, 16mL). The resultant mixture was cooled to 0°C and BF₃.Et₂O (0.75mL, 5.97mmol, 2.8eq) was slowly added. The reaction mixture was then stirred at room temperature for 3 hours. A saturated aqueous solution of NaHCO₃ was slowly added at 0°C. The aqueous layer was extracted with dichloromethane and the resultant organic layer was dried over MgSO₄, filtered and concentrated. The crude mixture was then recrystallized with MeOH to afford compound **44** (70% yield) as yellowish crystals.

10 Synthesis of compound 45

C₅₃H₄₉FO₅S M = 817.02 g.mol⁻¹

¹⁹F NMR (CDCl₃, 282.5MHz): -115.2 (m, 1F, Ar-F)

Mass (ESI⁺): 839.5 [M+Na]⁺; 855.4 [M+K]⁺



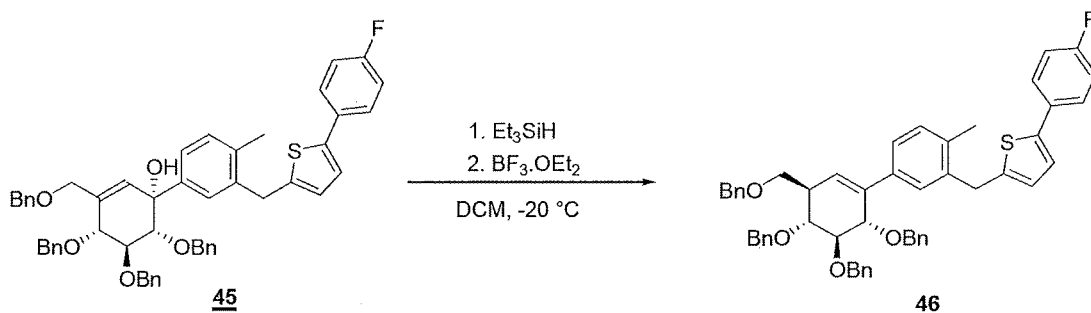
15 *n*-Butyllithium (1.4M in hexanes, 0.30mL, 0.412mmol, 1.1eq) was slowly added to a cooled solution (-70°C) of **44** (149mg, 0.412mmol, 1.1eq) in anhydrous THF-toluene (1:1, v/v, 4.8mL) under inert atmosphere. The resultant dark blue solution was stirred for 5 min at the same temperature before a cooled solution (-70°C) of cyclohexenone **8** was slowly added. The reaction mixture was stirred for 15 min at -70°C before being
20 poured into water. The organic layer was then dried over sodium sulphate, filtered and concentrated to afford crude **45** (300mg, 98% yield) as yellow oil which was used in the next step without further purification.

25 Synthesis of compound 46

C₅₃H₄₉FO₄S M = 801.02 g.mol⁻¹

¹⁹F NMR (CDCl₃, 282.5MHz): -115.3 (m, 1F, Ar-F)

Mass (ESI⁺): 823.5 [M+Na]⁺; 839.4 [M+K]⁺



Et₃SiH (0.025mL, 0.157mmol, 3eq) and BF₃.Et₂O (0.013mL, 0.105mmol, 2eq) were successively added to a cooled solution (-20°C) of **45** (43mg, 0.052mmol, 1eq) in anhydrous dichloromethane (0.55mL) under inert atmosphere. The resultant solution was stirred at -20°C for 1h45, diluted with dichloromethane and poured into brine. The organic layer was dried over sodium sulphate, filtered and concentrated to yield a green oil which was then purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 82:18) to afford compound **46** (27mg, 64% yield) as a green oil.

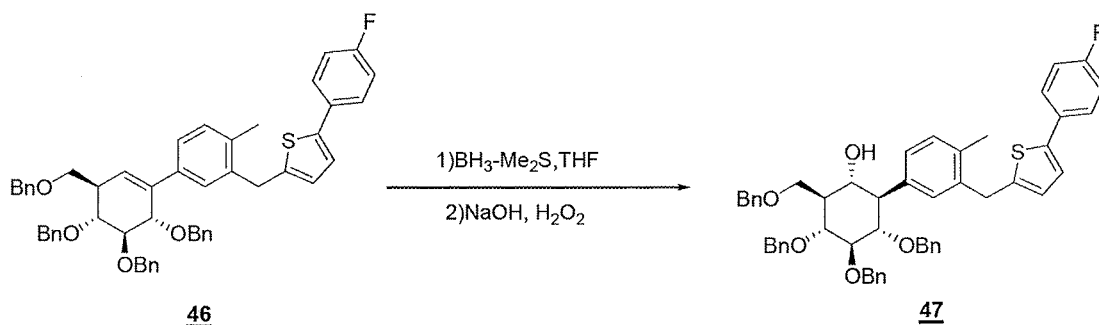
10 Synthesis of compound 47

C₅₃H₅₁FO₅S

M = 819.03 g.mol⁻¹

¹⁹F NMR (CDCl₃, 282.5MHz): -115.3 (m, 1F, Ar-F)

Mass (ESI⁺): 841.4 [M+Na]⁺; 857.4 [M+K]⁺



BH₃.Me₂S (2M in THF, 0.065mL, 0.130mmol, 4eq) was added to a cooled solution (0°C) of **46** (26mg, 0.032mmol, 1eq) in dry THF (0.335mL) under inert atmosphere. The resultant solution was stirred at room temperature overnight before being cooled to 0°C. Water (0.041mL, 2.27mmol, 70eq) was then added carefully followed by hydrogen peroxide (30%w/v, 0.11mL, 0.97mmol, 30eq) and 2N aqueous sodium hydroxide (0.13mL, 0.26mmol, 8eq). The white suspension was stirred at room temperature for 4h. The reaction mixture was then diluted with ethyl acetate and poured onto water. The organic layer was dried over sodium sulphate, filtered and concentrated to yield a

colorless residue which was then purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 77:23) to afford alcohol **47** (7mg, 26% yield) as a yellowish residue.

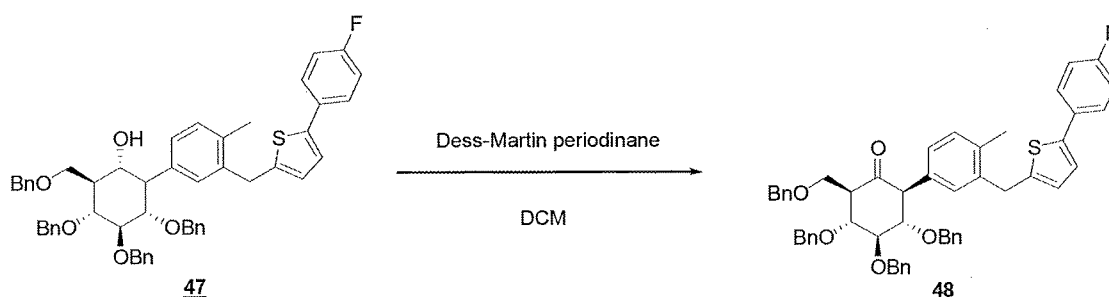
5 Synthesis of compound 48



$$M = 817.02 \text{ g.mol}^{-1}$$

^{19}F NMR (CDCl_3 , 282.5MHz): -115.4 (m, 1F, Ar-F)

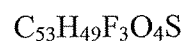
Mass (ESI^+): 839.4[M+Na] $^+$; 855.4[M+K] $^+$



- 10 Dess Martin periodinane (5mg, 0.013mmol, 1.5eq) was added to a solution of alcohol **47** (7mg, 0.009mmol, 1eq) in dichloromethane (0.150mL). The resultant mixture was stirred at room temperature for 1h30 before being poured in 1N aqueous sodium hydroxide. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulphate,
- 15 filtered and concentrated. The crude residue was then purified on silica gel chromatography (cyclohexane / ethyl acetate 100:0 to 80:20) to afford ketone **48** (6mg, 86% yield) as a yellowish residue.

Synthesis of compound 49

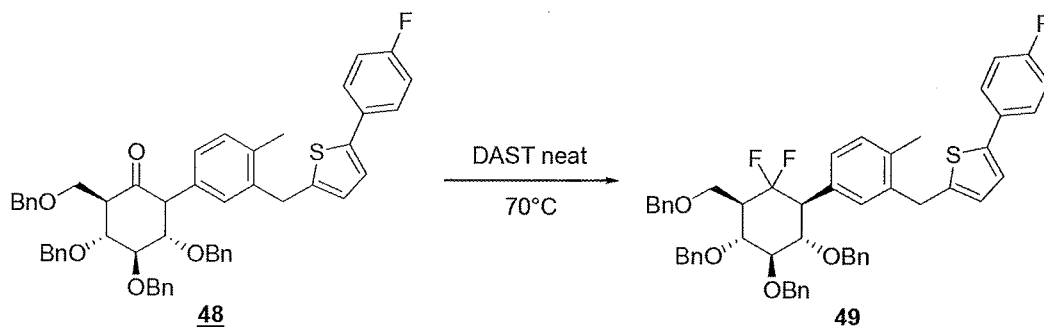
20



$$M = 839.01 \text{ g.mol}^{-1}$$

^{19}F NMR (CDCl_3 , 282.5MHz): -115.3 (m, 1F, Ar-F); 113.75 (dt, $J_1=254\text{Hz}$, $J_2=29\text{Hz}$, 1F, CFF); -100.4 (d, $J=254\text{Hz}$, 1F, CFF).

Mass (ESI^+): 861.3 [M+Na] $^+$; 877.4 [M+K] $^+$



Ketone **48** (316mg, 0.39mmol, 1eq) was dissolved in DAST (1.4mL, 11.4mmol, 30eq) and the reaction mixture was stirred overnight under inert atmosphere at 70°C. Dichloromethane was added at room temperature and the reaction was poured into water. The aqueous phase was extracted with dichloromethane and the organic phase was dried over Na₂SO₄, filtered and concentrated. The crude product was purified on silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 78:12) followed by preparative HPLC (Kromasil C18, MeOH/H₂O 95:5) to afford **49** (84mg, 26% yield) as a colorless oil.

Synthesis of compound **50**

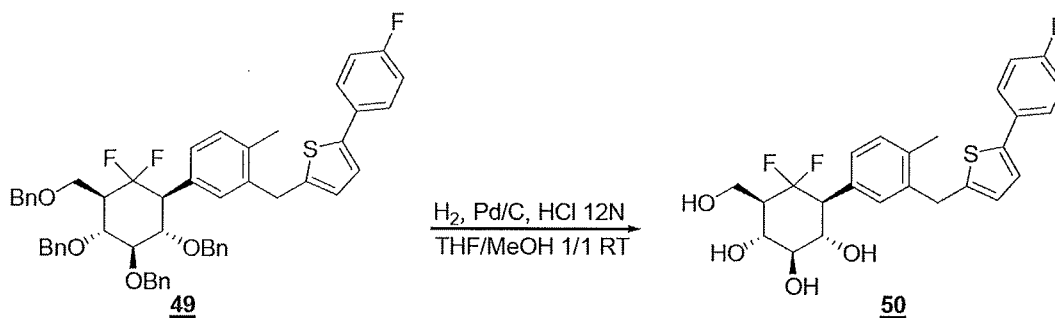
C₂₅H₂₅F₃O₄S

M = 478.52 g.mol⁻¹

¹⁹F NMR (CDCl₃, 282.5MHz): -100.2 (d, J=254Hz, 1F, CFF); -116.2 (dt, J1=254Hz, J2=28Hz, 1F, CFF); -117.6 (m, 1F, Ar-F).

Mass (ESI⁺): 501.2 [M+Na]⁺

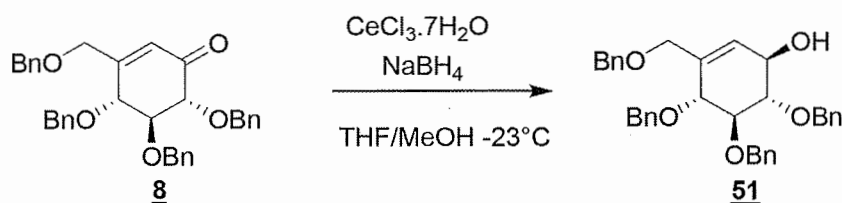
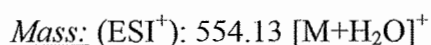
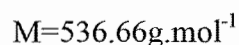
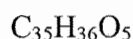
Mass (ESI⁻): 513.2 [M+Cl]⁻



Compound **49** (48mg, 0.057mmol, 1eq) was dissolved in THF-MeOH (1:1, v/v, 4.2mL) under inert atmosphere. 10% Pd/C (96mg, 0.02 mmol, 0.35eq) and 5 drops of 12N aqueous hydrochloric acid were added to the mixture which was degassed 5 times with H₂. The resultant black suspension was stirred under an atmosphere of H₂ at room temperature for 72h. The reaction mixture was filtered over a pad of Celite 545 and the

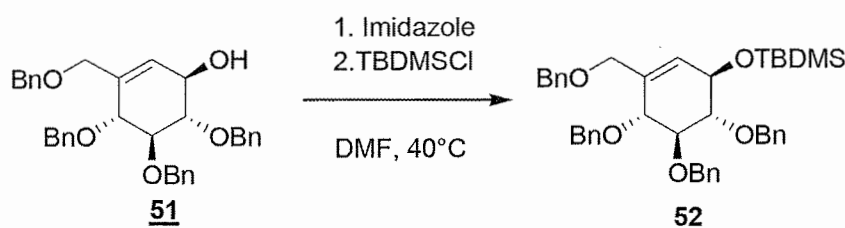
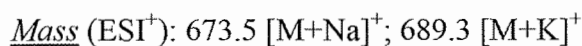
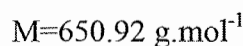
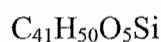
filtrate was concentrated. The crude product was purified on silica gel chromatography (dichloromethane/Methanol 100:0 to 91:9) followed by preparative HPLC (5-amide C18, MeCN/H₂O 38:62) to afford compound **50** in 27% yield as a white solid.

