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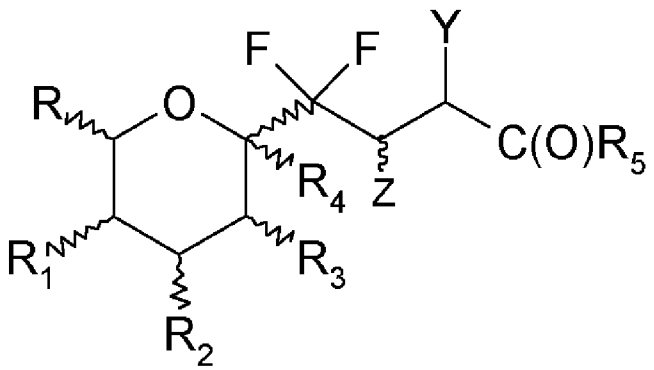
(54) **Title**: DERIVATIVES OF GLYCO-CF2-SERINE AND GLYCO-CF2-THREONINE



(I)

(57) **Abstract**: The present invention relates to compounds of formula (I): or a pharmaceutically 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, as well as to their process of preparation, their use in the peptide synthesis, said peptide and the use of said peptide.

Derivatives of glyco-CF_2-serine and glyco-CF_2-threonine

The present invention relates to glycoside-CF_2-serine or glycoside-CF_2-threonine derivatives, useful as glycoside-O-serine or glycoside-O-threonine mimics, as well as their preparation process, their use in peptide synthesis, said peptide and the use of said peptide.

Glycosylation is a co- or post-translational modification present in more than 50 % of all proteins. O-glycosylation on the hydroxyl function of amino acids, such as serine, threonine, tyrosine, hydroxylysine or hydroxyproline, is the most common modification.

Glycoproteins, which are present in the cellular membranes, are implicated in numerous biochemical processes such as fertilisation, embryogenesis, neuronal development, immune responses, inflammatory reactions, intercellular recognition and regulation of the cell growth. Important changes are observed in the structure of sugars present on the surface of cells during the canceration process. Moreover, sugars of host cells are often used by different pathogens to allow their entry into cells.

For all these reasons, glycoproteins are an important key messengers for numerous therapies such as anti-inflammatory, antibacterial, antiviral and in particular anticancer therapies.

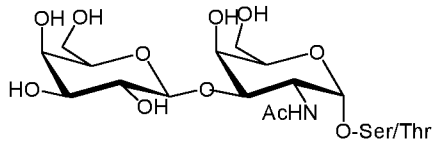
Cancer represents the first cause of mortality. In a global point of view, a doubling of the number of cancers is expected in the next 30 years. The discovery of novel anticancer compounds is thus a major endeavor.

Several treatments are actually used for treating cancer such as surgery, chemotherapy, radiotherapy or immunotherapy. However, the 3 first possibilities either are very invasive or lead to side effects such as, for chemotherapy, hair loss, nauseas, diarrheas and diminution of erythrocyte.

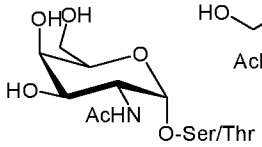
New approaches are thus studied to improve the treatments against cancer, notably through “passive” or “active” immunotherapy. The last one seems very promising and consists in the stimulation of the immune response against specific tumoral antigens.

Indeed, a modification of mucins expression has been observed on the surface of cancer cells. Those glycoproteins are over-expressed on the surface of tumoral epithelial cells.

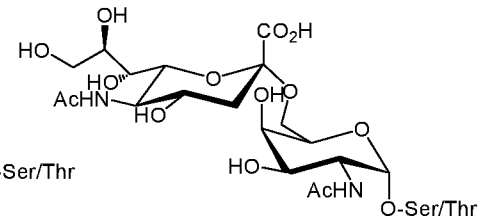
Moreover, contrary to healthy cells, cancerous cells have, on their surface, because of abnormal glycosylations, shorter peptide units, which allowed the identification of specific tumoral antigens of saccharide type. Examples of oside epitopes are described below:



antigen TF



antigen Tn



antigen sTn

The common synthon of these antigens is the moiety Gal-O-Ser/Thr. This moiety is currently being extensively studied towards the development of synthetic anticancer vaccines.

The drawback of such structures is the ease in which the O-glycosyl bond is cleaved by enzymatic systems such as hydrolases.

This prompted numerous research teams to design mimics of natural glycoconjugates in order to improve their stability in a biological medium. In this field, C-glycosides are the most studied, with the replacement of the oxygen atom of the O-glycosyl bond with a methylene group which is less sensitive to circulating enzymes. However, even if the stability is improved, the CH_2 group is not a good oxygen mimic, and access to this compound is not that straightforward.

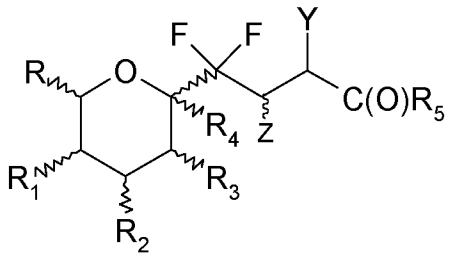
The inventors of the present invention have thus developed a synthesis of glyco-CF_2-serine or glyco-CF_2-threonine derivatives which also constitute a synthetic challenge. Extensive synthetic methodology development was necessary to successfully synthesize the target compounds.

Indeed, a difluoromethylene moiety (-CF_2-) is a better mimic of an oxygen atom for electronic reasons. The CF_2 group has an electronegativity very closed to the one of the oxygen atom, the two fluorine atoms playing the role of the two electronic doublets of the oxygen. Moreover, the C-F bond is more stable thereby improving the stability of

the final molecule. A CF_2 group is thus a better mimic of an oxygen atom than a CH_2 group.

The introduction of such glyco-CF_2-serine or glyco-CF_2-threonine derivatives in peptides or proteins moieties stabilizes the resulting glycopeptides or glycoproteins, notably against glycosidases, proteases and acid or basic conditions.

The present invention relates thus to a compound of formula (I):



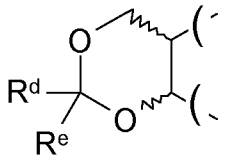
(I)

or a pharmaceutically 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,

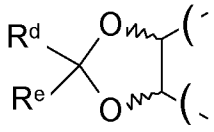
wherein:

- Y represents a CN, NO_2, NR_6R_7 or $CH_2NR_6R_7$ group,
- Z represents H or CH_3,
- R represents a hydrogen or fluorine atom or a CH_3, CH_2F, $CH_2OSiR^{a1}R^{b1}R^{c1}$, CH_2OR_8, $CH_2OC(O)R_9$, $CH_2OCO_2R_{10}$, $CH_2OC(O)NR_{11}R_{12}$, $CH_2OP(O)(OR_{13})_2$ or $CH_2OSO_3R_{14}$ group,
- R_1 and R_2 represent, independently from one another, a fluorine atom or an $OSiR^{a2}R^{b2}R^{c2}$, OR_{15}, $OC(O)R_{16}$, OCO_2R_{17}, $OC(O)NR_{18}R_{19}$, $OP(O)(OR_{20})_2$ or OSO_3R_{21} group,
- R_3 represents a fluorine atom or an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22}, $OC(O)R_{23}$, OCO_2R_{24}, $OCONR_{25}R_{26}$, $OP(O)(OR_{27})_2$, OSO_3R_{28}, N_3, phtalimidyl, $NR_{29}R_{30}$, $NR_{31}C(O)R_{32}$, $NR_{33}C(O)OR_{34}$, $N(C(O)R_{35})C(O)R_{36}$, $N(C(O)R_{37})C(O)OR_{38}$ and $N(C(O)OR_{39})C(O)OR_{40}$ group,
- R_4 represents a hydrogen or halogen atom or an $OSiR^{a4}R^{b4}R^{c4}$, OR_{41}, $OC(O)R_{42}$, OCO_2R_{43}, $OCONR_{44}R_{45}$, $OP(O)(OR_{46})_2$, or OSO_3R_{47} group,

or R and R_1, together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



and/or (R_1 and R_2), (R_2 and R_3), and/or (R_3 and R_4), together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



, and

– R_5 represents a hydrogen or halogen atom or a R_{48}, OR_{49} or $NR_{50}R_{51}$ group,

with:

- R_6 representing:
  - a hydrogen atom,
  - a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; preferably a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkylgroup, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
  - a $C(O)R_{52}$ group, or
  - a $C(O)OR_{53}$ group,
- R_7 representing:
  - a hydrogen atom,
  - a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; preferably a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl-(C_1-

C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,

- a $C(O)R_{52}$ group,
- a $C(O)OR_{53}$ group, or
- a N-protecting group,

- R_8, R_{15}, R_{22} and R_{41} representing, independently from one another, a hydrogen atom, a O-protecting group or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl, (C_1-C_6)-alkyl-heteroaryl, saccharidic or polysaccharidic group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; and in particular a hydrogen atom, a (C_1-C_6)alkyl, aryl, aryl-(C_1-C_6)alkyl, saccharidic or polysaccharidic group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
- R_9, R_{10}, R_{16}, R_{17}, R_{23}, R_{24}, R_{32}, R_{34} to R_{40}, R_{42}, R_{43}, R_{48}, R_{52} and R_{53} 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-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; and in particular a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
- R_{11}, R_{12}, R_{18}, R_{19}, R_{25}, R_{26}, R_{29} to R_{31}, R_{33}, R_{44}, R_{45}, R_{50} and R_{51} representing, independently from one another, a hydrogen atom or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; advantageously a hydrogen atom or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkylgroup, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO; and in particular a hydrogen atom or a (C_1-C_6)alkyl,

aryl or aryl-(C_1-C_6)alkyl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,

- R_{13}, R_{14}, R_{20}, R_{21}, R_{27}, R_{28}, R_{46} and R_{47} representing, independently from one another, a hydrogen atom or a (C_1-C_6)alkyl group,
- R_{49} representing:
  - a hydrogen atom,
  - a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among an halogen atom, OH, COOH and CHO, or
  - a O-protecting group,
- R^{a1} to R^{a4}, R^{b1} to R^{b4} and R^{c1} to R^{c4} representing, independently from one another, a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group, and
- R^d and R^e representing, independently from one another, a hydrogen atom or a (C_1-C_6)alkyl group.

For the purpose of the invention, the term "pharmaceutically acceptable" is intended to mean what is useful to the preparation of a pharmaceutical composition, and what is generally safe and non toxic, for a pharmaceutical use.

The term « pharmaceutically acceptable salt » is intended to mean, in the framework of the present invention, a salt of a compound which is pharmaceutically acceptable, as defined above, and which possesses the pharmacological activity of the corresponding compound. Such salts comprise:

(1) hydrates and solvates,

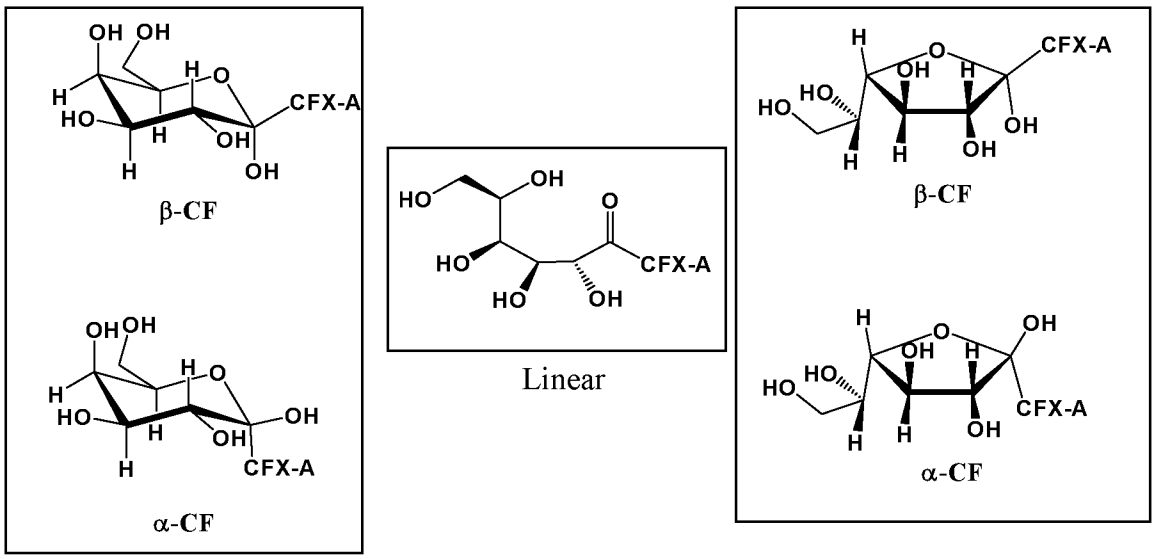
(2) acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as acetic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphtoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, methanesulfonic, muconic, 2-naphtalenesulfonic, propionic, succinic, dibenzoyl-L-tartaric, tartaric, p-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like, and

(3) salts formed when an acid proton present in the compound is either replaced by a metal ion, such as an alkali metal ion, an alkaline-earth metal ion, or an aluminium ion; or coordinated with an organic or inorganic base. Acceptable organic bases comprise diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases comprise aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

For the purpose of this invention, "tautomer" is intended to designate the various tautomer forms that the sugar of compound (I) may assume, namely a pyranose (6-membered ring), furanose (5-membered ring) or linear (open form) form.