5 Synthesis of compound 51



Under inert atmosphere, cerium chloride heptahydrate (167mg; 0.449mmol; 1.2eq) was added to a solution of cyclohexenone **8** (200mg; 0.374mmol; 1eq) in a MeOH-THF (3:1, v/v, 5mL) cooled to -23°C. The reaction mixture was stirred for 30 minutes at this temperature and sodium borohydride (21mg; 0.561mmol; 1.5eq) was added. After a further 45 minutes, a saturated aqueous solution of ammonium chloride (15mL) and sodium chloride (15mL) were added. The aqueous layer was extracted with ethyl acetate and the combined extracts were dried over sodium sulphate, filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/cyclohexane 3/97 to 35/65) to afford alcohol **51** (137mg, 68% yield), as a white solid.

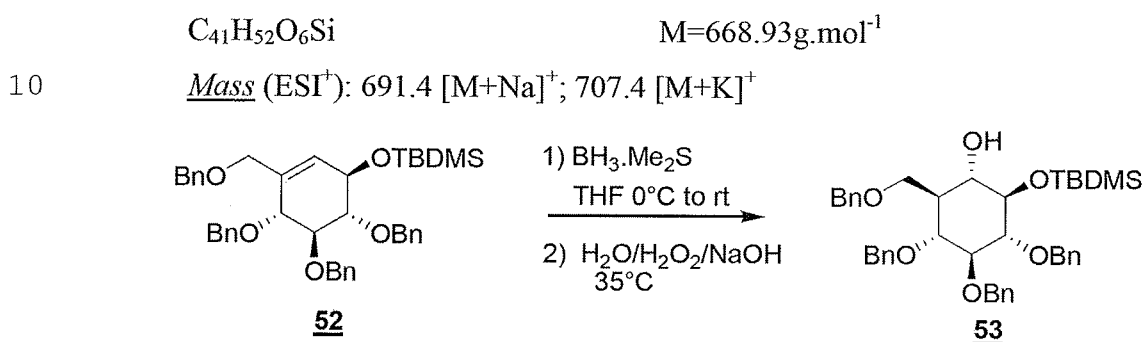
20 Synthesis of compound 52



To a solution of **51** (3.80g; 7.09mmol; 1eq) in dry dimethylformamide (25mL), under inert atmosphere, was added imidazole (1.45g; 21.3mmol; 3eq). The reaction mixture

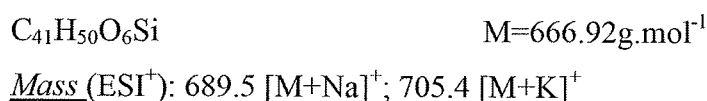
was stirred for 30 minutes at room temperature before *tert*-butyldimethylsilyl chloride (1.70g; 11.3mmol; 1.6eq) was added. The mixture was heated at 40°C for 12h then quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulphate, filtered and concentrated to afford compound **52** (4.57g, 99% yield), as yellow oil. This compound was engaged in the next step without further purification.

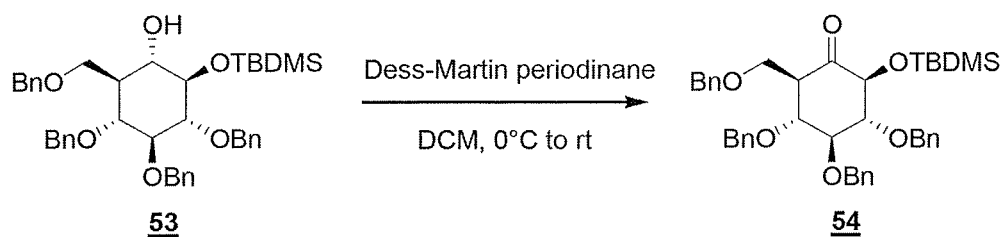
Synthesis of compound **53**



To a solution of **52** (4g; 6.15mmol; 1eq) in dry THF (60mL), under inert atmosphere, was added borane-dimethylsulfide complex (12.3mL; 2M in THF; 24.6mmol; 4eq) at 0°C. The reaction medium was stirred overnight at room temperature before water (7.8mL; 0.43mol; 70eq), hydrogen peroxide 30% in water (21.0mL; 0.19mol; 30eq) and 3M aqueous sodium hydroxide (16.4mL; 49.2mmol; 8eq) were successively added at 0°C. The mixture was stirred for 2h at room temperature before being quenched with a saturated aqueous solution of ammonium chloride (300mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane/ethyl acetate) to afford alcohol **53** (754mg, 63% yield), as a yellow oil. (Crude **53** can also be engaged in the next step without further purification).

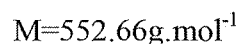
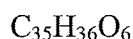
Synthesis of compound **54**





To a solution of **53** (1.51g; 2.26mmol; 1eq) in dry dichloromethane (23mL), under inert atmosphere, was added Dess-Martin periodinane (1.44g; 3.39mmol; 1.5eq) at 0°C. The mixture was stirred overnight at room temperature before a 1M aqueous solution of sodium hydroxide (50mL) was added. The aqueous layer was extracted with dichloromethane (2x100mL) and the combined organic layers were dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (EtOAc/cyclohexane 1/99 to 11/89) to afford ketone **54** (1.13g, 75% yield), as yellow oil. Alternatively, ketone **54** can be obtained with 55% yield over 3 steps from **51**, performing only one purification at this last step.

Synthesis of compound **55**

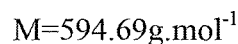
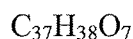


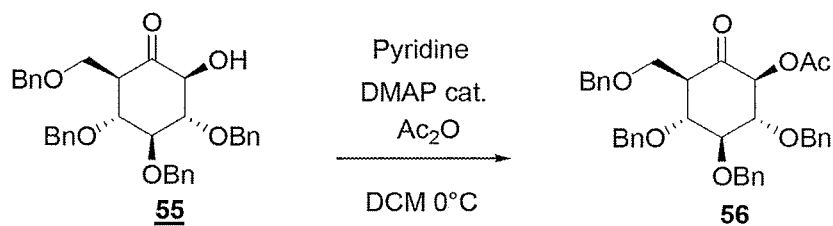
Mass (ESI⁺): 575.3 [M+Na]⁺; 591.3 [M+K]⁺



To a solution of **54** (560mg; 0.84mmol) in dichloromethane (4mL) was added a solution of 12N HCl in methanol (2% v/v, 4mL). The reaction mixture was stirred overnight at room temperature. Water was then added, followed by a saturated aqueous solution of sodium hydrogen carbonate until neutralization. The mixture was extracted with dichloromethane, dried over sodium sulfate, filtered and concentrated. The residue was triturated in ethanol and filtered to afford compound **55** (337mg, 73% yield) as white solid.

Synthesis of compound **56**



$$\text{Mass (ESI}^+ \text{): } 617.6 \text{ [M+Na]}^+; 633.6 \text{ [M+K]}^+$$


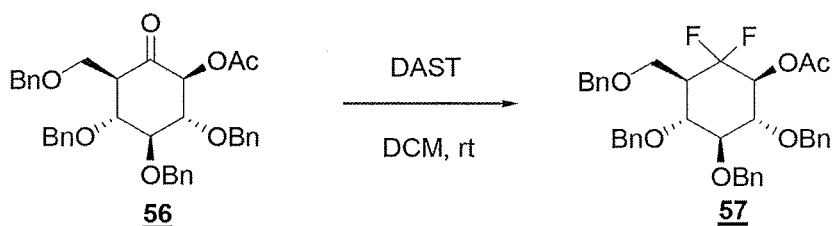
To a solution of **55** (1.27g; 2.30mmol; 1eq) in dry dichloromethane (3mL), under inert atmosphere, were successively added at 0°C, pyridine (0.93mL; 11.5mmol; 5eq), 4-dimethylaminopyridine (60mg; 0.46mmol; 0.2eq) and acetic anhydride (0.44mL; 4.60mmol; 2eq). The mixture was stirred at the same temperature for 45 minutes. Water followed by 1N aqueous solution of hydrochloric acid were then added. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated to afford quantitatively ketone **56** (1.39g) as a light yellow oil. Crude **56** was engaged in the next step without further purification.

Synthesis of compound 57

$$\text{C}_{37}\text{H}_{38}\text{F}_2\text{O}_6$$
$$M = 616.69 \text{ g.mol}^{-1}$$

15 ^{19}F NMR (CDCl_3 , 282.5MHz): -110.0 (d, $J=250\text{Hz}$, 1F, CFF); -119.4 (ddd,
J1=249Hz, J2=21Hz, J3=29Hz, 1F, CFF).

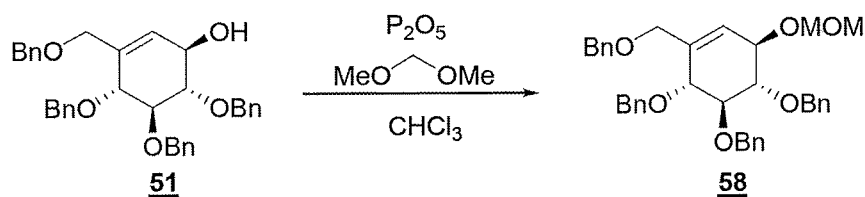
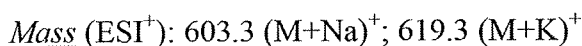
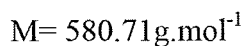
Mass (ESI⁺): 603.4 [M-HF+Li]⁺; 619.3 [M-HF+Li]⁺; 623.3 [M+Li]⁺; 639.3 [M+Na]⁺; 655.3 [M+K]⁺



To a solution of **56** (1.30g; 2.19mmol; 1eq) in dry dichloromethane (5.2mL), under inert atmosphere, was added diethylaminosulfur trifluoride (5.2mL; 42.4mmol; 19eq). The reaction medium was stirred for 16h at room temperature. The solution was then diluted with dichloromethane and solid sodium hydrogen carbonate was added. The mixture was stirred for additional 30 minutes at 0°C before water was added dropwise. The aqueous layer was extracted with dichloromethane and the combined organic layers

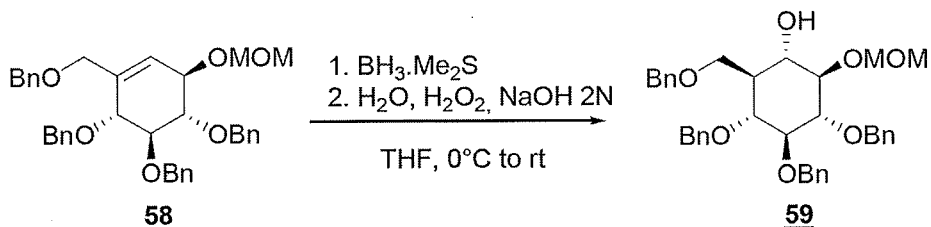
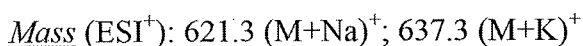
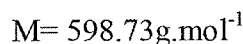
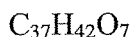
were dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (EtOAc/cyclohexane 2/98 to 12/88) to afford compound 57 (471mg, 35% yield) in the form of a light yellow oil.

5 Synthesis of compound 58



Under inert atmosphere, crude 51 (53.7g) was dissolved in a mixture of dry chloroform (500mL) and dimethoxymethane (292mL, 3.3mol, 33eq). P_2O_5 (73.9g, 521mmol, 5.2eq.) was added. The reaction was kept under mechanical stirring for 1h at room temperature. The mixture was then filtered on a pad of celite® 545 (elution with dichloromethane) and washed with a saturated aqueous solution of NaHCO_3 (700mL). Water (1L) was then added and the mixture was extracted with dichloromethane (2×300mL), washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford 58 (57.7g) in the form of a brown oil which slowly crystallized. 58 was engaged in the next step without further purification.

20 Synthesis of compound 59



Under inert atmosphere, borane-dimethyl sulfide complex (2M in THF, 199mL, 397mmol, 4eq) was added to a solution of 58 (57.7g) in dry THF (497mL) cooled to 0°C. The reaction mixture was then stirred overnight at room temperature before being cooled to 0°C and carefully treated with water (125mL, 6.96mol, 70eq.), followed by

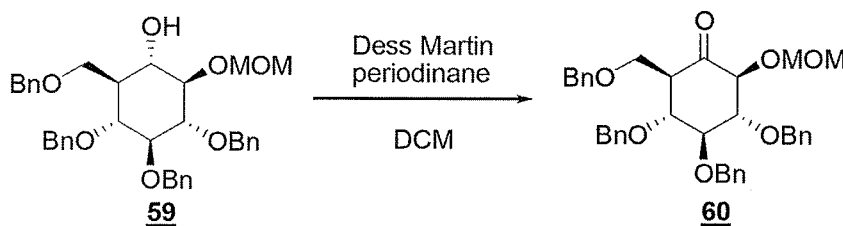
hydrogen peroxide (30%w/v in H₂O, 338mL, 2.98mol, 30eq) and sodium hydroxide (2M in H₂O, 397mL, 0.79mol, 8eq). The mixture was allowed to react for 2h at room temperature (~25°C) before a saturated aqueous solution of ammonium chloride (700mL) and water (300mL) were added to quench the reaction. The mixture was
 5 extracted with ethyl acetate (3×500mL) and the combined organic layers were washed with water (600mL) and brine (600mL), dried over Na₂SO₄, filtered, and concentrated to afford crude **59** (59.5g) in the form of a yellow oil. **59** was engaged in the next step without further purification.

10 Synthesis of compound 60

C₃₇H₄₀O₇

M= 596.71g.mol⁻¹

Mass (ESI⁺): 619.3 (M+Na)⁺; 635.3 (M+K)⁺



Dess-Martin periodinane (84.3g; 199mmol; 2eq) was added portionwise to a solution of
 15 crude **59** (59.5g) in dry dichloromethane (1L) at 0°C. The reaction was then stirred 18h at room temperature before sodium hydroxide (1N in H₂O, 1L) and water (500mL) were added. The aqueous layer was then extracted with dichloromethane (2×400mL) and the combined organic layers were dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane / ethyl acetate 98:2
 20 to 86:14, v/v on Biotage SNAP 750g cartridge), to afford the target ketone **60** (32g, 48% yield over 4 steps) as a yellow solid.

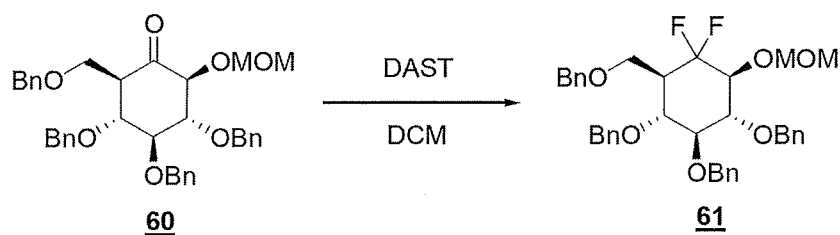
Synthesis of compound 61

C₃₇H₄₀F₂O₆

M= 618.71g.mol⁻¹

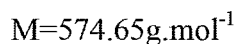
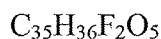
25 ¹⁹F NMR (CDCl₃, 282.5MHz): -108.5 (d, J=252Hz, 1F, CFF); -121.0 (ddd, J1=252Hz, J2=30Hz, J3=20Hz, 1F, CFF).

Mass (ESI⁺): 641.3 (M+Na)⁺; 657.3 (M+K)⁺



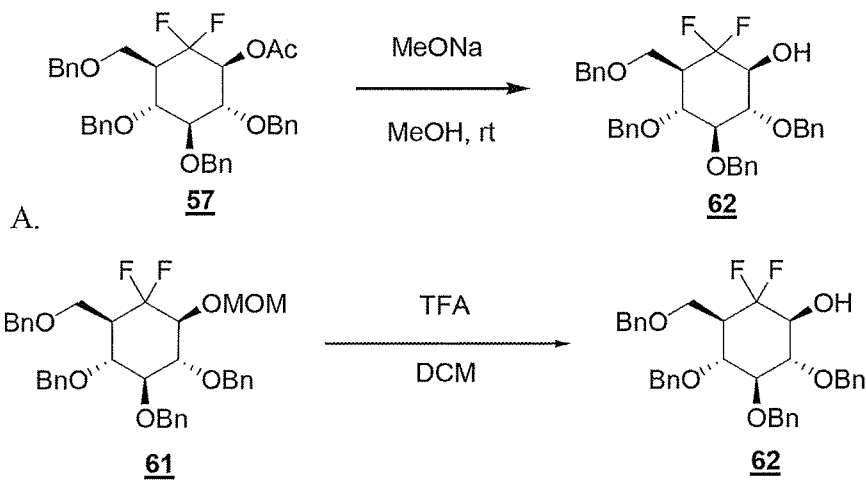
DAST (125mL, 1.02mol, 19eq.) was slowly added to a cooled solution (0°C) of **60** (32g, 53.6mmol, 1eq.) in dry dichloromethane (145mL). The reaction mixture was then allowed to reach room temperature and was stirred overnight. Dichloromethane (400mL) was then added and the mixture was slowly poured into a mixture of ice (1L), dichloromethane (300mL) and NaHCO₃ (400g). The mixture was vigorously stirred for 15min. Water (500mL) was added and the aqueous layer was extracted with dichloromethane (2×300mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated to afford crude **61** (32.6g) in the form of a yellowish oil. **61** was engaged in the next step without further purification.

Synthesis of compound **62**



¹⁹F NMR (CDCl₃, 282.5MHz): -110.7 (d, J=249Hz, 1F, CFF); -123.7 (ddd, J1=248Hz, J2=29Hz, J3=19Hz, 1F, CFF).

Mass (ESI⁺): 577.5 [M-HF+Na]⁺; 592.5 [M+H₂O]⁺; 597.5 [M+Na]⁺; 613.5 [M+K]⁺



A. To a solution of **57** (70mg; 0.114mmol; 1eq) in dry methanol, under inert atmosphere, was added sodium methanolate (8mg; 0.142mmol; 1.25eq). The reaction medium was

stirred overnight at room temperature. Water was then added followed by a 1N aqueous solution of hydrochloric acid which was added until pH=6. The mixture was extracted with ethyl acetate, washed with brine, dried over sodium sulphate, filtered and concentrated to afford alcohol **62** (65mg) in the form of a light orange solid, with a quantitative yield.

B. Trifluoroacetic acid (98.0mL, 1.32mol, 25eq.) was added to a solution of **61** (32.6g) in dry dichloromethane (260mL) under inert atmosphere. The reaction mixture was stirred overnight at room temperature. The mixture was cooled to 0°C and water (500mL) was added. The layers were separated and the organic layer was washed with water (500mL). The combined aqueous layers were combined and extracted with dichloromethane (2×100mL). The combined organic layers were washed with sat. NaHCO₃ (250mL), dried over sodium sulfate, filtered and concentrated. The crude mixture was purified on silica gel chromatography (cyclohexane/ethyl acetate 98:2 to 82:18, v/v on Biotage SNAP 750g cartridge) to afford **62** (13.6g, 30% over 2 steps) as a white solid.

Synthesis of compound **63**

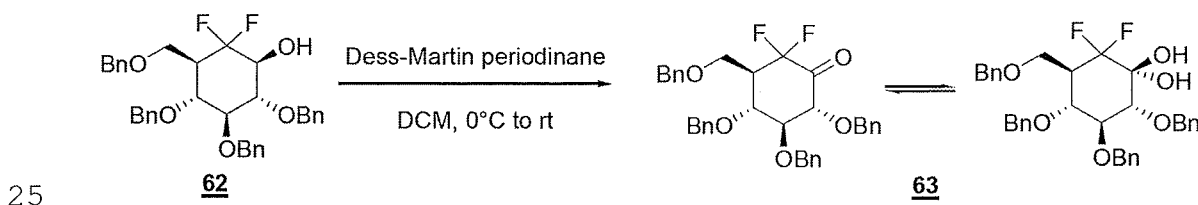
$C_{35}H_{36}F_2O_6$ / $C_{35}H_{34}F_2O_5$ $M=590.65g.mol^{-1}/572.64g.mol^{-1}$

^{19}F NMR ($CDCl_3$, 282.5MHz):

Hydrate form: -117.3 (dd, $J_1=257Hz$, $J_2=30Hz$, 1F, CFF); -125.6 (d, $J_1=258Hz$, 1F, CFF).

Ketone form: -112.1 (ddd, $J_1=260Hz$, $J_2=32Hz$, $J_3=6Hz$, 1F, CFF); -119.4 (dd, $J_1=260Hz$, $J_2=4Hz$, 1F, CFF).

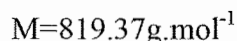
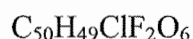
Mass (ESI⁺): 608.4 $[M+H_2O]^+$; 613.5 $[M+Na]^+$; 619.5 $[M+K]^+$



To a solution of **62** (200mg; 0.35mmol; 1eq) in dry dichloromethane, under inert atmosphere, was added Dess-Martin periodinane (295mg; 0.70mmol; 2eq). The reaction medium was stirred for 3h at room temperature before a 1N aqueous solution of sodium hydroxide (10mL) was added. The aqueous layer was extracted with dichloromethane

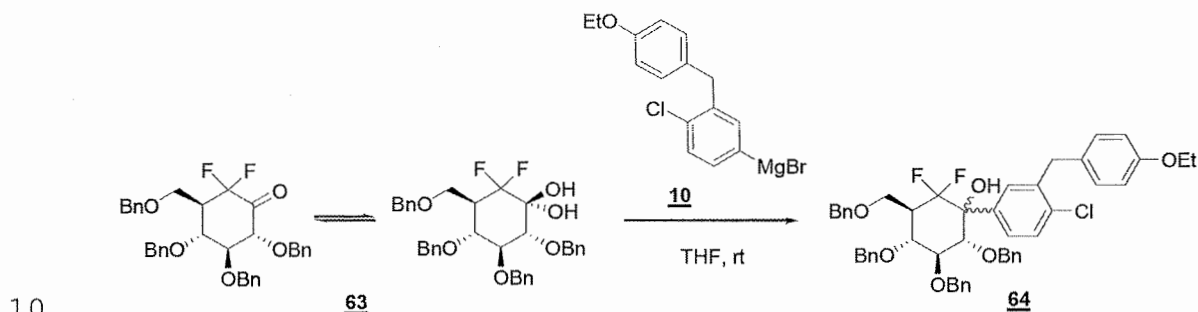
and dried over sodium sulphate, filtered and concentrated to afford ketone **63** (158mg, 77% yield) as a light orange solid which rapidly evolves toward the formation of the hydrate form until equilibrium is reached.

5 Synthesis of compound 64



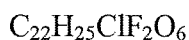
^{19}F NMR (CDCl_3 , 282.5MHz): -112.3 (dd, $J_1=266\text{Hz}$, $J_2=27\text{Hz}$, 1F, $\text{C}\underline{\text{F}}\text{F}$); -113.7 (dd, $J_1=266\text{Hz}$, $J_2=6\text{Hz}$, 1F, $\text{C}\text{F}\underline{\text{F}}$).

Mass (ESI⁺): 836.7[M+H₂O]⁺; 841.8[M+Na]⁺; 857.7[M+K]⁺



In a Schlenk tube under inert atmosphere containing magnesium turnings (50mg, 2.04mmol, 1.2eq) was added 2mL (out of 5mL) of a solution of **10** (552mg, 1.70mmol, 1eq) and 1,2-dibromoethane (15μL, 0.17mmol, 0.1eq) in dry THF (5mL). The mixture was heated at 75°C for 5 min to initiate the reaction and the last 3mL of the solution of **10** and 1,2-dibromoethane were then added dropwise at room temperature. This solution was then stirred at 75°C for 1h.

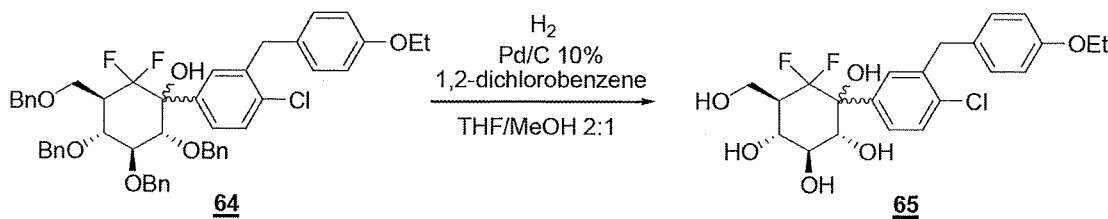
2.4mL of this Grignard solution, previously cooled to room temperature, were then added to a solution of **63** (158mg, 0.27mmol) in dry THF (2mL). The reaction mixture was stirred at room temperature for 2h before a saturated aqueous solution of ammonium chloride was added. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated. The residue was purified on silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 77:23) to afford compound **64** (152mg) as a mixture of two diastereomers with 69% yield. These diastereomers can be separated by semi-preparative HPLC.