However, the compounds of the invention can assume various tautomer forms only when the radical R_4 represents an OH group, R_1 having also to represent an OH group in order that the compounds of the invention can be in the furanose form.

Thus, for example, in the galactose series, the compounds of the invention might appear under the following various forms:



The anomeric carbon can appear in two different configurations in the closed pyranose and furanose forms.

The compounds of the invention can assume different tautomer forms which can be present in solution in equilibrium, with optionally a major tautomer form relatively to the other(s) tautomer form(s), or the compounds of the invention can assume only one tautomer form, such as only a furanose form, in some cases.

In this last case where the sugar assumes only one tautomer form, it is possible to block the configuration of the sugar in this tautomeric form when R_4 = OH is transformed, notably by substitution of the OH group or conversion in a hydrogen or halogen atom.

Within the meaning of this invention, "stereoisomers" is intended to designate diastereoisomers or enantiomers. These are therefore optical isomers. 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 bond to four non-identical substituents is called a "chiral centre".

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

The term "halogen" as used in the present invention refers to an atom of fluorine, bromine, chlorine or iodine. Advantageously, this is an atom of fluorine.

The term "(C_1-C_6)-alkyl" as used in the present invention refers to 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.

The term "(C_2-C_6)-alkenyl" as used in the present invention refers to 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.

The term "(C_2-C_6)-alkynyl" as used in the present invention refers to 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.

The term "(C_3-C_7)-cycloalkyl" as used in the present invention refers to a saturated hydrocarbon ring comprising from 3 to 7, advantageously from 5 to 7, carbon atoms, in particular the cyclohexyl, cyclopentyl or cycloheptyl group.

The term "heterocycloalkyl" as used in the present invention refers to a saturated hydrocarbon ring having 5 to 7 members and containing one or more, advantageously one or two, heteroatoms, e.g., such as sulphur, nitrogen or oxygen atoms, e.g., such as

the tetrahydrofuranyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, 1,3-dioxolanyl group.

The term "aryl" as used in the present invention refers to an aromatic group preferably comprising from 5 to 10 carbon atoms and including one or more fused rings, e.g., such as a phenyl or naphtyl group. This is advantageously phenyl.

The term "heteroaryl" as used in the present invention refers to any aryl group as defined above wherein one or more carbon atoms have been replaced by one or more heteroatoms, advantageously 1 to 4, and even more advantageously 1 to 2, e.g., such as sulphur, nitrogen or oxygen atoms. Examples of heteroaryl groups are the furyl, thiophenyl, pyrrolyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, tetrazolyl or else indyl groups.

The term "aryl-(C_1-C_6)-alkyl" as used in the present invention refers to any aryl group as defined above, which is bound to the molecule by means of a (C_1-C_6)-alkyl group as defined above. In particular, a group such as this can be a benzyl group.

The term "heteroaryl-(C_1-C_6)-alkyl" as used in the present invention refers to mean a heteroaryl group as defined above, which is bound to the molecule by means of a (C_1-C_6)-alkyl group as defined above.

The term "(C_1-C_6)-alkyl-aryl" as used in the present invention refers to a (C_1-C_6)-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.

The term "(C_1-C_6)-alkyl-heteroaryl" as used in the present invention refers to a (C_1-C_6)-alkyl group as defined above, which is bound to the molecule by means of a heteroaryl group as defined above.

The term "N-protecting group" as used in the present invention refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis", (John Wiley & Sons, New York (1981)). N-protecting groups comprise carbamates, amides, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. In particular, N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl (Bn), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), trichloroethoxycarbonyl (TROC), allyloxycarbonyl (Alloc),

fluorenylmethyloxycarbonyl (FMOC), and the like. In particular, it will be a t-butyloxycarbonyl, benzyloxycarbonyl or fluorenylmethyloxycarbonyl group.

The term "O-Protecting group" as used in the present invention refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic synthesis", (John Wiley & Sons, New York (1981)). O-protecting groups comprise (C_1-C_6)alkyl groups, such as methyl, ethyl, *tert*-butyl; substituted methyl ethers, for example, methoxymethyl (MOM), benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl) ethoxymethyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; and silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl (TBS) and t-butyldiphenylsilyl. In particular, it will be a benzyl or methoxymethyl group.

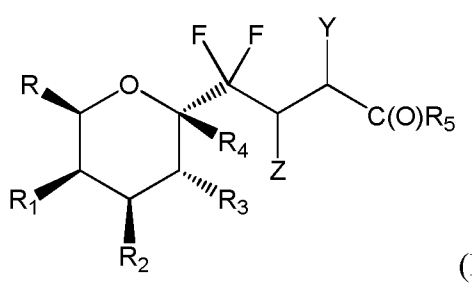
The term "saccharide" as used in the present invention refers to erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose or tagatose, in D or L form.

The term "saccharidic group" as used in the present invention refers to a saccharide as defined above bond to the molecule by means of its oxygen atom present at the anomeric centre.

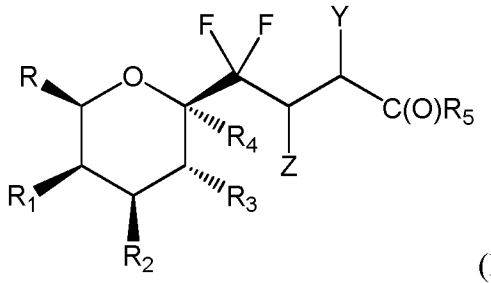
The term "polysaccharide" as used in the present invention refers to a chain comprising at least 2, and preferably 2 to 10 saccharides as defined above bound together by means of an oxygen bridge formed between the OH function at the anomeric position of a saccharide and the OH function not at the anomeric position of another saccharide.

The term "polysaccharidic group" as used in the present invention refers to a polysaccharide as defined above bond to the molecule by means of the oxygen atom present at the anomeric centre of the terminal saccharide.

The compounds of the invention are advantageously based on the following formulas (Iα) and (Iβ):



(Iα),



(Iβ),

with R, R_1, R_2, R_3, R_4, R_5, Z and Y as defined above.

R can represent a $CH_2OSiR^{a1}R^{b1}R^{c1}$, CH_2OR_8, $CH_2OC(O)R_9$, $CH_2OCO_2R_{10}$, $CH_2OC(O)NR_{11}R_{12}$, $CH_2OP(O)(OR_{13})_2$ or $CH_2OSO_3R_{14}$ group, advantageously a $CH_2OSiR^{a1}R^{b1}R^{c1}$, CH_2OR_8 or $CH_2OC(O)R_9$ group, more advantageously a CH_2OR_8 or $CH_2OC(O)R_9$ group, and even more advantageously a CH_2OR_8 group.

R can represent in particular a CH_2OR_8 group with R_8 representing a hydrogen atom, a O-protecting group or a $(C_1\text{-}C_6)$-alkyl, aryl or aryl-$(C_1\text{-}C_6)$-alkyl group; or a $CH_2OC(O)R_9$ group with R_9 representing a $(C_1\text{-}C_6)$-alkyl, aryl or aryl-$(C_1\text{-}C_6)$-alkyl group.

R can represent more particularly a CH_2OR_8 group with R_8 representing a hydrogen atom or a O-protecting group. For instance, R can represent a CH_2OH or CH_2OBn group.

R_1 and R_2 can represent, independently from one another, an $OSiR^{a2}R^{b2}R^{c2}$, OR_{15}, $OC(O)R_{16}$, OCO_2R_{17} or $OC(O)NR_{18}R_{19}$ group, advantageously an $OSiR^{a2}R^{b2}R^{c2}$, OR_{15} or $OC(O)R_{16}$ group, more advantageously an OR_{15} or $OC(O)R_{16}$ group, and even more advantageously an OR_{15} group.

R_1 and R_2 can represent in particular, independently from one another, an OR_{15} group with R_{15} representing a hydrogen atom, a O-protecting group or a $(C_1\text{-}C_6)$-alkyl, aryl or aryl-$(C_1\text{-}C_6)$-alkyl group; or an $OC(O)R_{16}$ group R_{16} representing a $(C_1\text{-}C_6)$-alkyl, aryl or aryl-$(C_1\text{-}C_6)$-alkyl group.

R_1 and R_2 can represent more particularly, independently from one another, an OR_{15} group with R_{15} representing a hydrogen atom or a O-protecting group. For instance, R_1 and R_2 can represent an OH or OBn group.

Preferably, R_1 and R_2 are identical, and represent notably an OH or OBn group.

In particular, R represents a CH_2OR_8 group and R_1 and R_2 represent, independently from one another, an OR_{15} group, R_8 and R_{15} representing advantageously a hydrogen atom or an O-protecting group. R_8 and the two R_{15} can be identical, such as H or an O-protecting group.

According to another particular embodiment, R = CH_2OH and $R_1 = R_2 = OH$ or R = CH_2OBn and $R_1 = R_2 = OBn$.

According to a first embodiment, R_3 represent an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22}, $OC(O)R_{23}$, OCO_2R_{24}, $OCONR_{25}R_{26}$, $NR_{29}R_{30}$, $NR_{31}C(O)R_{32}$, $NR_{33}C(O)OR_{34}$, $N(C(O)R_{35})C(O)R_{36}$, $N(C(O)R_{37})C(O)OR_{38}$ or $N(C(O)OR_{39})C(O)OR_{40}$ group, advantageously an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22}, $OC(O)R_{23}$, $NR_{29}R_{30}$, $NR_{31}C(O)R_{32}$ or $NR_{33}C(O)OR_{34}$ group, more advantageously an OR_{22}, $OC(O)R_{23}$ or $NR_{31}C(O)R_{32}$ group, and even more advantageously an OR_{22} or $NR_{31}C(O)R_{32}$ group.

R_3 can represent in particular an OR_{22} group with R_{22} representing a hydrogen atom, a O-protecting group or a (C_1-C_6)-alkyl, aryl or aryl-(C_1-C_6)-alkyl group; an $OC(O)R_{23}$ group with R_{23} representing a (C_1-C_6)-alkyl, aryl or aryl-(C_1-C_6)-alkyl group; or a $NR_{31}C(O)R_{32}$ group with R_{31} representing a hydrogen atom or a (C_1-C_6)-alkyl, aryl or aryl-(C_1-C_6)-alkyl group and R_{32} representing a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group.

R_3 can represent more particularly an OR_{22} group with R_{22} representing a hydrogen atom or a O-protecting group; or a $NR_{31}C(O)R_{32}$ group with R_{31} representing a hydrogen atom and R_{32} representing a (C_1-C_6)alkyl. For instance, R_3 can represent an OH, OBn, OMOM or NHAc group.