Synthesis of compound 65

$$M=458.88\text{g}\cdot\text{mol}^{-1}$$

^{19}F NMR (MeOD, 282.5MHz): -114.0 (dd, J1=262Hz, J2=7Hz, 1F, CFF); -115.4 (dd, J1=262Hz, J2=26Hz, 1F, CFF).

5 Mass (ESI⁺): 481.3 [M+Na]⁺; 497.3 [M+K]⁺



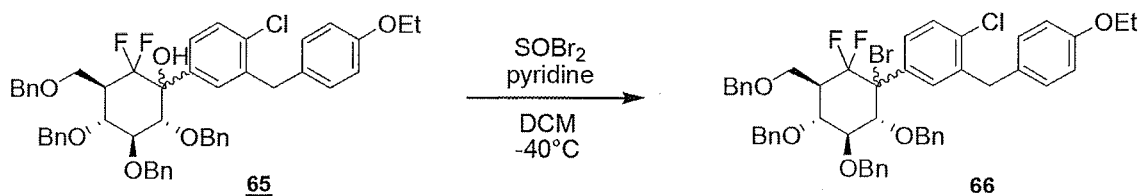
o-Dichlorobenzene (53μL, 0.47mmol, 10eq) followed by Pd/C 10% (56.0mg, 53.3μmol, 1.1eq) were added to a solution of **64** (38.0mg, 46.4μmol, 1eq) in a mixture of THF and MeOH (2:1, v/v, 26mL). The reaction was placed under hydrogen atmosphere and stirred at room temperature for 2h. The reaction mixture was filtered and concentrated before being purified on silica gel chromatography to afford the target compound **65**.

Synthesis of compound 66

$$M=882.27\text{g}\cdot\text{mol}^{-1}$$

15 ^{19}F NMR (CDCl₃, 282.5MHz): Major anomer: -97.8 (dd, J1=246Hz, J2=30Hz, CFF); -102.6 (d, J=246Hz, CFF).

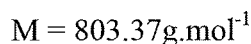
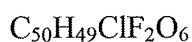
Mass (ESI⁺): 4881.2 (M+H)⁺; 898.3 (M+H₂O)⁺.



20 SOBr₂ (85μL, 1.10mmol, 15eq) was added at -40°C to a solution of **65** (60mg, 0.07mmol, 1eq) in dry dichloromethane (0.73mL) under inert atmosphere. The mixture was stirred while the temperature was gradually raised to 0°C over 5h. Pyridine (89μL, 1.10mmol, 15eq) was then added and the solution was stirred for an additional 1h at 0°C. A solution of aqueous 1M HCl was added and the solution was allowed to reach room temperature. The organic layer was collected and the aqueous layer was extracted with dichloromethane. The combined organic layer was then dried over sodium sulfate,

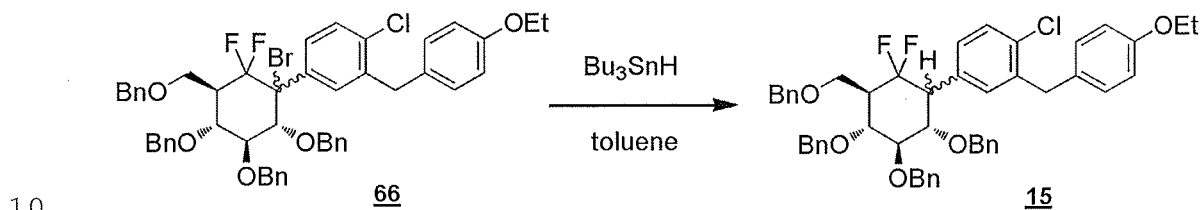
filtered and concentrated. The crude mixture was purified on silica gel chromatography (Biotage SNAP10g, cyclohexane/ethyl acetate 100:0 to 92/8) to afford **66** (15mg, 23%) as a colorless oil. The collected fraction contains one major isomer.

5 Synthesis of compound 15



^{19}F NMR (CDCl_3 , 282.5MHz): -100.3 (d, $J=254\text{Hz}$, 1F, CF_2); -113.3 (td, $J_1=254\text{Hz}$, $J_2=29\text{Hz}$, 1F, CF).

Mass: (ESI⁺): 820.00 (M+H₂O)

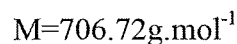


Bu_3SnH (7 μL , 25.5mmol, 1.5eq) was added to a solution of **66** (15mg, 17.0mmol) in dry toluene (170 μL) at room temperature. The mixture was then heated and stirred at 110°C for 3h. One additional portion of Bu_3SnH (7 μL , 25.5mmol, 1.5eq) was then added and the mixture was stirred at 110°C for an additional period of 3h. This step was repeated once more until no more evolution was noticed on TLC. The mixture was concentrated and purified by preparative TLC (cyclohexane/ethyl acetate 90:10, v/v) to afford **15** (2mg, 17%, β -anomer and 4mg contains α -anomer).

15

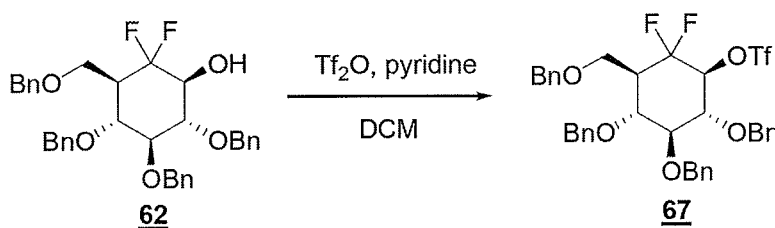
Synthesis of compound 67

20



^{19}F NMR (CDCl_3 , 282.5MHz): -74.0 (d, $J=12\text{Hz}$, CF_3); -108.2 (dq, $J_1=252\text{Hz}$, $J_2=12\text{Hz}$, CF); -119.5 (ddd, $J_1=253\text{Hz}$, $J_2=31\text{Hz}$, $J_3=18\text{Hz}$, CF).

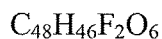
Mass (ESI⁺): 724.3 (M+H₂O⁺); 729.2 (M+Na)⁺; 745.2 (M+K)⁺



Trifluoromethanesulfonic anhydride (9.5mL, 57.4mmol, 3eq) and pyridine (4.6mL, 57.4mmol, 3eq.) were added to a cooled solution (0°C) of **62** (11.0g, 19.1mmol, 1eq.) in dry dichloromethane (190mL) under inert atmosphere. The solution was allowed to warm to room temperature and was stirred overnight. Water (400mL) was then added to the cooled mixture (0°C) which was then extracted with dichloromethane (2×150mL), dried over sodium sulfate, filtered and concentrated to afford crude **67** (13.6g) as a brown solid. **67** was engaged in the next step without further purification.

Synthesis of compound **68**

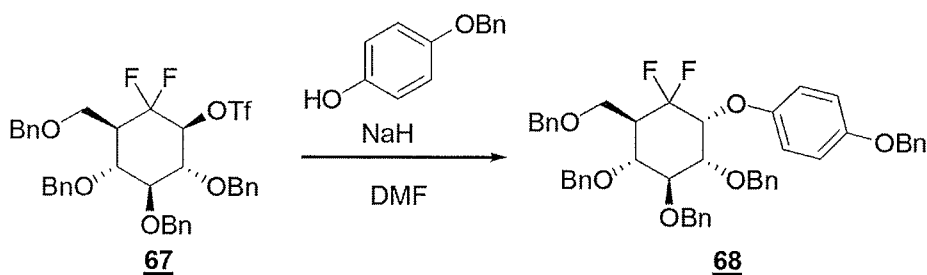
10



$$M=756.87\text{g}\cdot\text{mol}^{-1}$$

^{19}F NMR (CDCl_3 , 282.5MHz): -107.9 (brd, $J_1=256\text{Hz}$, CFF); -110.8 (ddd, $J_1=257\text{Hz}$, $J_2=30\text{Hz}$, $J_3=3\text{Hz}$, CFF).

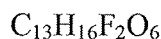
Mass (ESI⁺): 779.4 (M+Na)⁺; 795.3 (M+K)⁺



Sodium hydride (95%, 1.38g, 57.3mmol, 3eq.) was added to a cooled (0°C) solution of 4-(benzyloxy)phenol (13.4g, 66.9mmol, 3.5eq.) in dry DMF (95mL). The reaction mixture was stirred 1h at the same temperature before a solution of **67** (11.0g) in dry DMF (95mL) was added. The reaction mixture was stirred at 50°C overnight before being cooled again at 0°C. Water (250mL) followed by a 1N aqueous solution of sodium hydroxide (600mL) were then added. The mixture was extracted with diethyl ether (300mL then 2×150mL) and the combined organic layers were washed with water (2×600mL) and brine (600mL) before being dried over sodium sulfate, filtered and concentrated to afford crude **68** (13.5g) in the form of a purple oil. **68** was engaged in the next step without further purification.

25

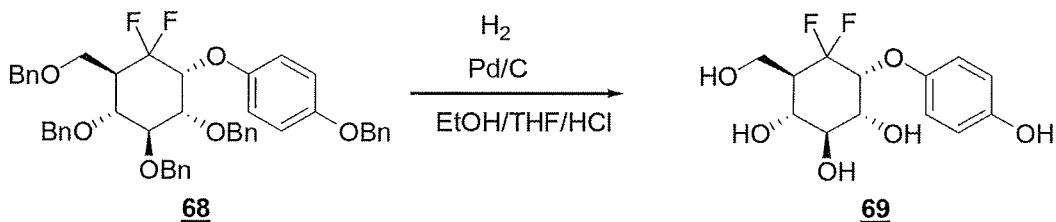
Synthesis of compound **69**



$$M=306.26\text{g}\cdot\text{mol}^{-1}$$

^{19}F NMR (D_2O , 282.5MHz): -107.6 (brd, $J=262\text{Hz}$, 1F, CFF); -111.6 (brdd, $J_1=262\text{Hz}$, $J_2=31\text{Hz}$, 1F, CFF).

Mass (ESI-): 285.1 (M-H-HF) $^-$; 305.1 (M-H) $^-$; 341.1 (M+Cl) $^-$; 351.1 (M+HCO $_2$) $^-$



- 5 Crude **68** (13.5g) was dissolved in a mixture of ethanol/12N HCl 4% (v/v, 117mL), tetrahydrofurane (63mL). Palladium on activated carbon (10%, 3.8g, 0.2eq.) was then suspended in the solution and the reaction mixture was placed under hydrogen atmosphere and stirred for 3 days at room temperature. The reaction medium was filtered and concentrated before being purified on silica gel chromatography
- 10 (dichloromethane / methanol 100:0 to 85:15, v/v on Biotage SNAP 340g cartridge) to afford **69** (4.92g, 90%) which was freeze-dried in the form of a white solid.

2. Biological activity

- 15 a) Assay for the facilitatory effect on glucose excretion.

As experimental animal, female CD1 mice (CDM or Charles River) were used. A test compound was dissolved in the vehicle (5% N-methyl pyrrolidone, 20% PEG 400, 75% 20 mM Na $_4$ P $_2$ O $_7$ buffer, v/v/v) at the concentration of 1 mg/mL. After the body weights of the mice were measured and the mice randomized, the test article was orally administered at the dose of 1 mg/kg, 3 mg/kg and 10 mg/kg. For control, just the vehicle (5% N-methyl pyrrolidone, 20% PEG 400, 75% 20 mM Na $_4$ P $_2$ O $_7$ buffer, v/v/v) was orally administered. The oral administration was performed with gastric tube for mice and a 1 mL syringe. The minimum count in one group was 3 but could reach 12 for some groups. Collection of the urine was performed manually by gentling massaging

20 the abdomen in order to collect urine (3 μL) via a calibrated pipette. Urine was collected at 1, 2, 4, 6, 8 and then 16, 18, 20, 22, 24, 26 and 28 hrs. The urine glucose concentration was measured using a WAKO glucose kit as follows: 3 μL of urine was deposited into a 96-well micro plate for spectrometric readout. The urine aliquot was

25 diluted with 350 μL of the WAKO working solution. For glucose concentrations that

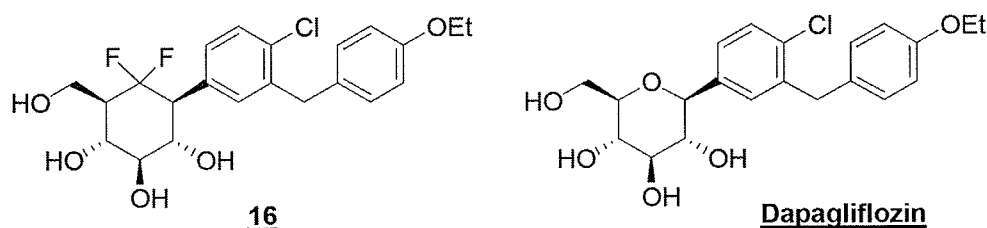
may be over the range of the WAKO glucose kit, an aliquot (35 μ L) of the last solution was deposited into another 96-well micro plate and further diluted (10 x) with 315 μ L of the WAKO working solution. The absorbance of the 96-well plates were then read at 505 nm using a BioTek SynergyMX plate fluorometer/absorbance photometer and the glucose concentration was calculated. The glucose concentrations for controls and test articles at the different time points were averaged using Excel 2007 and plotted using GraphPad Prism 5.

The results obtained with **16** and **50** are shown on figures 1 and 2. It appears thus that **16** (3 mg/kg) triggered a lasting glucosuria (up to 26 hrs, Figure 2).

b) Assays to compare the duration of action of compounds according to the invention to the one of compounds of prior art by studying the facilitatory effect on glucose excretion

The assays have been performed as described for a).

- Compound **16** according to the invention has been compared to Dapagliflozin to underline the improvement of the duration of action, i.e. the longer duration of glucosuria, of the compound when the intracyclic oxygen atom of the glucose moiety is replaced by a CF_2 moiety.

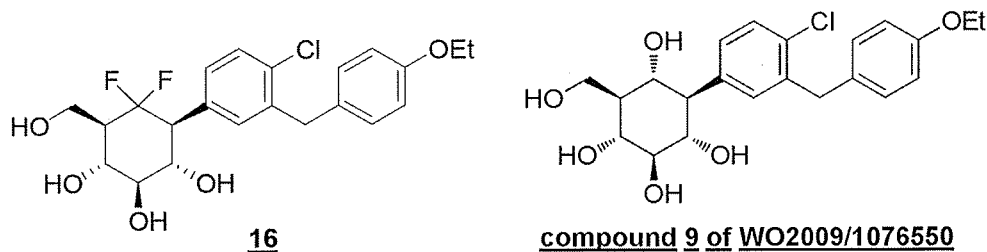


This assay has been carried out at a dose of 3 mg/ kg.

The results obtained are presented on Figure 5. It appears thus that **16** (3 mg/kg) triggered glucosuria that lasted beyond 24 hours compared to Dapagliflozin.

- Compound **16** according to the invention has been compared to the compound 9 of WO 2009/1076550 to underline the improvement of the duration of action of the compound when a mimic of glucose bearing a CH-OH moiety instead of the intracyclic

oxygen atom is replaced by a mimic of glucose bearing a CF₂ in place of the CH-OH moiety.



This assay has been carried out at a dose of 3 mg/ kg.

- 5 The results obtained are presented on Figure 6. It appears thus that **16** (3 mg/kg) triggered a longer lasting glucosuria (up to 24 hrs) when none could be detected for the same time period for the compound 9 of WO 2009/1076550.

c) Assay for the facilitatory effect in decreasing blood glucose excursions following glucose challenge.

10

As experimental animal, 18 hrs fasted female CD1 mice (CDM or Charles River) were used. A test compound was dissolved in the vehicle (5% N-methyl pyrrolidone, 20% PEG 400, 75% 20 mM Na₄P₂O₇ buffer, v/v/v) at the concentration of 1 mg/mL. After the body weights of the mice were measured and the mice randomized, the test article

15 was orally administered at the dose of 1 mg/kg, 3 mg/kg and 10 mg/kg. For control, just the vehicle (5% N-methyl pyrrolidone, 20% PEG 400, 75% 20 mM Na₄P₂O₇ buffer, v/v/v) was orally administered. 15 min after this oral administration, a 20% glucose solution in deionised water was orally administered to all mice. The oral administration was performed with gastric tube for mice and a 1 mL syringe. The minimum count in

20 one group was 3 but could reach 5 for some groups. Collection of the blood was performed via the saphenous vein. Blood was collected at 5, 10, 30, 45, 60 and 120 min post glucose challenge. One experiment consisted in administering the test article 18 hrs prior to a glucose challenge i.e. 18 hrs post po of test article. The blood glucose concentration was measured using Johnson and Johnson's OneTouch® Ultra Blood

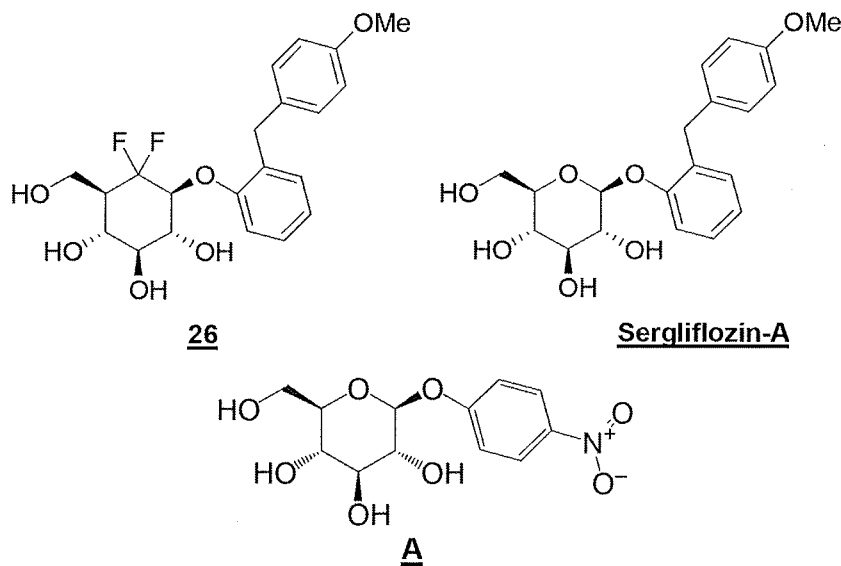
25 Glucose Monitoring System. The glucose concentrations for controls and test articles at the different time points were averaged using Excel 2007 and plotted using GraphPad Prism 5.

The results obtained with **16** are shown on figures 3 and 4.

It appears thus that **16** reduced blood glucose levels in a dose-dependent manner in normal mice following glucose challenge (Figure 3). Moreover, **16** (3 mg/kg) administered orally 18 hrs prior to glucose challenge still reduced blood glucose excursions following glucose challenge (Figure 4).

d) Assay to evaluate and compare the stability against glycosidase of compound **26** according to the invention to a compound of prior art (Sergliflozin-A).

The enzymatic stability assay has been performed with compound **26** according to the invention and compound A used as a reference compound to control the efficacy of the β -glucosidase. The sergliflozin-A stability has also been evaluated in order to compare the improvement of metabolic stability obtained through the replacement of the intracyclic oxygen atom of the glucose moiety by a CF_2 moiety.



All the compounds have been treated with β -glucosidase. The stability of compound **26** and Sergliflozin-A has been assessed by HPLC analysis after incubation with β -glucosidase.

A Gilson HPLC system was used, equipped with a manual injection system ($V=20\mu\text{L}$), a Diode Array Detector (DAD172) set at a wavelength of 230nm and a $150\text{mm}\times 4.6\text{mm}$,

5 μm HICHROM Kromasil 100-5C18 reverse phase column. A linear HPLC binary gradient was used as follows: solvent A was water and solvent B was acetonitrile. Following the injection of 20 μL of a sample, solvent B was held at 20% for 3 min, increased from 20% to 90% in 17min, held at 90% for 4 min; finally, solvent B was decreased back to 20% over 5.5 min and was held at 20% for 3.5 min.

The procedure has been adapted from J. Agric. Food Chem. 2005, 53, 4918-4924.

10 100 μL of a solution of compound **26** at $4.5 \cdot 10^{-4} \text{mol.L}^{-1}$ in acetonitrile was added to a solution containing 800 μL of phosphate buffer (73173 Fluka, pH 7) in the presence of β -glucosidase from Almonds (10 U, 100 μL of a 5.6 mg.mL^{-1} solution in phosphate buffer, (G4511sigma 18.7 U per mg)) and was kept 4h at 37 °C.

100 μL of a solution of sergliflozin-A at $4.5 \cdot 10^{-4} \text{mol.L}^{-1}$ in acetonitrile has been treated in the presence of β -glucosidase following the same process.

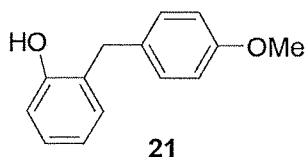
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In parallel, 100 μL of a solution of p-nitrophenyl- β -glucoside (compound A) at $4.5 \cdot 10^{-4} \text{mol.L}^{-1}$ in phosphate buffer (73173 Fluka, pH 7) was added to a solution containing 700 μL of phosphate buffer and 100 μL of acetonitrile, with the presence of β -glucosidase from Almonds (10 U, 100 μL of a 5.6 mg.mL^{-1} solution in phosphate buffer, (G4511sigma 18.7 U per mg)) and was kept 4h at 37 °C. During the process in the presence of β -glucosidase, a yellow coloration was observed that underlines the decomposition of compound A.

25 Sergliflozin A as referred in several publications (*Discov. Med.* 2011, (58):255-263; *Nature Reviews Drug Discovery* 2010, 9, 551-559) is known to undergo cleavage by β -glucosidase.

HPLC of compound **21** (Figure 7), compound **26** (Figure 8) and Sergliflozin-A (Figure 10) have been performed to follow up in the experiments the formation of compound **21** (the aglycone part) implying a degradation of the starting material.

30



HPLC of compound 26 in the presence of β -glucosidase has been performed (Figure 9) and underlines that no degradation occurs as the formation of compound 21 was not observed.

- 5 HPLC of Sergliflozin-A in the presence of β -glucosidase has been performed (Figure 11) and underlines that degradation occurs as the formation of compound 21 was observed. In order to evaluate the percentage of degradation, a calibration has been done on compound 21 giving the following results:

Concentration g/L	Area %
0.005	260
0.01	506
0.05	2962
0.1	5226

- 10 Data have been plotted (Area% versus concentration) and the linear regression obtained was characterized by the equation $y=53629x$ and a $R^2 = 0.994$.

In figure 11, the HPLC spectrum of Sergliflozin-A in the presence of β -glucosidase underlines that degradation occurs with the formation of compound 21 (Area%=416).

- The previous equation allows us to determine that the concentration of compound 21 is
 15 $7.76 \cdot 10^{-3}$ g/L, which corresponds to $3.6 \cdot 10^{-8}$ mol.

This equals to 80% of degradation for Sergliflozin-A after 4h of incubation at 37°C with β -glucosidase, while no degradation occurs for Compound 26 in the same condition.

e) Assay for the inhibition of Tyrosine-Tyrosinase reaction

- 20 Inhibition of tyrosinase, i.e. inhibition of the hydroxylation of Tyrosine into DOPA, was measured by visible spectrophotometry, and more specifically by measuring the absorbance at 477 nm, indicative of the amount of melanine produced *in vitro* from the Tyrosine substrate by Tyrosinase.

In order to make sure that the measured absorbance is proportional to the enzymatic activity in the range of studied concentrations, five standard solutions were prepared as follows.

Standard solution #	Solution A	Bis Tris buffer	Solution B	milliQ water QS	Absorbance (477 nm)
1	0 mL	2 mL	2 mL	10 mL	0.0002
2	2 mL	2 mL	2 mL	10 mL	0.2626
3	4 mL	2 mL	2 mL	10 mL	0.4832
4	6 mL	2 mL	2 mL	10 mL	0.5774
5	8 mL	2 mL	2 mL	10 mL	0.5447

- 5 Absorbance has been measured on a Perkin Elmer UV/Vis Spectrometer Lambda 12.

Solution A (1,000 U/mL mother solution of Tyrosinase) was prepared by dissolving 40 mg of 1,250 U/mg Mushroom Tyrosinase in 1 mL 100mM pH6.5 bis Tris buffer and QS to 50 mL with milliQ water.

- 10 Bis Tris buffer (100 mM pH6.5 bis Tris buffer) was prepared by dissolving 2.09 g of Bis Tris in milliQ water and QS to 100mL.

Solution B (mother solution of Tyrosine) was prepared by dissolving 100 mg of Tyrosine in milliQ water and QS to 100 mL.

- 15 The standard solutions were incubated for 2h at 37°C, then quickly cooled to 4°C. The absorbance of the solutions #2-5 was measured at 477 nm against the blank solution free of Tyrosinase (solution #1). Data have been graphed (absorbance versus Tyrosinase concentration) and the straight line obtained, in the range of absorbance from 0 to 0.5, was characterized by the equation $y=0.2415x-0.2343$ and a $R^2 = 0.9975$.

20

The following test solutions were prepared and their absorbance was measured at 477 nm:

	Solution C	Solution D	Solution E
Description	Witness Solution (100% of Tyrosinase activity)	Compound 31 ($n=5.10^{-5}$ mol)	Hydroquinone ($n=5.10^{-5}$ mol)
Test compound (mg)	0	15.3	5.5
Solution A (mL)	1	1	1
Solution B (mL)	0.5	0.5	0.5
Bis Tris buffer (mL)	0.5	0.5	0.5
Absorbance (477 nm)	0.4354	0.1292	0.1528

With an absorbance of 0.1292, compound **31** (solution D) shows an inhibition of tyrosinase as hydroquinone (solution E).

5

- f) Assay to evaluate and to compare the IC₅₀ of compound **31** according to the invention to a compound of prior art (β -Arbutin).