According to a second embodiment R_3 can represent an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22}, $OC(O)R_{23}$, OCO_2R_{24} or $OCONR_{25}R_{26}$ group, advantageously an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22} or $OC(O)R_{23}$ group, more advantageously an OR_{22} or $OC(O)R_{23}$ group, and even more advantageously an OR_{22} group.

R_3 can represent in particular an OR_{22} group with R_{22} representing a hydrogen atom, a O-protecting group or a (C_1-C_6)-alkyl, aryl or aryl-(C_1-C_6)-alkyl group; or an $OC(O)R_{23}$ group R_{23} with representing a (C_1-C_6)-alkyl, aryl or aryl-(C_1-C_6)-alkyl group.

R_3 can represent more particularly an OR_{22} group with R_{22} representing a hydrogen atom or a O-protecting group. For instance, R_3 can represent an OH, OBn or OMOM group.

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

According to another particular embodiment, R represents a CH_2OR_8 group; R_1 and R_2 represent, independently from one another, an OR_{15} group; and R_3 represents an OR_{22} group, R_8, R_{15} and R_{22} representing advantageously a hydrogen atom or an O-protecting group. R_8 and the two R_{15} can be identical, such as H or an O-protecting group. R_8, the two R_{15} and R_{22} can also be identical, such as H or an O-protecting group.

According to another particular embodiment, R = CH_2OH, $R_1 = R_2 = OH$ or $R_1 = R_2 = R_3 = OH$.

R_4 can advantageously represent a hydrogen or halogen atom or an OR_{41} group, and in particular a hydrogen atom or an OR_{41} group.

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

R_4 can also represent a hydrogen or halogen atom or 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 or O-protecting group, and advantageously, a hydrogen atom or an OH or O-protecting group, such as H, OH or OBn.

R_4 can also represent a hydrogen or halogen (such as Br, Cl, F) atom or an OH group, such as H or OH.

According to a particular embodiment, R_4 represents a hydrogen atom.

According to a first embodiment, Y represents a NO_2 or NR_6R_7 group, and notably a NR_6R_7 group, with R_6 and R_7 as defined previously and notably with R_6 representing a hydrogen atom or a (C_1-C_6)alkyl group and R_7 representing:

- a hydrogen atom,

- a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group; in particular a (C_1-C_6)alkyl or aryl-(C_1-C_6)alkyl group,
- a $C(O)R_{52}$ group, with R_{52} as defined above and representing in particular a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group,
- a $C(O)OR_{53}$ group, with R_{53} as defined above and representing in particular a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group, or
- a N-protecting group.

According to a second embodiment, Y represents a CN or $CH_2NR_6R_7$ group, and notably a $CH_2NR_6R_7$ group, with R_6 and R_7 as defined previously and notably with R_6 representing a hydrogen atom or a (C_1-C_6)alkyl group and R_7 representing:

- a hydrogen atom,
- a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group; in particular a (C_1-C_6)alkyl or aryl-(C_1-C_6)alkyl group,
- a $C(O)R_{52}$ group, with R_{52} as defined above and representing in particular a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group,
- a $C(O)OR_{53}$ group, with R_{53} as defined above and representing in particular a (C_1-C_6)alkyl, aryl or aryl-(C_1-C_6)alkyl group, or
- a N-protecting group.

R_5 represents advantageously an OR_{49} group, with R_{49} as defined previously and advantageously representing a hydrogen atom, a (C_1-C_6)alkyl group or a O-protecting group.

According to a particular embodiment (compounds of formula (I-1)), Y represents a NR_6R_7 or $CH_2NR_6R_7$ group, and notably a NR_6R_7 group, and R_5 represents an OR_{49} group, with:

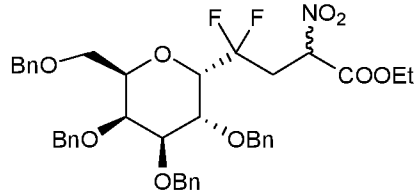
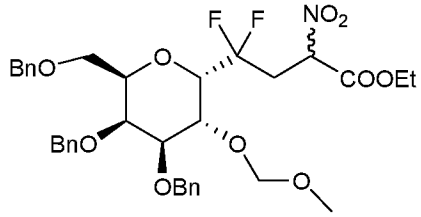
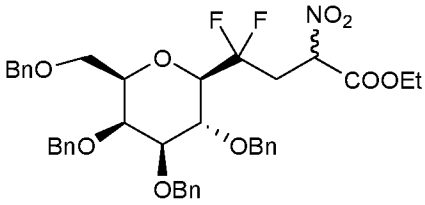
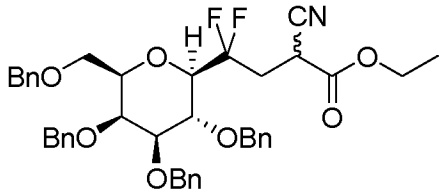
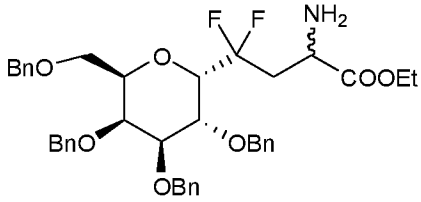
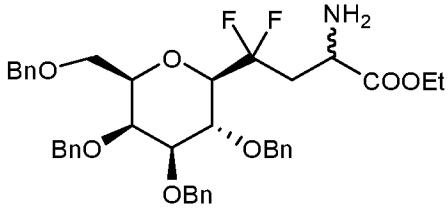
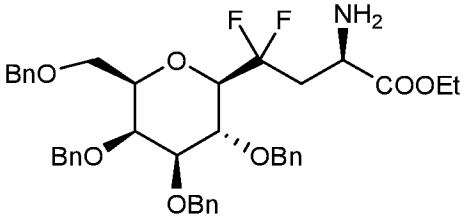
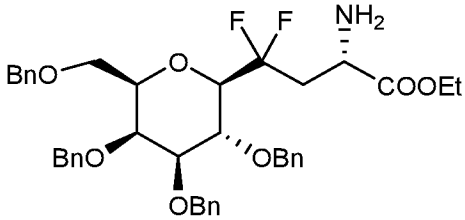
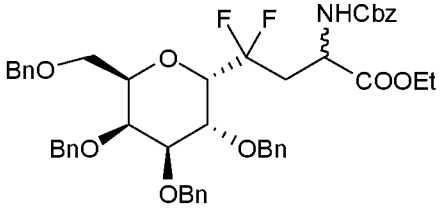
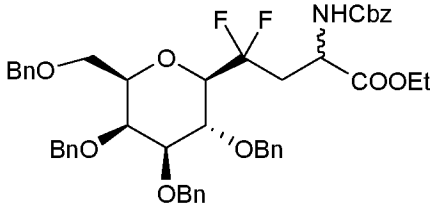
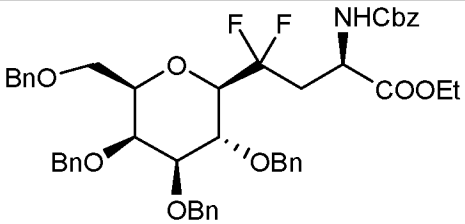
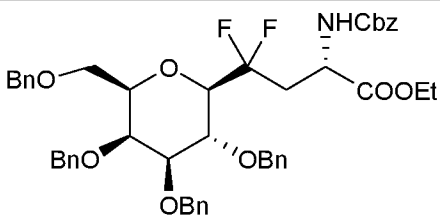
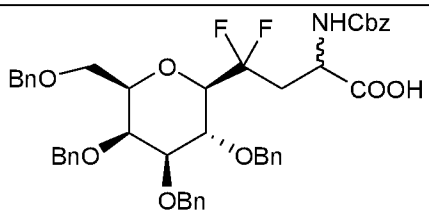
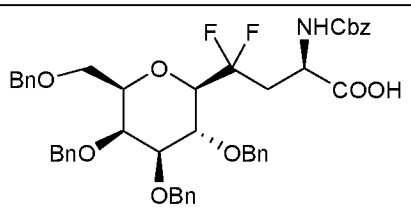
- R_6 and R_7 representing each a hydrogen atom and R_{49} representing a O-protecting group such as a (C_1-C_6)alkyl group, or
- R_{49} and R_6 representing each a hydrogen atom and R_7 representing a N-protecting group such as a Boc, Cbz or FMOC group.

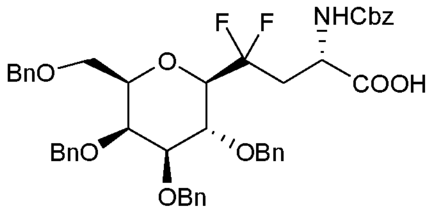
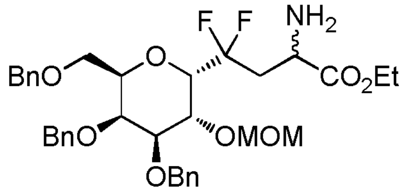
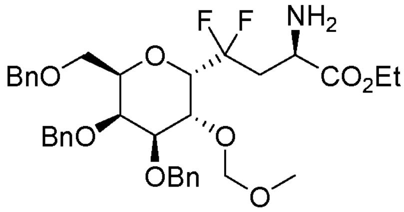
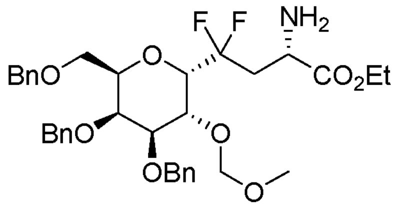
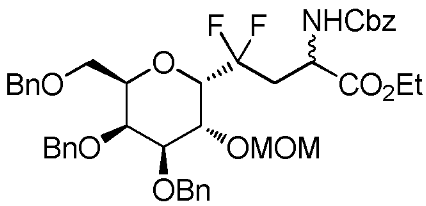
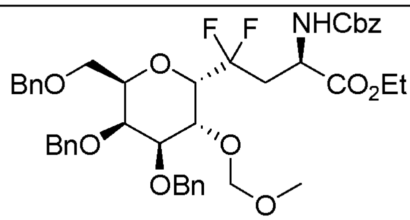
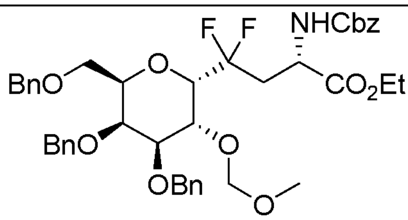
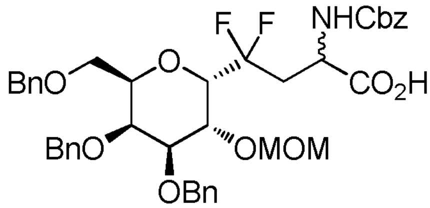
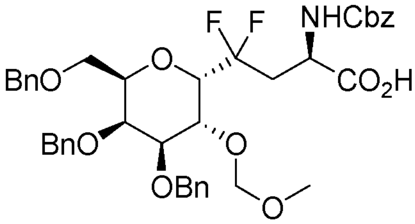
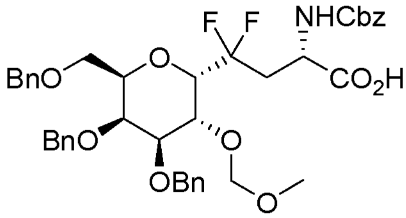
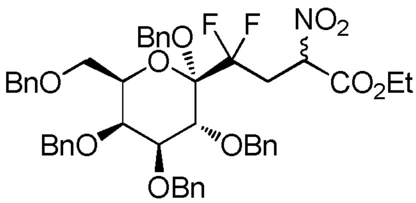
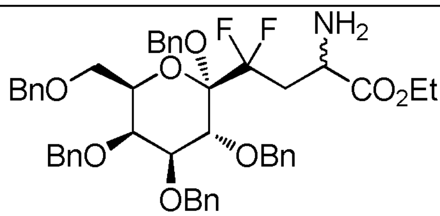
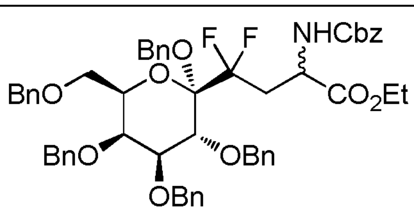
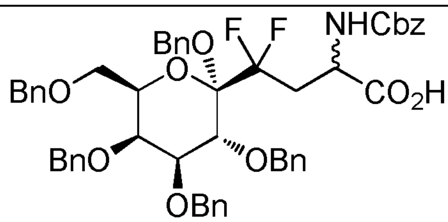
In this case, R represents preferably a CH_2OR_8 group with R_8 representing a O-protecting group; R_1 and R_2 represent preferably, independently from one another, an