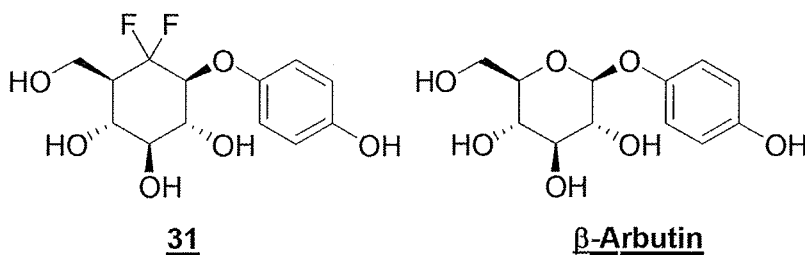
The protocol performed is the same as in assay e.

- 10 Solution A (1,000 U/mL mother solution of Tyrosinase) was prepared by dissolving all of 50kU Mushroom Tyrosinase in 1 mL 100mM pH6.5 bis Tris buffer and QS to 50 mL with milliQ water.

Bis Tris buffer (100 mM pH6.5 bis Tris buffer) was prepared by dissolving 2.09 g of Bis Tris in milliQ water and QS to 100mL. pH was adjusted at 6.5 using hydrochloric acid.

15

Solution B (mother solution of Tyrosine) was prepared by dissolving 20 mg of Tyrosine in milliQ water and QS to 20 mL.



- 20 Stock solution of compound **31** was prepared as follow: 10mg of compound **31** was dissolved in Bis Tris buffer up to 1ml.

Stock solution of β -arbutin was prepared as follow: 20mg of compound β -arbutin was dissolved in Bis Tris buffer up to 1ml.

The solutions were incubated for 1h30 at 37°C, then quickly cooled to 4°C. 100 μ L of each solution were deposited on 96-well plate. The absorbance of the different solutions were measured at 477 nm (Molecular Devices: Spectra Max 340PC).

The different solutions were prepared as described in the different tables below and their absorbances were reported. The absorbance of witness solution (without inhibitor) was set at 100% of enzymatic activity, allowing us to determine the percentage of enzymatic activity of the different solutions.

	Entry 1	Entry 2	Entry 3	Entry 4	Entry 5	Witness
Solution B (μ L)	50	50	50	50	50	50
Solution of compound 31 (μ L)	10	20	30	50	60	0
Water (μ L)	240	230	220	200	190	250
Solution A(μ L)	30	30	30	30	30	30
Absorbance (477 nm)	0.5855	0.3535	0.255	0.220	0.200	0.718
Inhibitor Concentration mg/mL	0.17	0.33	0.50	0.67	0.83	0.00
% activity	81.55	49.23	35.52	30.57	27.86	100.00

10

	Entry 1	Entry 2	Entry 3	Entry 4	Entry 5	Witness
Solution B (μ L)	50	50	50	50	50	50
Solution of β -Arbutin (μ L)	10	20	30	40	50	0
Water (μ L)	210	200	190	180	170	220
Solution A(μ L)	30	30	30	30	30	30
Absorbance (477 nm)	0.5010	0.3040	0.2380	0.2035	0.1970	0.722
Inhibitor Concentration mg/mL	0.67	1.33	2.00	2.67	3.33	0.00
% activity	66.62	40.43	31.65	27.06	26.20	100.00

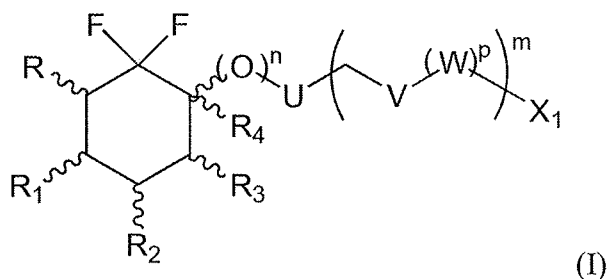
Data have been plotted (% of activity versus concentration of inhibitors) and the linear regression of the curve was used to calculate the IC₅₀ of both compounds. The results obtained are presented in the table below:

IC50	Concentration Tyrosinase 100 U/mL		
	Compound 31	0,328	mg/mL
	□□Arbutin	1.1	mg/mL

The results clearly underline that compound 31 is a better tyrosinase inhibitor than β -Arbutin.

CLAIMS

1. A compound having the following formula (I):

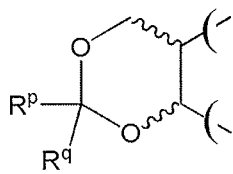


5 or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

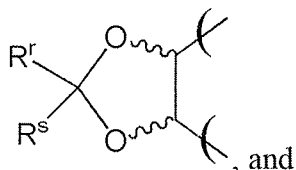
wherein:

- n, m and p represent, independently from one another, 0 or 1,
- 10 - R represents a hydrogen or a fluorine atom or a CH₃, CH₂F, CH₂OH, CH₂OSiR^aR^bR^c, CH₂OR¹¹, CH₂OCOR¹¹, CH₂OCO₂R¹¹, CH₂OCONR¹²R¹³, CH₂OP(O)(OR¹⁴)₂ or CH₂OSO₃R¹⁴ group,
- R₁ and R₂ represent, independently from one another, a fluorine atom or an OH, OSiR^dR^eR^f, OR¹⁵, OCOR¹⁵, OCO₂R¹⁵ or OCONR¹⁶R¹⁷ group,
- 15 - R₃ represents a hydrogen or fluorine atom or an OH, OSiR^gR^hRⁱ, OR¹⁸, OCOR¹⁸, OCO₂R¹⁸, OCONR¹⁹R²⁰, NR¹⁹R²⁰ or NR¹⁹COR¹⁸ group,
- R₄ represents a hydrogen atom when n = 1, and R₄ represents a hydrogen atom, an halogen atom or an OH, OSiR^jR^kR^l, OR²¹, OCOR²¹, OCO₂R²¹, or OCONR²²R²³ group when n = 0,

20 or R and R₁, together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



and/or (R₁ and R₂), (R₂ and R₃), and/or (R₃ and R₄), together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



- 5 - X_1 represents a hydrogen atom, an halogen atom, a CN, OH, SO_2 , $SiR^mR^nR^o$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$, $CONR^{25}R^{26}$, SR^{24} , SO_2R^{24} , CSR^{24} or OSO_3R^{24} group, and

- U, V and W represent, independently from one another, a phenyl, pyrazolyl, N- (C_1-C_6) alkyl-pyrazolyl, or thienyl ring,

the said ring being optionally substituted with one or more substituents selected from the group consisting of an halogen atom, a CN, OH, SO_2 , $SiR^mR^nR^o$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, OR^{24} , COR^{24} , $OCOR^{24}$, CO_2R^{24} , $NR^{25}R^{26}$, $NR^{25}COR^{24}$, $CONR^{25}R^{26}$, SR^{24} , SO_2R^{24} , CSR^{24} and OSO_3R^{24} group,

with:

- 15 - R^{11} , R^{15} , R^{18} , R^{21} and R^{24} representing, independently from one another, a (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl, 5 to 7 ring-membered heterocycloalkyl, aryl, aryl- (C_1-C_6) -alkyl or (C_1-C_6) -alkyl-aryl group, this group being possibly substituted by one or more groups chosen among an halogen atom, an OH, COOH and CHO group,

- R^{12} , R^{13} , R^{16} , R^{17} , R^{19} , R^{20} , R^{22} , R^{23} , R^{25} and R^{26} representing, independently from one another, a hydrogen atom or a (C_1-C_6) -alkyl or aryl- (C_1-C_6) -alkyl group,

- 20 - R^{14} representing a hydrogen atom or a (C_1-C_6) -alkyl group,

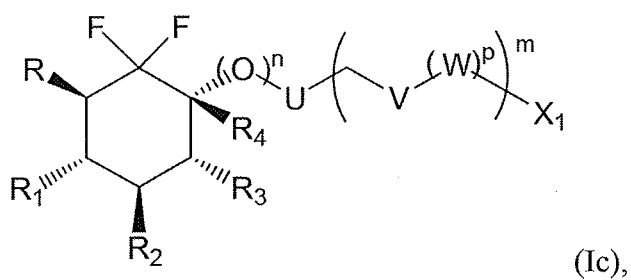
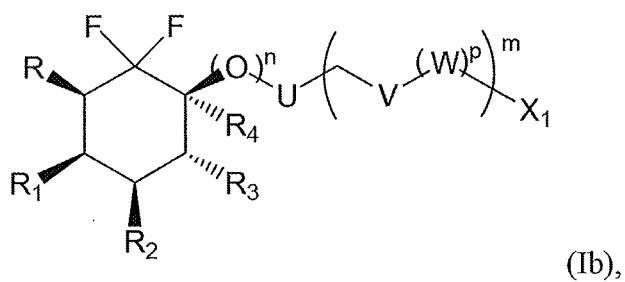
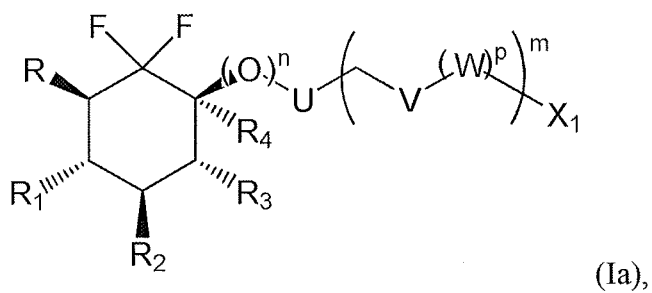
- R^a to R^o representing, independently from one another, a (C_1-C_6) -alkyl, aryl or aryl- (C_1-C_6) -alkyl group, and

- R^p to R^s representing, independently from one another, a hydrogen atom or a (C_1-C_6) -alkyl group, aryl or aryl- (C_1-C_6) -alkyl group.

25

2. The compound according to claim 1, characterized in that it responds to the following formula (Ia), (Ib) or (Ic):

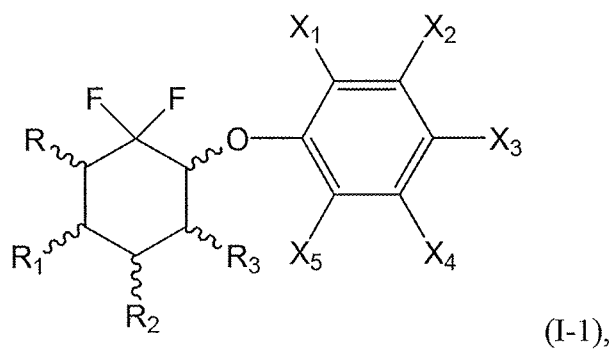
101

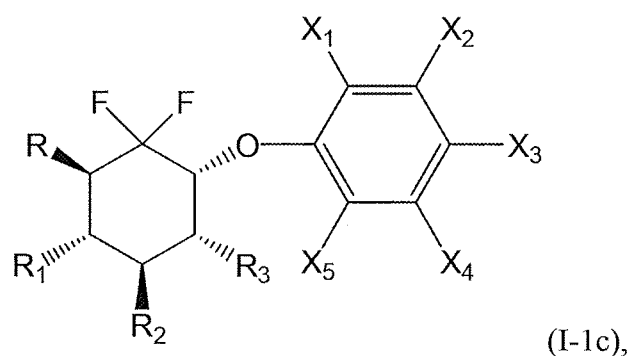
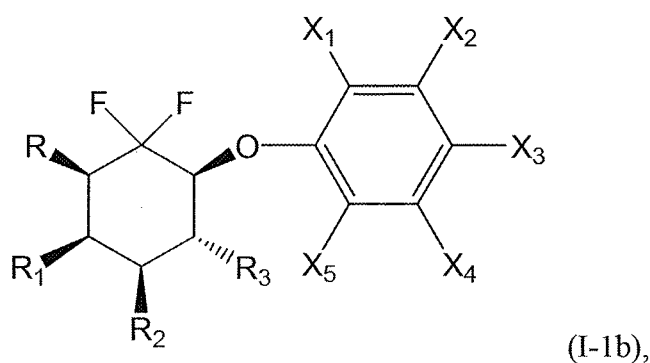
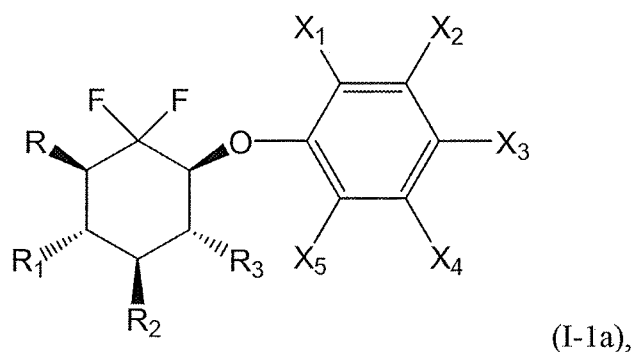


5

with R, R₁, R₂, R₃, R₄, X₁, U, V, W, n, m and p as defined in claim 1.