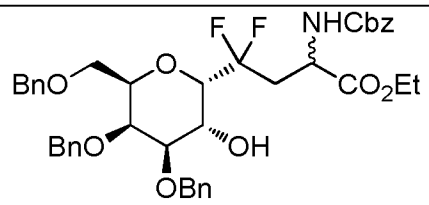
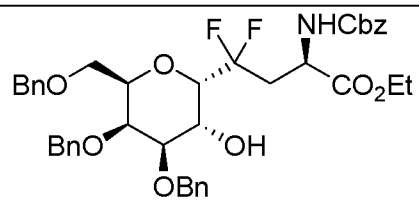
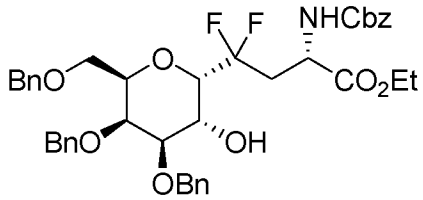
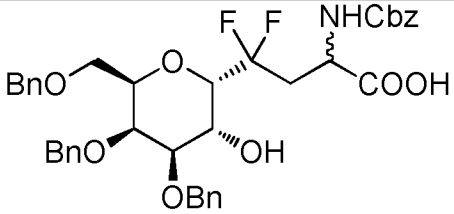
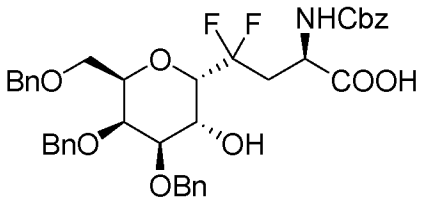
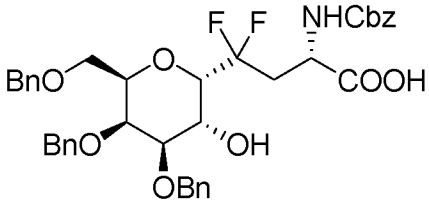
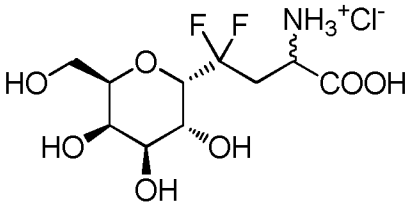
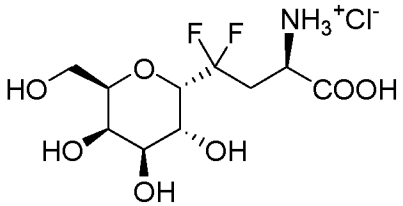
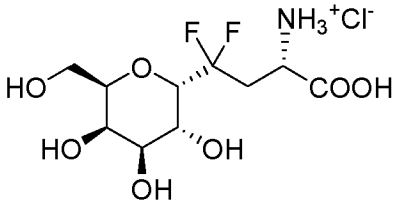
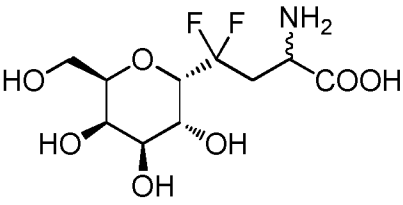
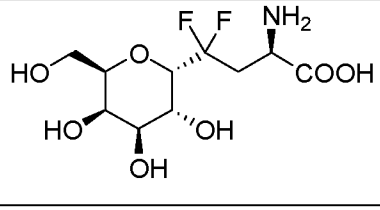
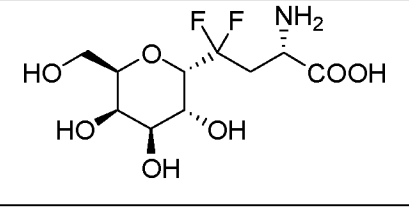
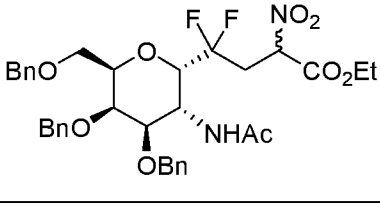
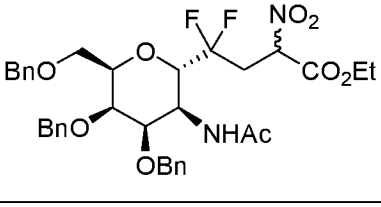
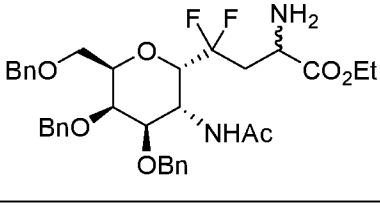
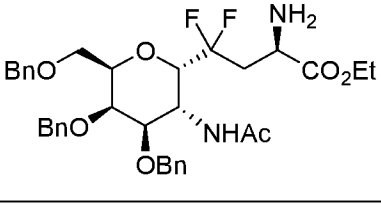
OR_{15} group with R_{15} representing a O-protecting group; and R_3 represents preferably an OR_{22} group with R_{22} representing a O-protecting group or a $NR_{31}C(O)R_{32}$ group with R_{31} representing a hydrogen atom and R_{32} representing a $(C_1\text{-}C_6)$alkyl, and notably R_3 represents an OR_{22} group.

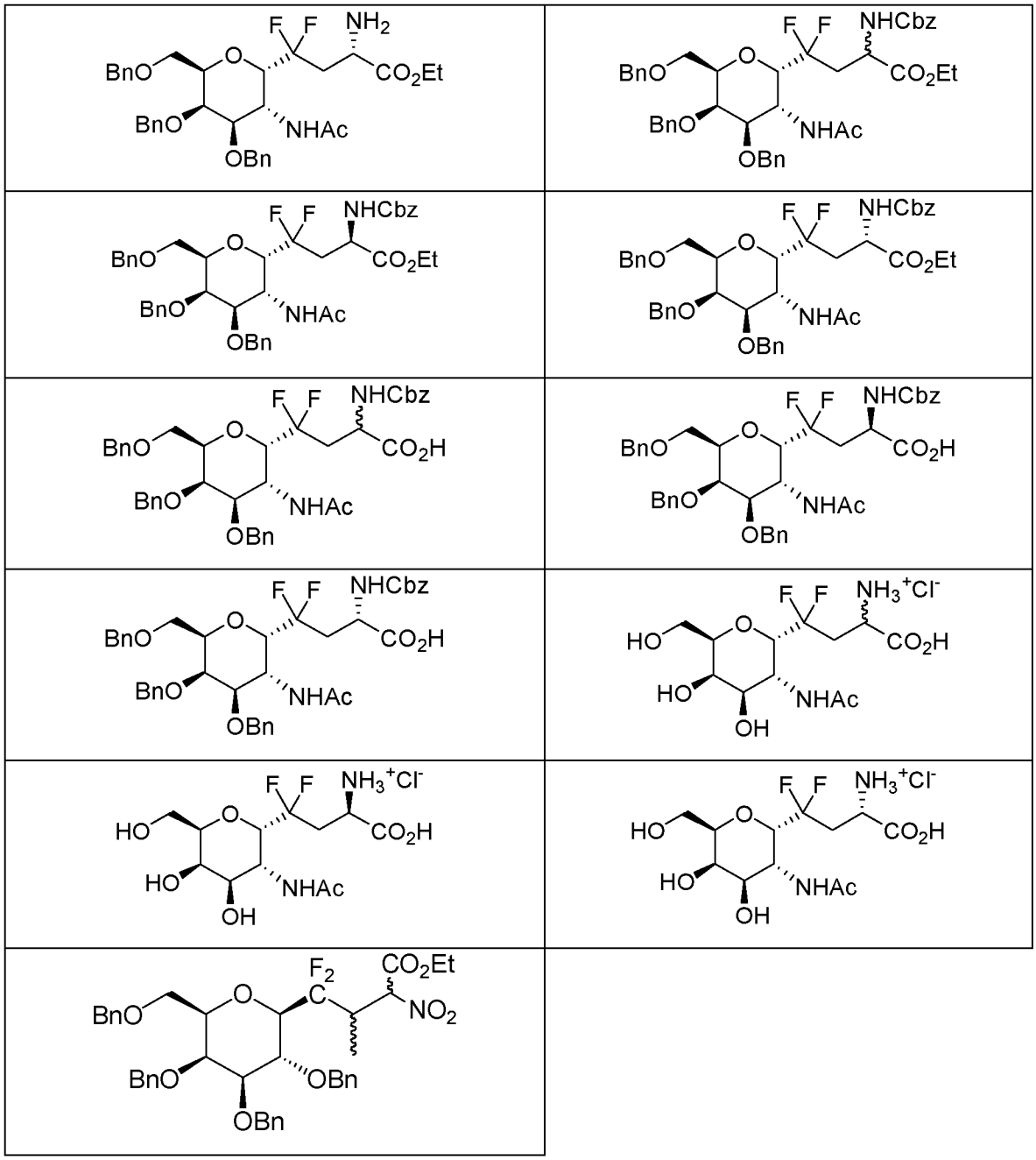
R_4 can represent a hydrogen atom or an OR_{41} group with R_{41} representing a O-protecting group, and notably R_4 can represent a hydrogen atom.

According to a particular embodiment of the present invention, the compound of formula (I) can be chosen among:

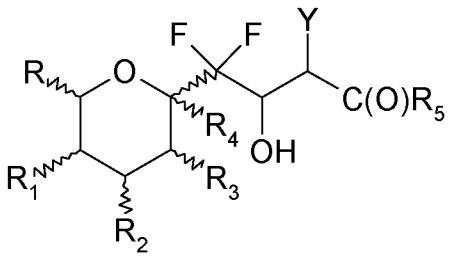
	
	
	
	
	
	
	



The present invention relates also to a process for preparing a compound of formula (I) as defined above with Z = H, comprising the following successive steps:

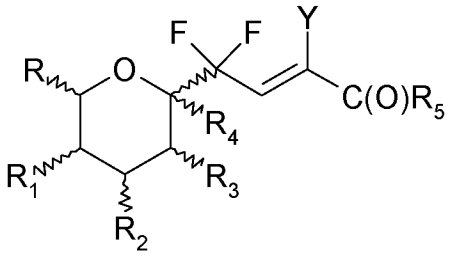
i) dehydration of a compound of formula (II):



(II)

in which R, R_1, R_2, R_3, R_4, R_5 and Y are as defined above,

to give a compound of formula (III):



(III)

in which R, R_1, R_2, R_3, R_4, R_5 and Y are as defined above, and

ii) hydrogenation of the compound of formula (III) obtained in the previous step to give a compound of formula (I) with Z = H.

Step a):

This step can be carried out by transforming the hydroxy function in a leaving group such as a halogen atom, a sulfate ($-OS(O)_2O-A_1$), a sulfonate ($-OS(O)O-A_1$) or a carboxylate ($-OC(O)-A_1$), with A_1 representing a (C_1-C_6)alkyl, aryl, (C_1-C_6)alkyl-aryl or aryl-(C_1-C_6)alkyl group, said group being optionally substituted with one or more fluorine atoms. Such a leaving group can be, for example, a mesylate ($-OSO_2Me$), a tosylate ($-OSO_2$-PhMe), a triflate ($-OSO_2CF_3$) or an acetate ($-OC(O)CH_3$).

The leaving group is then eliminated in the presence of a base such as triethylamine.

For instance, this step can be carried out in the presence of mesyl chloride (MsCl) and a base such as triethylamine.

The elimination step can also be carried out directly from the hydroxy function, i.e. without transforming it first in a leaving group, by reaction with Burgess' reactive or with Martins' persulfane.

Step b):

This step can be carried out by hydrogenation methods well known to the person skilled in the art, notably in the presence of a hydride donor such as a borohydride, notably $NaBH_4$, or by a radical reaction in the presence of Bu_3SnH.

The compound thus obtained can be separated 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, chromatography on a column of silica gel or high performance liquid chromatography (HPLC).

According to a first embodiment of the invention, this process can be carried out with a compound of formula (IIa1), which is a compound of formula (II) in which Y = NO_2. The compound of formula (Ia1) obtained, i.e. a compound of formula (I) in which Z = H and Y = NO_2, can be then hydrogenated to give a compound of formula (Ib1), i.e. a compound of formula (I) in which Z = H and Y = NH_2. Compounds of formula (Ic1), i.e. compounds of formula (I) in which Z = H and Y = NR_6R_7, at least R_6 or R_7 being not a hydrogen atom, are then obtained by substitution of the amino group of a compound of formula (Ib1).

According to a second embodiment of the invention, this process can be carried out with a compound of formula (IIa2), which is a compound of formula (II) in which Y = CN. The compound of formula (Ia2) obtained, i.e. a compound of formula (I) in which Z = H and Y = CN, can be then hydrogenated or reduced to give a compound of formula (Ib2), i.e. a compound of formula (I) in which Z = H and Y = CH_2NH_2. However, the compound of formula (Ib2) can be also obtained directly in one step from the compound of formula (IIIa2), corresponding to a compound of formula (III) in which Z = H and Y = CN. Compounds of formula (Ic2), i.e. compounds of formula (I) in which Z = H and Y = $CH_2NR_6R_7$, at least R_6 or R_7 being not a hydrogen atom, are then obtained by substitution of the amino group of a compound of formula (Ib2).

Thus, according to a particular embodiment, the process comprises the following successive steps:

a1) dehydration of a compound of formula (IIa) corresponding to a compound of formula (II) in which Y = NO_2 or CN to give a compound of formula (IIIa) corresponding to a compound of formula (III) in which Y = NO_2 or CN,

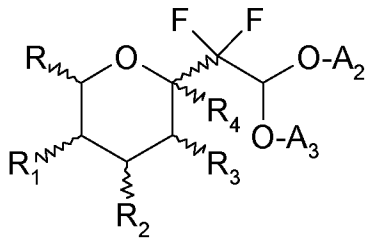
b1) reduction of the compound of formula (IIIa) obtained in the previous step to give a compound of formula (Ia) corresponding to a compound of formula (I) in which Z = H and Y = NO_2 or CN, or a compound of formula (Ib) corresponding to a compound of formula (I) in which Z = H and Y = NH_2 or CH_2NH_2,

c1) optionally reduction of the NO_2 or CN function of the compound of formula (Ia) obtained in the previous step to give a compound of formula (Ib) as defined in step b1), and

d1) optionally substitution of the amino function of the compound of formula (Ib) obtained in the previous step to give a compound of formula (Ic) corresponding to a compound of formula (I) in which Z = H and Y = NR_6R_7 or $CH_2NR_6R_7$ respectively, with at least R_6 or R_7 being not a hydrogen atom.

Step a1): see step a).

It is to be noted that the compound of formula (IIa) can be obtained by reaction of a compound of formula (IV):



(IV)

in which R, R_1, R_2, R_3 and R_4 are as defined above and A_2 and A_3 represent, independently from one another, a hydrogen atom or a (C_1-C_6)alkyl or aryl-(C_1-C_6)-alkyl group,

with a compound of formula (V)

$$Y\text{-}CH_2\text{-}COR_5 \quad (V)$$

in which R_5 is as defined previously and Y = NO_2 or CN,

in the presence of a base such as $HNEt_2$.

This reaction is carried out in the Henry's conditions.

The compound of formula (IV) can be obtained by methods well known to the person skilled in the art (see for example the experimental part).

Preferably, R_5 represents a R_{48} or OR_{49} group, with R_{48} and R_{49} as defined above but with the proviso that R_{49} is not a hydrogen atom.

Step b1): see step b).

Step c1):

This step can be carried out by methods well known to the person skilled in the art.

Notably, this step can be carried out under a hydrogen atmosphere in the presence of a hydrogenation catalyst, at an atmospheric pressure or at a higher pressure. The catalyst can be based on palladium, nickel or platinum, such as palladium on carbon (Pd/C), Raney's nickel or PtO_2. The reaction can be carried out in the presence of an acid or a base to activate the catalyst.

The reduction of the nitro function can be carried out also in the presence of a borohydride, such as $NaBH_4$, and a salt of nickel, cobalt, palladium, tin, copper or lanthanide, e.g. $NiCl_2$, $TiCl_4$, or $CoCl_2$.

Another method consists in the hydrogenation of the nitro function with hydrogen formed *in situ* by the action of an acid, such as HCl, AcOH, Me_3SiCl, CF_3COOH or HCO_2H, on a metal chosen among zinc, tin and iron.

The nitro function can also be reduced in an oxime (=N-OH) which is then reduced in an amino group. This method is well known to the person skilled in the art.

The reduction of the nitro functionality into an oxime group can be obtained in the presence of a metal salt such as a tin salt (e.g. $SnCl_2$ or $Sn(Ph)_2$), associated or not to Et_3N / PhSH or TMSPhSH / Et_3N. $NaNO_2$ can also be used in the presence of a proton source such as CH_3COOH or H_2O in DMSO to reduce the nitro function. These reactions can be carried out at a temperature between 65 and 100°C.

The oxime can then be reduced into an amino function under a hydrogen atmosphere in the presence of a hydrogenation catalyst, at an atmospheric pressure or at a higher pressure. The catalyst can be based on palladium, nickel, platinum, ruthenium,

rhodium or iridium, such as palladium on carbon (Pd/C), $Pd(OH)_2$, Pd on graphite, Raney's nickel, PtO_2, $RuCl_3$ or $IrCl_3$. The reaction can be carried out in the presence of an acid or a base to activate the catalyst.

This reduction can also be carried out in the presence of an aluminum amalgam prepared from aluminum and $HgCl_2$. The oxime can also be reduced with hydrogen formed *in situ* by the action of an acid on a metal. Hydrides can also be used, such as $NaBH_4$ or $LiAlH_4$.

All these methods are well known to the person skilled in the art. However, other methods known to the person skilled in the art can be used.

Step d1):

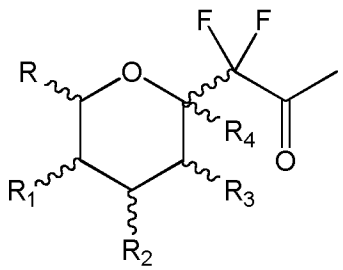
The substitution of the amino function can be carried out by methods well known to the person skilled in the art.

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

The present invention relates also to a process for preparing a compound of formula (I) as defined above with $Z = CH_3$, comprising the following successive steps:

i) reaction of a compound of formula (VII):



(VII)

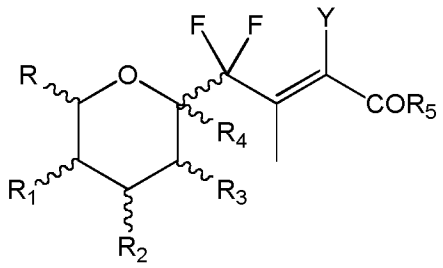
in which R, R_1, R_2, R_3 and R_4 are as defined above,

with a compound of formula (V):

$$Y\text{-}CH_2\text{-}COR_5 \quad (V)$$

in which R_5 is as defined previously and $Y = NO_2$ or CN,

to give a compound of formula (VIII):



(VIII)

ii) in which R, R_1, R_2, R_3, R_4 and R_5 are as defined above and Y = NO_2 or CN,optionally reduction of the compound of formula (VIII) obtained in the previous step i) to give a compound of formula (I) with Z = CH_3 and Y = NO_2 or CN,

iii) optionally reduction of the NO_2 or CN function of the compound of formula (I) obtained in the previous step ii) to give a compound of formula (I) with Z = CH_3 and Y = NH_2 or CH_2NH_2, and

iv) optionally substitution of the amino function of the compound of formula (I) obtained in the previous step iii) to give a compound of formula (I) with Z = CH_3 and Y = NR_6R_7 or $CH_2NR_6R_7$, with at least R_6 or R_7 being not a hydrogen atom.

Step i):

This reaction can be carried out in the presence of a Lewis acid such as $TiCl_4$ and a base such as N-methyl-morpholine (NMM). Tetrahydrofurane, dichloromethane or a mixture thereof can be used as solvent.

The compounds of formula (VII) can be prepared as described in the experimental part below.

Step ii): see step b1).

Step iii): see step c1).

Step iv): see step d1).

The compound thus obtained can be separated 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, chromatography on a column of silica gel or high performance liquid chromatography (HPLC).

If the two processes described above, to prepare compounds of formula (I) with Z = H or CH_3 respectively, are carried out from a compound of formula (II) or (VII) with R_5 representing a OR_{49} group, with R_{49} as defined above but with the proviso that R_{49} is not a hydrogen atom, a final compound of formula (I) with R_5 = H or OH can be obtained by reduction or deprotection of the OR_{49} group in conditions well known to the person skilled in the art.

The OH can thus be halogenated to give access to compounds of formula (I) with R_5 representing a halogen atom, in conditions well known to the person skilled in the art.

Compounds of formula (I) with R_5 representing a $NR_{50}R_{51}$ group can be obtained by methods well known to the person skilled in the arts from a compound of formula (I) with R_5 = OH, notably by a peptide coupling.

It is to be noted moreover that the compound of formula (I) with Z = H can be obtained directly in one step from compound of formula (IV) and a compound of formula $Y\text{-}CH_2\text{-}COR_5$, by carrying out a cascade reaction of olefination and hydrogenation, such as described in *Eur. J. org. Chem.* 2008, 975.

In the synthesis of compounds of formula (I), R represents preferably a CH_2OR_8 group with R_8 representing a O-protecting group; R_1 and R_2 represent preferably, independently from one another, an OR_{15} group with R_{15} representing a O-protecting group; and R_3 represents preferably an OR_{22} group with R_{22} representing a O-protecting group; or a $NR_{31}C(O)R_{32}$ group with R_{31} representing a hydrogen atom and R_{32} representing a $(C_1\text{-}C_6)$alkyl; and notably R_3 represents an OR_{22} group. R_4 can represent a hydrogen atom or an OR_{41} group with R_{41} representing a O-protecting group, and notably R_4 represents a hydrogen atom.

The present invention relates also to the use of a compound of formula (I) with Y = NH_2 or CH_2NH_2, notably NH_2, and/or R_5 = OH, and in particular a compound of formula (I-1), i.e. a compound of formula (I) for which Y represents a NR_6R_7 or $CH_2NR_6R_7$ group, and notably a NR_6R_7 group, and R_5 represents an OR_{49} group, with:

- R_6 and R_7 representing each a hydrogen atom and R_{49} representing a O-protecting group such as a $(C_1$-$C_6)$alkyl group, or
- R_{49} and R_6 representing each a hydrogen atom and R_7 representing a N-protecting group such as a Boc or Cbz group,

in the synthesis of a peptide, in place of an amino acid such as a serine or a threonine.