3. The compound according to claim 1 or 2, characterized in that it responds to the
10 following formula (I-1), (I-1a), (I-1b) or (I-1c):



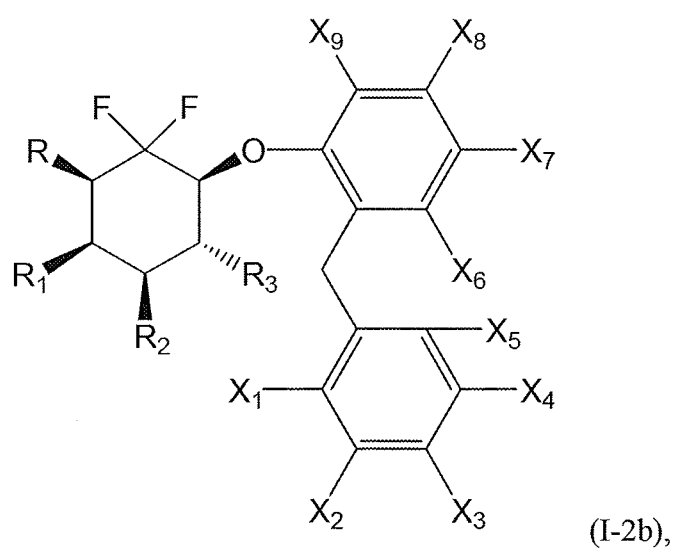
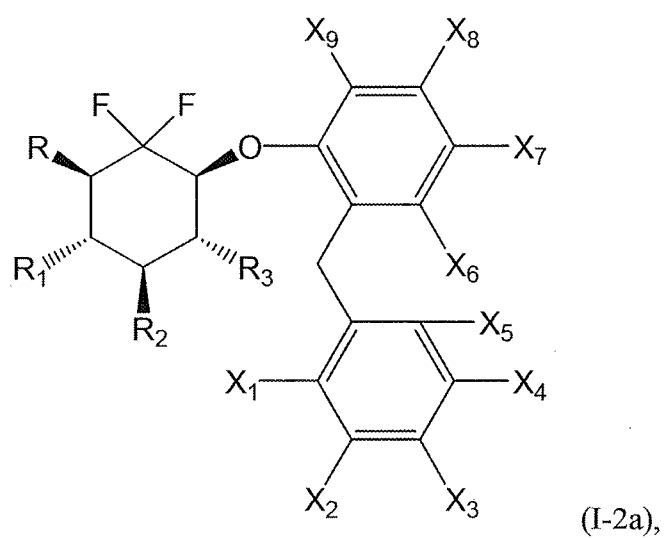
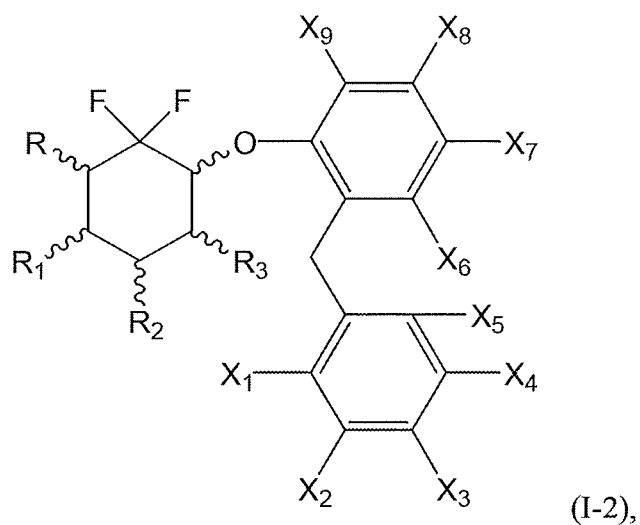


or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer
 5 or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers,
 and particularly a racemate mixture,

wherein:

- R, R₁, R₂, and R₃ are as defined in claim 1, and
- X₁, X₂, X₃, X₄ and X₅ represent, independently from one another, a hydrogen
 10 atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-
 alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴,
 NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group.

4. The compound according to claim 1 or 2, characterized in that it responds to the
 15 following formula (I-2), (I-2a) or (I-2b):

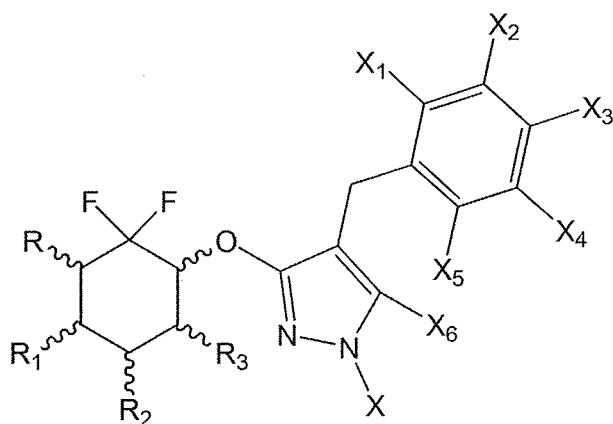


or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer
 5 or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers,
 and particularly a racemate mixture,

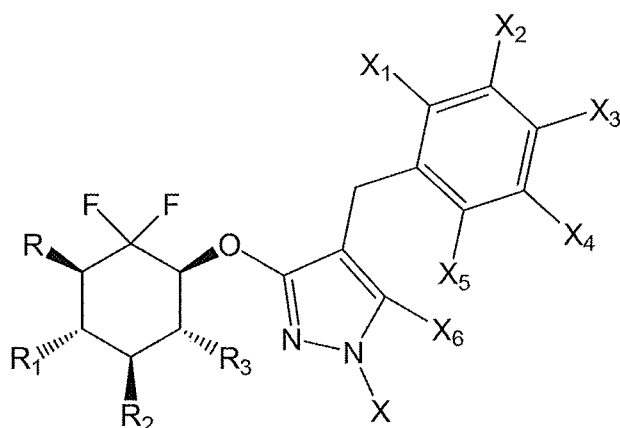
wherein:

- R, R₁, R₂, and R₃ are as defined in claim 1, and
- X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ and X₉ represent, independently from one another,
 5 a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴
 group.

5. The compound according to claim 1 or 2, characterized in that it responds to the
 10 following formula (I-3), (I-3a) or (I-3b):

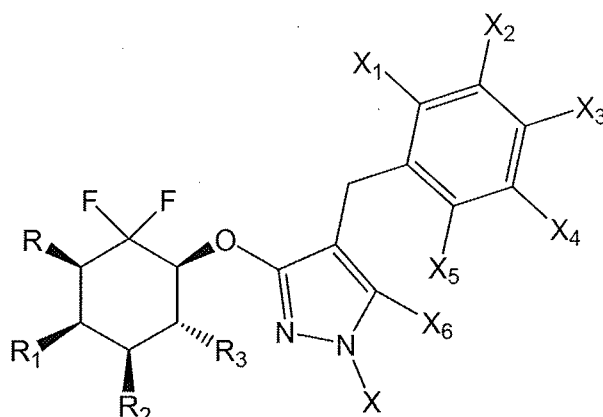


(I-3),



(I-3a),

105



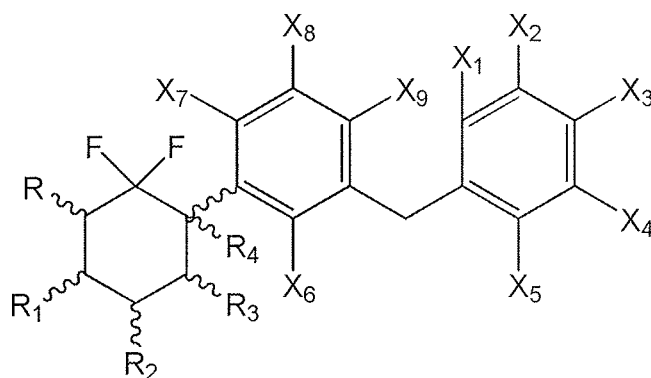
(I-3b),

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

5 wherein:

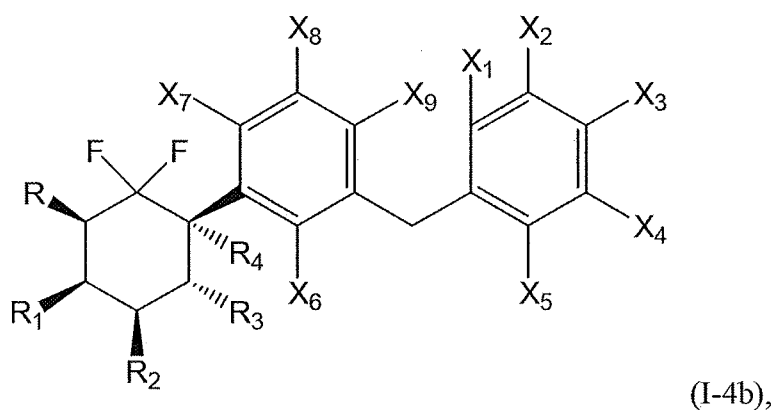
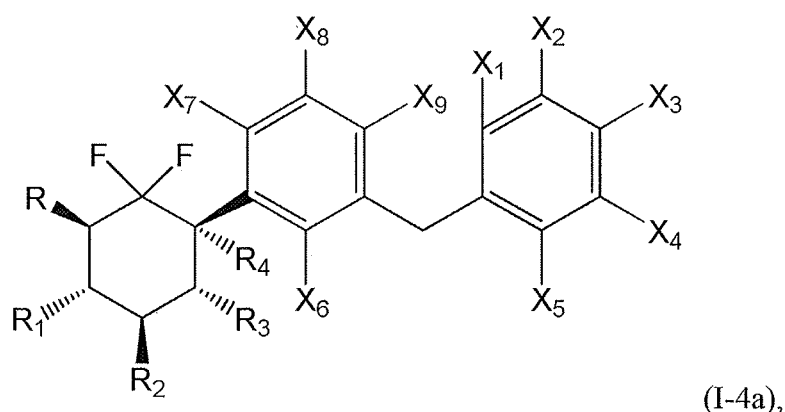
- R, R₁, R₂, and R₃ are as defined in claim 1,
- X₁, X₂, X₃, X₄, X₅ and X₆ represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴,
 10 NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group, and
- X represents a hydrogen atom or a (C₁-C₆)-alkyl group.

6. The compound according to claim 1 or 2, characterized in that it responds to the following formula (I-4), (I-4a) or (I-4b):



(I-4),

15



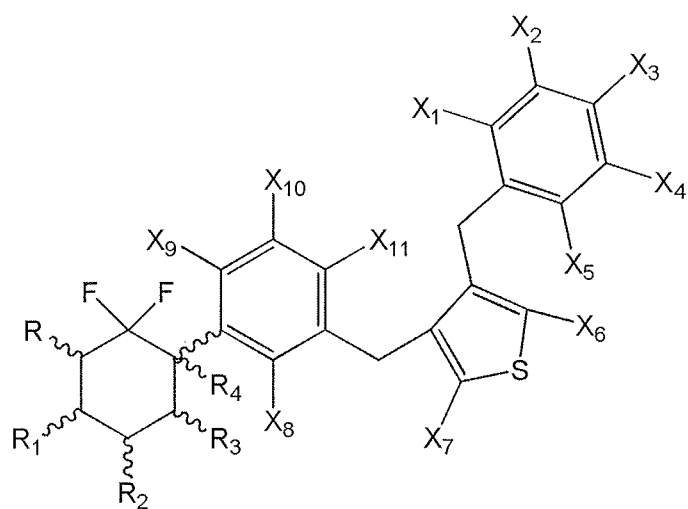
or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers, and particularly a racemate mixture,

5 wherein:

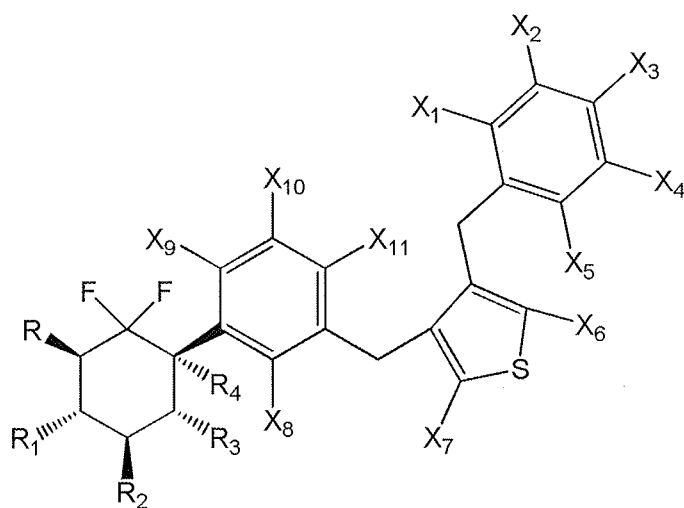
- R, R₁, R₂, R₃ and R₄ are as defined in claim 1, and
 - X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ and X₉ represent, independently from one another,
- 10 a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group.