The term "amino acid" as used in the present invention refers to natural α-amino acids (e.g. Alanine (Ala), Arginine (Arg), Asparagine (Asn), Aspartic acid (Asp), Cysteine (Cys), Glutamine (Gln), Glutamic acid (Glu), Glycine (Gly), Histidine (His), Isoleucine (Ile), Leucine (Leu), Lysine (Lys), Méthionine (Met), Phenylalanine (Phe), Proline (Pro), Serine (Ser), Threonine (Thr), Tryptophan (Trp), Tyrosine (Tyr) and Valine (Val)) in the D or L form, as well as non-natural amino acid (e.g. β-alanine, allylglycine, *tert*-leucine, 3-amino-adipic acid, 2-aminobenzoic acid, 3-aminobenzoic acid, 4-aminobenzoic acid, 2-aminobutanoic acid, 4-amino-1-carboxymethyl piperidine, 1-amino-1-cyclobutanecarboxylic acid, 4-aminocyclohexaneacetic acid, 1-amino-1-cyclohexanecarboxyilic acid, (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid, (1*R*,2*S*)-2-aminocyclohexanecarboxylic acid, (1*S*,2*R*)-2-aminocyclohexanecarboxylic acid, (1*S*,2*S*)-2-aminocyclohexanecarboxylic acid, 3-aminocyclohexanecarboxylic acid, 4-aminocyclohexanecarboxylic acid, (1*R*,2*R*)-2-aminocyclopentanecarboxylic acid, (l*R*,2*S*)-2-aminocyclopentanecarboxyilic acid, 1-amino-1-cyclopentanecarboxylic acid, 1-amino-1-cyclopropanecarboxylic acid, 4-(2-aminoethoxy)-benzoic acid, 3-aminomethylbenzoic acid, 4-aminomethylbenzoic acid, 2-aminobutanoic acid, 4-aminobutanoic acid, 6-aminohexanoic acid, 1-aminoindane-1-carboxylic acid, 4-aminomethyl-phenylacetic acid, 4-aminophenylacetic acid, 3-amino-2-naphtoic acid, 4-aminophenylbutanoic acid, 4-amino-5-(3-indolyl)-pentanoic acid, (4*R*,5*S*)-4-amino-5-methylheptanoic acid, (*R*)-4-amino-5-methylhexanoic acid, (*R*)-4-amino-6-methylthiohexanoic acid, (*S*)-4-amino-pentanoic acid, (*R*)-4-amino-5-phenylpentanoic acid, 4-aminophenylpropionic acid, (*R*)-4-aminopimeric acid, (4*R*,5*R*)-4-amino-5-

hyroxyhexanoic acid, (*R*)-4-amino-5-hydroxypentanoic acid, (*R*)-4-amino-5-(*p*-hydroxyphenyl)-pentanoic acid, 8-aminooctanoic acid, (2*S*,4*R*)-4-amino-pyrrolidine-2-carboxylic acid, (2*S*,4*S*)-4-amino-pyrrolidine-2-carboxylic acid, azetidine-2-carboxylic acid, (2*S*,4*R*)-4-benzyl-pyrrolidine-2-carboxylic acid, (S)-4,8-diaminooctanoic acid, *tert*-butylglycine acid, γ-carboxyglutamate, β-cyclohexylalanine, citrulline, 2,3-diamino propionic acid, hippuric acid, homocyclohexylalanine, moleucine, homophenylalanine, 4-hydroxyproline, indoline-2-carboxylic acid, isonipecotic acid, α-methyl-alanine, nicopetic acid, norleucine, norvaline, octahydroindole-2-carboxylic acid, ornithine, penicillamine, phenylglycine, 4-phenyl-pyrrolidine-2-carboxylic acid, pipecolic acid, propargylglycine, 3-pyridinylalanine, 4-pyridinylalanine, 1-pyrrolidine-3-carboxylic acid, sarcosine, statines, tetrahydroisoquinoline-1-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, or tranexamic acid). Preferably, it will be a natural or non-natural α-amino acid and preferably a natural α-amino acid.

The term "peptide" as used in the present invention refers to a chain comprising at least 2, and notably 2 to 30, amino acids as defined above (and preferably natural α-amino acid) bound together by means of peptide bounds (i.e. amide function). It can be in particular an oligopeptide having in particular 2 to 20 amino acids.

The synthesis of the peptide will be carried out by classical methods well known to the person skilled in the art, using notably steps of protection / deprotection and peptide coupling.

The peptide can notably be an oligopeptide comprising 2 to 20 amino acids.

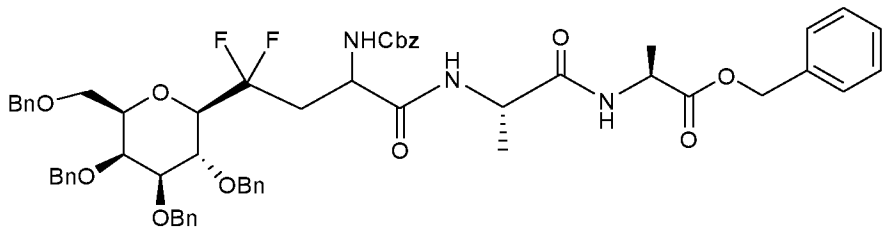
The present invention concerns also a peptide of formula (VI) in which at least one amino acid, such as a serine or a threonine, has been replaced with a compound of formula (I) in which Y = NHR_7 or CH_2NHR_7, and notably NHR_7, and/or R_5 = OH, and in particular with Y = NH_2 or CH_2NH_2, and notably NH_2, and R_5 = OH, the Y and/or R_5 group being linked to an amino acid of the peptide by means of peptide bond (i.e. an amide bond).

This means that the hydrogen of the NHR_7 or CH_2NHR_7 moiety of Y is replaced by a bond with a C(=O) moiety derived from the acid function of an amino acid, and/or

the OH moiety of R_5 is replaced by a bond with a nitrogen derived from the amino function of another amino acid.

The groups R, R_1, R_2, R_3 and R_4 of the compound of formula (I) are moreover as defined previously.

The peptide can notably be an oligopeptide comprising 2 to 20 amino acids. It can be chosen notably among the following oligopeptides:

VI-1 

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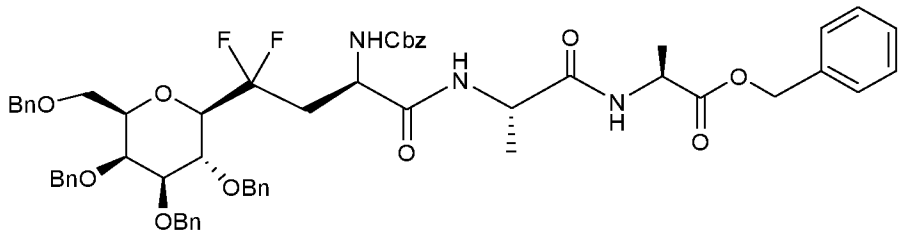
VI-2 

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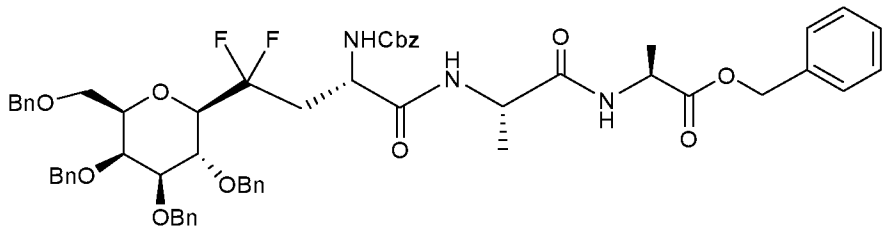
VI-3 

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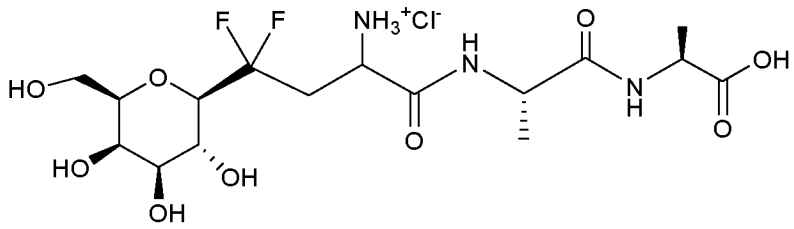
VI-4 

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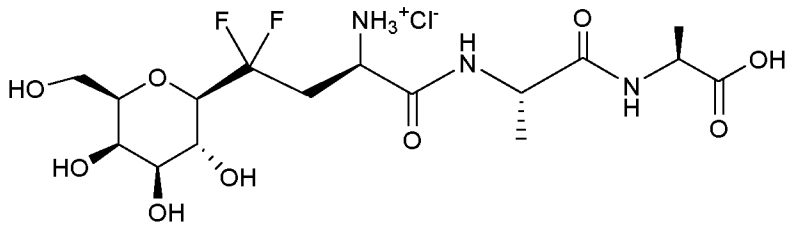
VI-5 

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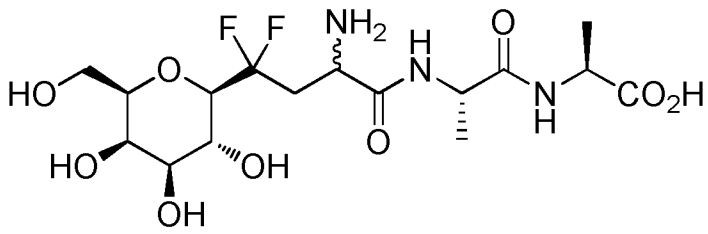
VI-6 

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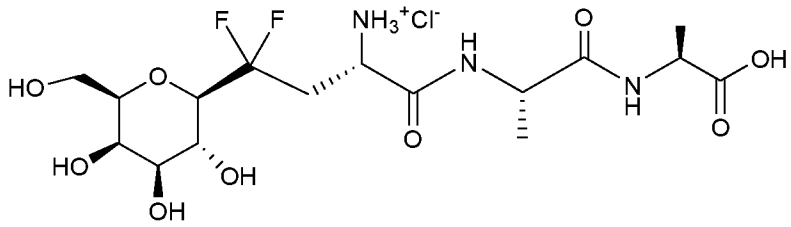
VI-7 

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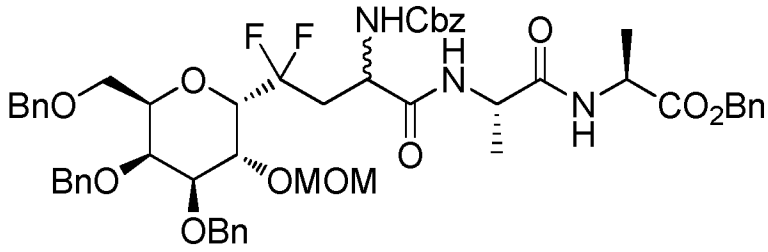
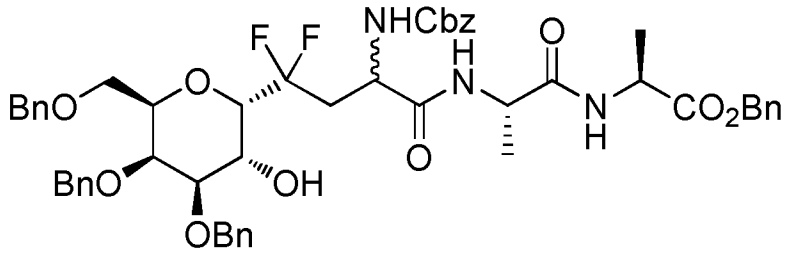
VI-8 

VI-9 

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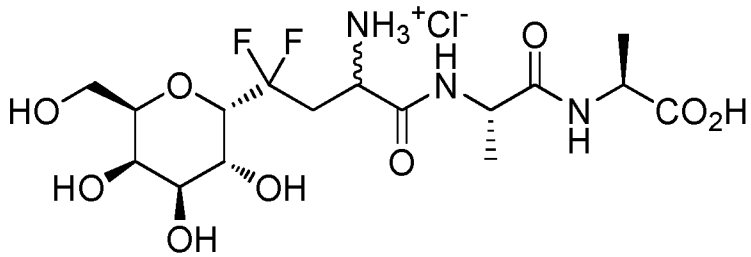
VI-10 

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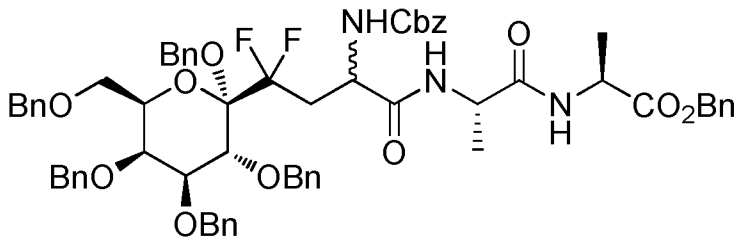
VI-11 

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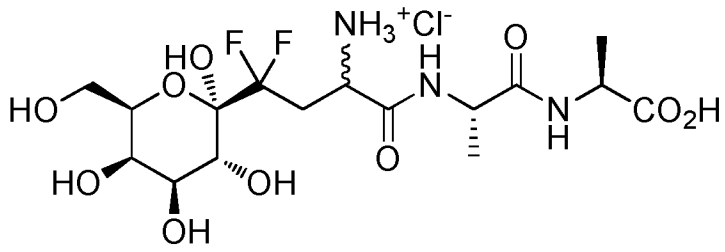
VI-12



The invention relates also to a peptide (VI) as defined previously for use as medicament, notably for the treatment or the prevention of viral, bacterial or inflammatory diseases.