7. The compound according to claim 1 or 2, characterized in that it responds to the

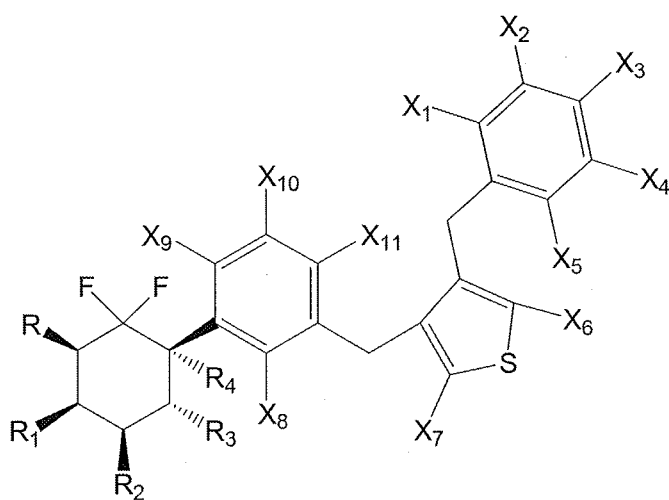
15 following formula (I-5), (I-5a) or (I-5b):



(I-5),



(I-5a),

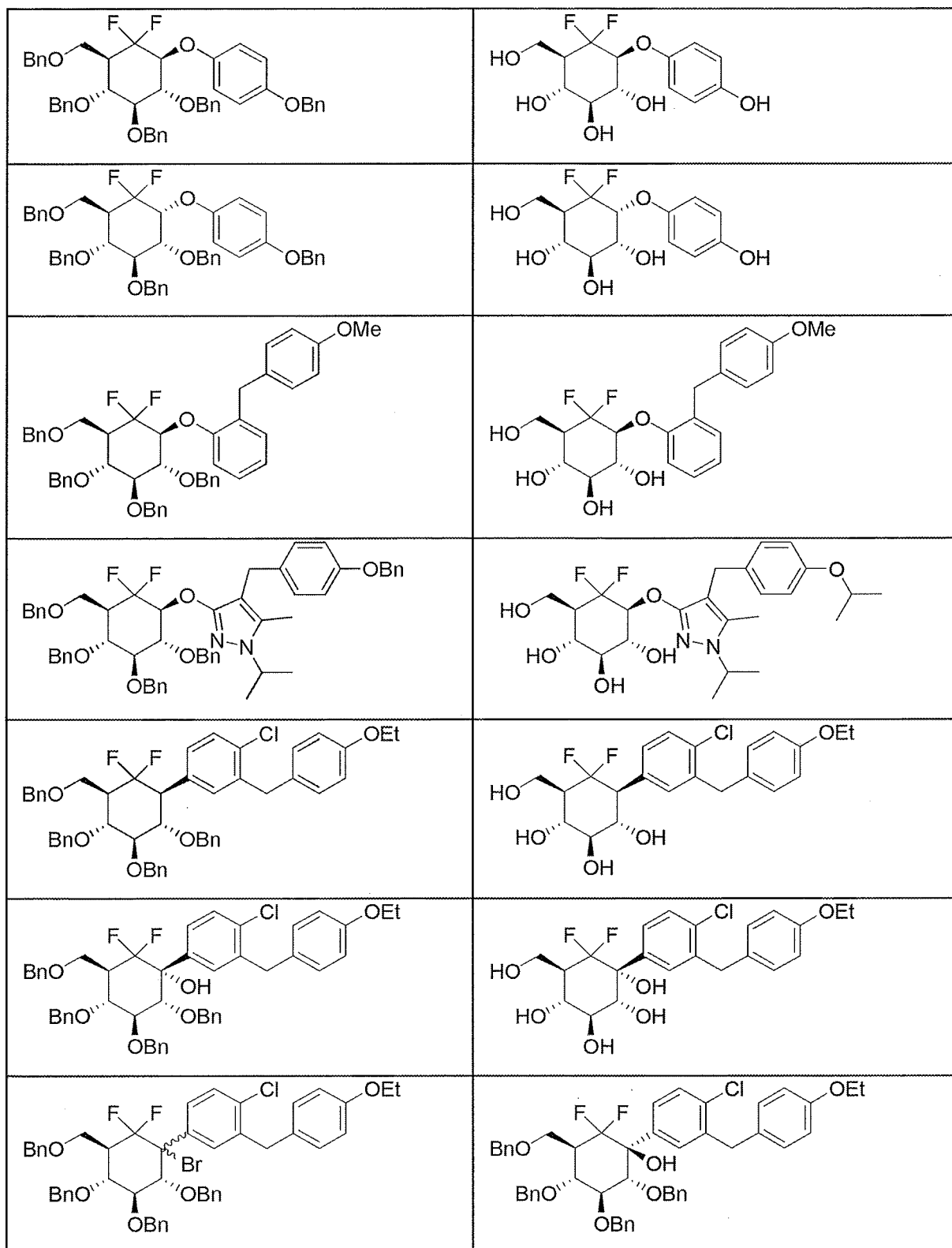


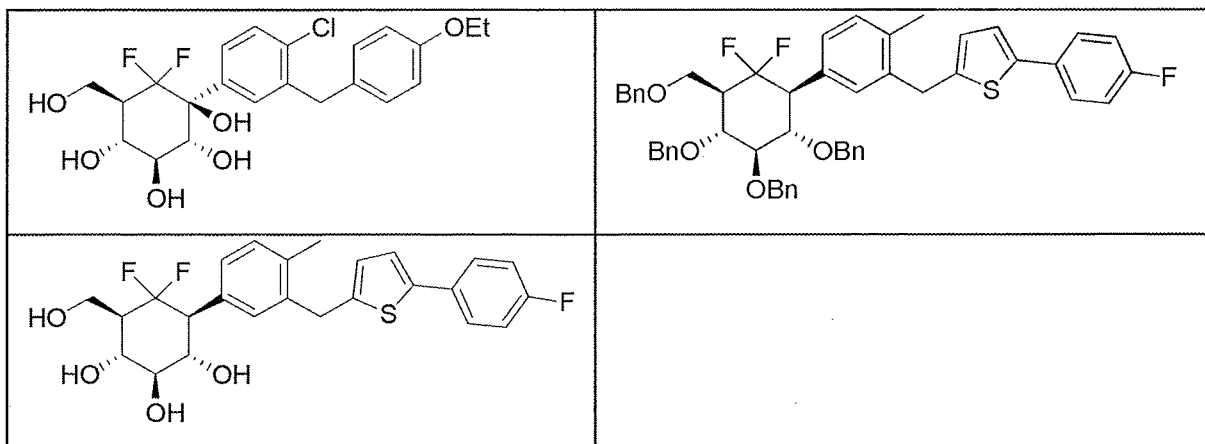
(I-5b),

or a pharmaceutically or cosmetically acceptable salt thereof, a tautomer, a stereoisomer
 5 or a mixture of stereoisomers in any proportion, in particular a mixture of enantiomers,
 and particularly a racemate mixture,

wherein:

- R, R₁, R₂, R₃ and R₄ are as defined in claim 1, and
 - X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀ and X₁₁ represent, independently from one another, a hydrogen atom, an halogen atom, a CN, OH, SO₂, SiR^mRⁿR^o, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴, CO₂R²⁴, NR²⁵R²⁶, NR²⁵COR²⁴, CONR²⁵R²⁶, SR²⁴, SO₂R²⁴, CSR²⁴ or OSO₃R²⁴ group.
8. The compound according to any of claims 1 to 7, characterized in that R₁, R₂ and R₃ are chosen, independently from one another, among an OH, -O-(C₁-C₆)-alkyl, -O-aryl, -O-(C₁-C₆)-alkyl-aryl and -OCO-(C₁-C₆)-alkyl group.
9. The compound according to any of claims 1 to 8, characterized in that R represents a CH₂OH, -CH₂O-(C₁-C₆)-alkyl, -CH₂O-aryl, -CH₂O-(C₁-C₆)-alkyl-aryl and -CH₂OCO-(C₁-C₆)-alkyl group.
10. The compound according to any of claims 1 to 9, characterized in that R₄ = H when n = 1 and R₄ = H or OH when n = 0.
11. The compound according to any one of claims 1 to 10, characterized in that U, V and W represent, independently from one another, a phenyl, pyrazolyl, N-(C₁-C₆)-alkyl-pyrazolyl, or thienyl ring, the said ring being optionally substituted with one or more substituents selected from the group consisting of an halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴ and CO₂R²⁴ group, and X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀ and X₁₁ are, independently from one another, selected from the group consisting of a hydrogen atom, a halogen atom, a OH, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl, OR²⁴, COR²⁴, OCOR²⁴ and CO₂R²⁴ group.
12. The compound according to any of claims 1 to 11, characterized in that it is chosen from the following compounds:





13. A compound according to any of claims 1 to 12, for use thereof as a drug, in particular as an inhibitor of the sodium-dependent glucose co-transporter, such as SGLT1, SGLT2 and SGLT3.

5

14. A compound according to any of claims 1 to 12, for use in the treatment or prevention of diabetes, and more particularly type-II diabetes, diabetes-related complications, such as arteritis of the lower extremities, cardiac infarction, renal insufficiency, neuropathy or blindness, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, X syndrome and arteriosclerosis, as well as for use as an anti-cancer, anti-infective, anti-viral, anti-thrombotic or anti-inflammatory drug.

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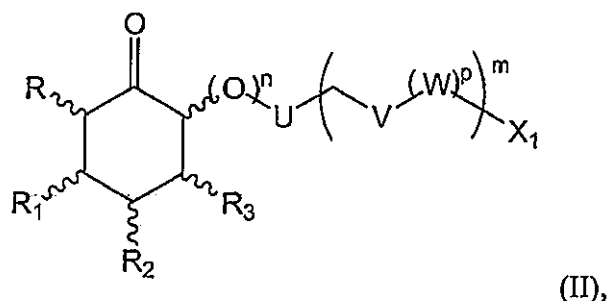
15. A cosmetic use of at least one compound according to any of claims 1 to 12, for lightening, bleaching, depigmenting the skin, removing blemishes from the skin, particularly age spots and freckles, or preventing pigmentation of the skin, or as antioxidant.

15

16. A pharmaceutical or cosmetic composition including at least one compound according to any of claims 1 to 12 and at least one pharmaceutically or cosmetically acceptable vehicle.

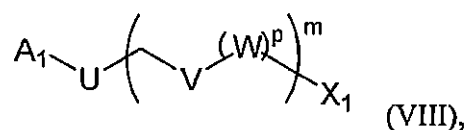
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17. A process for preparing a compound according to any one of claims 1 to 12 for which $R_4 = H$ comprising the fluorination of a compound of the following formula (II):



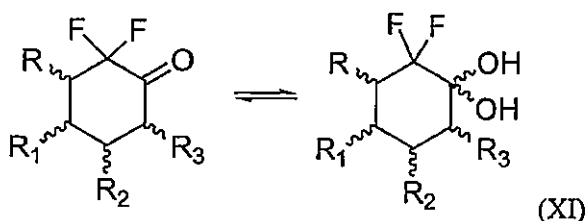
wherein R, R₁, R₂, R₃, X₁, U, V, W, n, m and p are as defined in claim 1.

18. A process for preparing a compound according to any one of claims 1 to 12 for which n = 0 and R₄ ≠ H comprising the coupling of a compound of the following formula (VIII):



wherein X₁, U, V, W, m and p are as defined in claim 1 and A₁ represents -Li or -Mg-Hal, Hal being a halogen atom,

- and a compound of the following formula (XI)



wherein R, R₁, R₂, and R₃ are as defined in claim 1,

to give a compound of formula (I) according to claim 1 for which n = 0 and R₄ = OH,

followed optionally by the substitution of the OH function to give a compound of

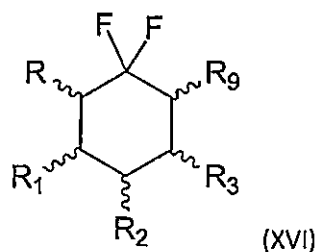
- formula (I) according to claim 1 for which n = 0 and R₄ = halogen, OSiR^jR^kR^l, OR²¹, OCOR²¹, OCO₂R²¹, or OCONR²²R²³.

19. A process for preparing a compound according to any one of claims 1 to 12 for which R₄ = H comprising the following steps:

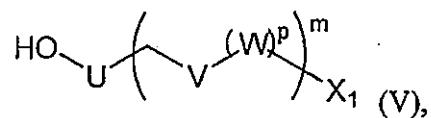
- (a4) bromination of a compound of formula (I) with R₄ = OH to give a compound of formula (I) with R₄ = Br, and

- (b4) reduction of the compound of formula (I) with $R_4 = \text{Br}$ obtained in previous step (a4) to give a compound of formula (I) with $R_4 = \text{H}$.

20. A process for preparing a compound according to any one of claims 1 to 12 for which comprising a coupling reaction between a compound of the following formula (XVI):



wherein R, R_1 , R_2 , and R_3 are as defined in claim 1 and R_9 represents a leaving group, with a compound of the following formula (V):



wherein X_1 , U, V, W, m and p are as defined in claim 1.