The invention concerns also the use of a peptide (VI) in the manufacture of a medicament, intended notably for the treatment or the prevention of viral, bacterial or inflammatory diseases.

More specifically, the invention concerns also a method for treating or preventing viral, bacterial or inflammatory diseases comprising the administration to a person in need thereof of a sufficient quantity of a peptide (VI).

The invention concerns also a method for cosmetic treatment comprising the administration to a person in need thereof of a sufficient quantity of a peptide (VI).

The invention relates also to a peptide (VI) as defined previously for use as cancer vaccine.

The invention concerns also the use of a peptide (VI) in the manufacture of a medicament, intended notably for use as cancer vaccine.

More specifically, the invention concerns also a method for preventing cancer comprising the administration to a person in need thereof of a sufficient quantity of a peptide (VI).

Indeed, the compound of formula (I) integrated in the peptide (VI) represents a mimic of antigen Tn.

In this case, advantageously R = CH_2OH and R_1 = R_2 = OH. R_4 can also represent advantageously a hydrogen atom. R_3 will be in particular an OH or NHAc group, preferably a NHAc group.

Advantageously, the Y group of the compound of formula (I) integrated in the peptide (VI) will be a NH_2 group not bound to another amino acid of the peptide (VI).

The cancer in question can be in particular breast, lung, prostate or colon cancer.

The present invention relates thus also to the use of a compound of formula (I) according to the present invention as a mimic of antigen Tn.

In this case, advantageously R = CH_2OH and R_1 = R_2 = OH. R_4 can also represent advantageously a hydrogen atom. R_3 will be in particular an OH or NHAc group, preferably a NHAc group. Advantageously, Y will represent a NH_2 group.

The present invention relates also to pharmaceutical or cosmetic compositions comprising at least one peptide (VI) and a pharmaceutically acceptable carrier. Said pharmaceutically acceptable carrier can be a hapten, a protein, a chemical scaffold or a carrier matrix.

The pharmaceutical compositions of the invention can be intended to oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration. The active ingredient can be administered in unit forms for administration, mixed with conventional pharmaceutical carriers, to animals or to humans. Suitable unit forms for administration comprise the forms for oral administration, such as tablets, gelatin capsules, powders, granules and oral solutions or suspensions, the forms for sublingual and buccal administration, the forms for subcutaneous, intramuscular, intravenous, intranasal or intraoccular administration and the forms for rectal administration.

The cosmetic compositions of the invention can be intended to oral, sublingual, cutaneous, topical, transdermal or local administration. The active ingredient can be administered in unit forms for administration, mixed with conventional pharmaceutical carriers, to animals or to humans. Suitable unit forms for administration comprise the forms for oral administration, such as tablets, gelatin capsules, powders, granules and oral solutions or suspensions, the forms for sublingual and buccal administration, the forms for topical, cutaneous, transdermal or local administration.

When a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic and the like. The tablets may be coated with

sucrose or with other suitable materials, or they may be treated in such a way that they have a prolonged or delayed activity and they continuously release a predetermined amount of active principle.

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

A preparation in the form of syrup or elixir may contain the active ingredient together with a sweetener, an antiseptic, or also a taste enhancer or a suitable coloring agent.

The water-dispersible powders or granules may contain the active ingredient mixed with dispersing agents or wetting agents, or suspending agents, and with flavor correctors or sweeteners.

For rectal administration, suppositories are used which are prepared with binders which melt at rectal temperature, for example cocoa butter or polyethylene glycols.

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

The active principle may also be formulated in the form of microcapsules, optionally with one or more carrier additives.

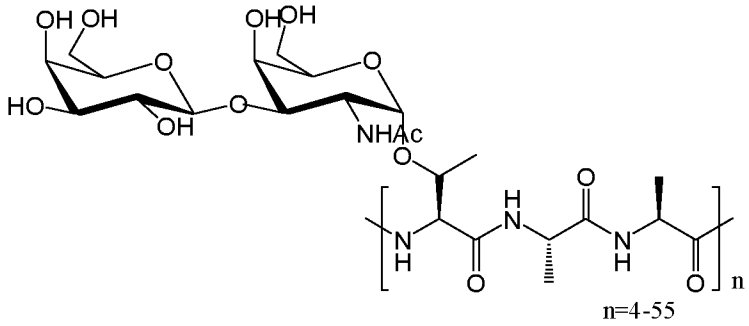
The compounds of the invention can be used in a pharmaceutical or cosmetic composition at a dose ranging from 0.01 mg to 1000 mg a day, administered in only one dose once a day or in several doses along the day, for example twice a day. The daily administered dose is advantageously comprises between 5 mg and 500 mg, and more advantageously between 10 mg and 200 mg. However, it can be necessary to use doses out of these ranges, which could be noticed by the person skilled in the art.

The present invention relates also to the use of a peptide (VI) in the preservation of biological materials, such as cells, tissues and organs, notably below 37°C, such as below 0°C, notably for the cryopreservation of biological materials (human organs or tissues (e.g. for transplant) or cells), and the preservation of food.

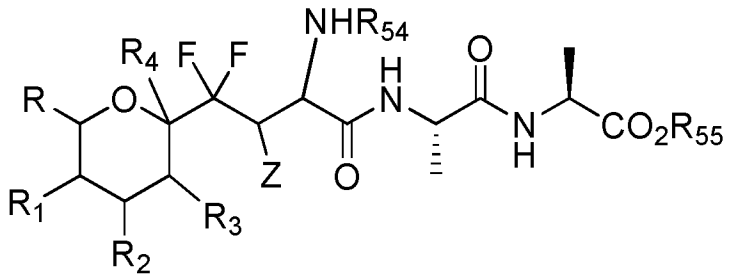
The present invention relates also to the cosmetic use of a peptide (VI), especially its cosmetic use in anti-aging applications.

Indeed the study of fish present in the iced water of the polar area shown that they resist to temperatures below 0°C because of the presence in their blood and in their organism of particular proteins protecting them against frost (*Chem. Rev.* 1996, 16, 2).

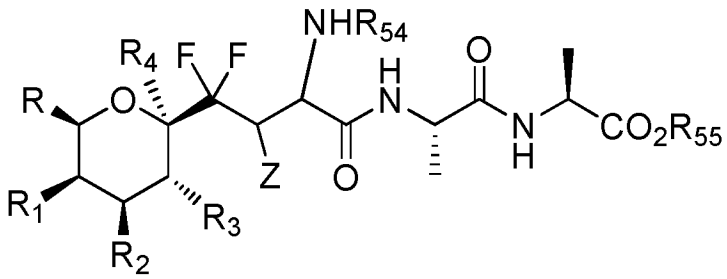
These proteins are called anti-freeze glycoprotein (AFGP), they contain a repetitive moiety consisting of a glycosylated peptide containing 3 amino acids (threonine - alanine or proline - alanine) and can have the following structure:



In this case, the peptide will advantageously respond to the following formula (IX), and in particular (IXa):



(IX)



(IXa)

in which R, R_1, R_2, R_3, R_4 and Z are as defined above (including the preferred embodiments), R_{54} represents a hydrogen atom or a N-protecting group such as Cbz and R_{55} represents a hydrogen atom or an O-protecting group such as Bn.

Advantageously, R = CH_2OH, R_1 = R_2 = R_3 = OH and R_4 = H or OH. R_{54} and R_{55} each represent advantageously a hydrogen atom. Z can be also a hydrogen atom.

It will be in particular a peptide chosen from examples VI-1 to VI-12.

Examples of such compound preparations of the present invention, as well as results of their biological activity are described below for non-limiting and illustrative purposes.

FIGURES

Figures 1a to 6b represent mass spectra (ESI+) of the following compounds:

- figure 1a: compound Ad1 without β-Galactosidase,
- figure 1b: compound Ad1 with β-Galactosidase,
- figure 2a: compound Ad2 without β-Galactosidase,
- figure 2b: compound Ad2 with β-Galactosidase,
- figure 3a: compound Cd1 without α-Galactosidase,
- figure 3b: compound Cd1 with α-Galactosidase,
- figure 4a: compound Cd2 without α-Galactosidase,
- figure 4b: compound Cd2 with α-Galactosidase,
- figure 5a: compound Dd1 without α-Galactosidase,
- figure 5b: compound Dd1 with α-Galactosidase,
- figure 6a: compound Dd2 without α-Galactosidase, and
- figure 6b: compound Dd2 with α-Galactosidase.

Figure 7 represents the evolution of the percentage of fibroblast viability for 7 days after serum deprivation.

EXAMPLES

I – Preparation of the compounds according to the invention

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

The ^{19}F NMR spectra were recorded on BRUKER DPX 300 and DPX 600 spectrometers. The internal reference used is fluorotrichloromethane ($CFCl_3$). Chemical shifts are expressed in parts per million (ppm) and coupling constants (J) in Hertz (Hz).

The following abbreviations were used:

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

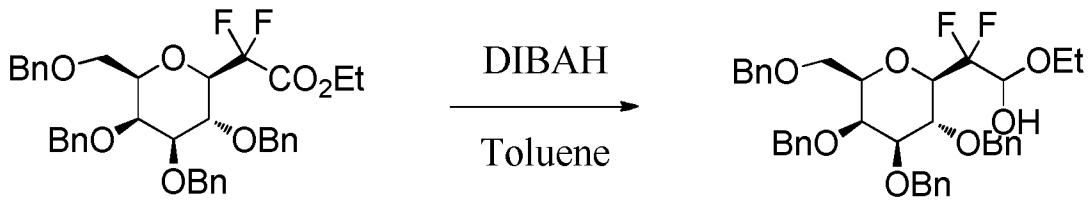
The mass spectra were obtained on a spectrophotometer Micromass TOF-SPEC E 20 kV, α-cyano type, for MALDI ionization and JEOL AX500, 3 kV, Canon FAB JEOL, Xe, 4 kV, 10 μA limiting current, Gly-NBA 50:50 for FAB ionization.

Separations via column chromatography are carried out under light pressure on Kieselgel 60 silica (230-400 Mesh, Merck).

Monitoring of reactions is performed by thin-layer chromatography (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.

The compounds have been numbered by assigning the symbol α to the alpha derivatives and β to the beta derivatives, and when necessary by assigning the letter G to the galactose derivatives and the letter T to the talose derivatives.

***Synthesis of compound* <u>2β</u>**



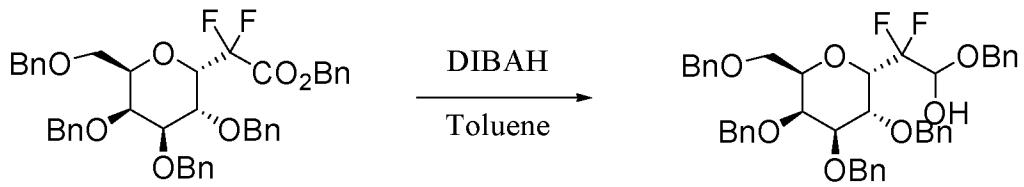
<u>1β</u> **<u>2β</u>**

To a cooled (-78°C) solution of compound **<u>1β</u>** (1.03g; 1.60mmol; 1eq.), synthesized according to *Synlett 2005, 17, 2627-2630* and *Org. Lett. 2002, 4, 757-759* – see also WO 2004/014928, WO 2007/125203 and WO 2007/125194, in anhydrous toluene (40 mL) was added a solution of diisobutylaluminium hydride (1.2 M in toluene; 2.00 mL; 2.40 mmol; 1.5eq.) and the resultant mixture was stirred for 1 h at this temperature. The reaction was then quenched with ethanol (10 mL) and the solution was warmed to -20°C for 10 min. A Rochelle's salt solution (20 %, 45 mL) was then added and the solution was vigorously stirred for 1 h. The reaction medium was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to give compound **<u>2β</u>** (1.03g; yellow oil).

<u>2β</u>: $C_{38}H_{42}F_2O_7$ M=648.73g.mol^{-1}

Mass (ESI$^+$): 666.51(M+H_2O); 671.43(M+Na)

***Synthesis of compound* 2(a)α**



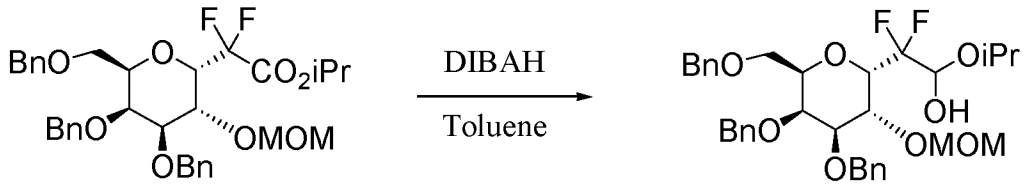
1(a) α **2(a)α**

To a cooled (-78°C) solution of compound **1(a)α** (0.112 g, 0.157 mmol, 1 eq), (synthesized according to *Org. Lett. 2007, 9, 2477-2480* with the use of Al(OiPr)$_3$/ iPrOH in refluxing DCM for the reducing step, in anhydrous toluene (4.1 mL) was added a solution of diisobutylaluminium hydride (1.2 M in toluene; 0.211 mL; 0.253 mmol; 1.6eq.) and the resultant mixture was stirred for 1 h at this temperature. The reaction media was warmed to -20°C for 10 min and then quenched with ethanol (5 mL). A Rochelle's salt solution (20 %, 10 mL) was then added and the solution was vigorously stirred for 1h. The reaction medium was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to give compound **2(a)α** (0.100g) which was used in the next step without any further purification.

2(a)α: $C_{43}H_{44}F_2O_7$ M=710.80g.mol^{-1}

Mass (ESI$^+$): 728.20=[M+H_2O]$^+$; 733.33=[M+Na]$^+$

***Synthesis of compound* 2(b)α**



1(b)α **2(b)α**

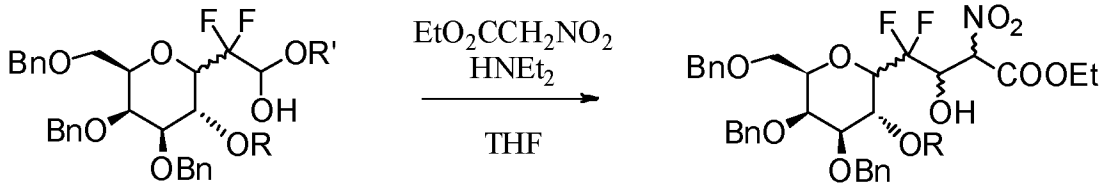
To a cooled (-78°C) solution of compound **1(b)α** (0.248 g, 0.404 mmol, 1 eq), synthesized according to *Org. Lett. 2007, 9, 2477-2480* with the use of Al(OiPr)$_3$/ iPrOH in refluxing DCM for the reducing step, in anhydrous toluene (9 mL) was added a solution of diisobutylaluminium hydride (1 M in toluene; 0.600 mL; 0.605 mmol; 1.5 eq.) and the resultant mixture was stirred for 1 h at this temperature. The reaction

medium was warmed to -20°C for 10 min and then quenched with ethanol (2 mL). A Rochelle's salt solution (20 %, 10 mL) was then added and the solution was vigorously stirred for 1 h. The reaction medium was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to give compound **2(b)α** (0.244 g) which was used in the next step without further purification.

2(b)α: $C_{34}H_{42}F_2O_8$ M=616.69 g.mol^{-1}

Mass (ESI$^+$): 639.20[M+Na]$^+$; 1255.07[2M+Na]$^+$

***Synthesis of compounds* 3(b)α *and* 3β**



2(b)α (R = MOM; R' = *i*Pr) **3(b)α** (R = MOM)

2β (R = Bn; R' = Et) **3β** (R = Bn)

Compound **3β**: Diethylamine (246 µL; 2.39 mmol; 1.5 eq.) was added to a solution of compound **2β** (1.03 g) and ethyl nitroacetate (264 µL; 2.39 mmol; 1.5 eq.) in THF (5 mL) at 0°C. The mixture was stirred for 3h, then at 0°C, ethyl acetate (5 mL) and HCl (0.5N, 5 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to produce compound **3β** (1.19 g; yellow oil). Compound **3β** was used in the next step without further purification.

3β: $C_{40}H_{43}F_2NO_{10}$ M=735.77 g.mol^{-1}

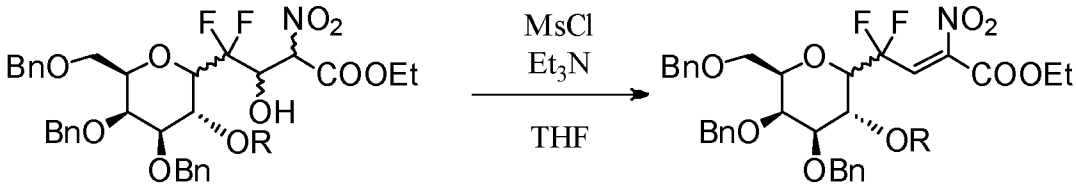
Mass (ESI$^+$): 753.00(M+H_2O); 758.13(M+Na)

Compound **3(b)α**: This compound (145 mg) was prepared from compound **2(b)α** (244 mg) following the same procedure as for compound**3β**.

3(b)α: $C_{35}H_{41}F_2NO_{11}$ M=689.70 g.mol^{-1}

Mass (ESI$^+$): 707.33(M+H_2O)

***Synthesis of compounds* 4(b)α *et* 4β**



3(b)α (R = MOM) **4(b)α** (R = MOM)

3β (R=Bn) **4β** (R=Bn)

Compound **4β**: To a chilled (0°C) solution of compound **3β** (1.19g) in THF (30 mL) was added mesyl chloride (377 µL; 4.87 mmol) and triethylamine (684 µL; 4.87 mmol). After stirring for 4 h, water was added (20 mL) and the mixture was extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography (cyclohexane/ethyl acetate 100/0 to 80/20) to give compound**4β** (0.50g; 0.70 mmol, yellow oil) as a diastereomeric mixture (50/50 ratio as measured by ^{19}F NMR).

4β: $C_{40}H_{41}F_2NO_9$ M=717.75 g.mol^{-1}

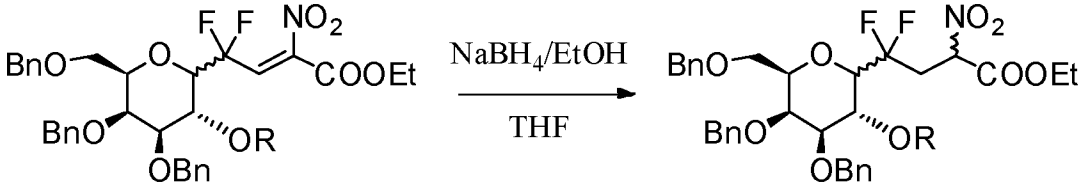
Mass (ESI$^+$): 735.33(M+H_2O); 740.33(M+Na)

Compound **4(b)α**: This compound (55 mg) was prepared from compound **3(b)α** (64 mg) following the same procedure as for compound **4β**.

4(b)α: $C_{35}H_{39}F_2NO_{10}$ M=671.68 g.mol^{-1}

Mass (ESI$^+$): 689.13(M+H_2O)

***Synthesis of compounds* 5(b)α and 5β**



4(b)α (R=MOM) **5(b)α** (R=MOM)

4β (R=Bn) **5β** (R=Bn)

Compound **5β**: To a chilled (0°C) solution of compound **4β** (3.90 g; 5.43 mmol) in THF (150 mL) and ethanol (150 mL) was added $NaBH_4$ (410 mg; 10.84 mmol; 2 eq.). The reaction mixture was quenched with HCl 2N and was extracted with Et_2O. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated. The residue was then purified by chromatography (cyclohexane/ethyl acetate 95/5 to 60/40) to give compound **5β** as a diastereomeric mixture (2.49 g; 3.46 mmol; yellow

oil) with a yield of 64 %. The two diastereomers were present in a 50/50 ratio as measured by ^{19}F NMR.

5β: $C_{40}H_{43}F_2NO_9$ M=719.77 g.mol^{-1}

Mass (ESI$^+$): 737.13(M+H_2O); 742.20(M+Na)

NMR ^{19}F ($CDCl_3$, 282.5 MHz) (with H coupled): -101.9/-103.7 (4 m, 2F); -107.1/-108.7 (4 m, 2F).

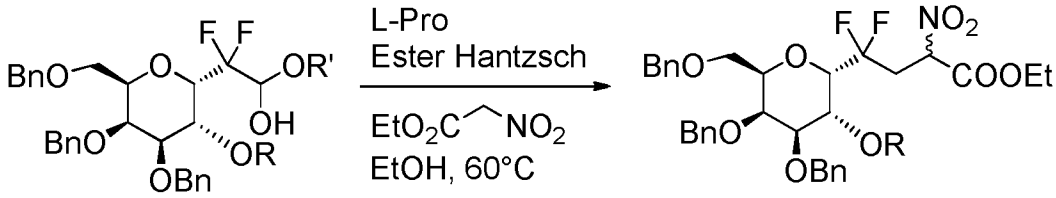
NMR ^{19}F ($CDCl_3$, 282.5 MHz) (without H coupled): -102.5 (d, J=258 Hz, 1F); -103.2 (d, J=258Hz, 1F); -107.7 (d, J=258Hz, 1F); -108.2 (d, J=258Hz, 1F).

Compound **5(b)α**: This compound (25 mg; 0.04 mmol; yellow oil) was prepared from compound **4(b)α** (53 mg) following the same procedure as for compound **5β**.

5(b)α: $C_{35}H_{41}F_2NO_{10}$ M=673.70 g.mol^{-1}

Mass (ESI$^+$): 691.13(M+H_2O)

Synthesis of compounds 5(a)α and 5(b)α



2(a)α (R=R'=Bn) **5(a)α** (R=Bn)

2(b)α (R=MOM, R'=iPr) **5(b)α** (R=MOM)

Compound **5(a)α**: To a mixture of compound **2a(α)** (0.100 g, 0.142 mmol, 1 eq), L-proline (L-Pro) (0.5 eq) and Hantzsch ester (1.3 eq) in ethanol (1 ml) was added ethyl nitroacetate (1.5 eq). The reaction mixture was stirred overnight at 60°C. Ether (15 ml) was added and the organic phase was washed with water (3x10 ml), dried over magnesium sulfate, filtered and evaporated. The residue was then purified by chromatography (cyclohexane/ethyle acetate 97/3 to 40/60) to give compound **5(a)α** (68.4 mg, n=0.095 mmol, yield 67%)

5(a)α : $C_{40}H_{43}F_2NO_9$ M= 719.77 g/mol

NMR ^{19}F ($CDCl_3$) 282,5MHz (with H coupled): -96.7/-98.5 (2F; 3m); -107.5/-108.7 (2F; 2m)

NMR^{19}F ($CDCl_3$) 282.5 MHz (without H coupled): -97.2 (1F; d; *J*=260Hz); -97.9 (1F; d; *J*=260Hz); -108.1 (1F; d; *J*=257Hz); -108.2 (1F; d; *J*=257Hz);

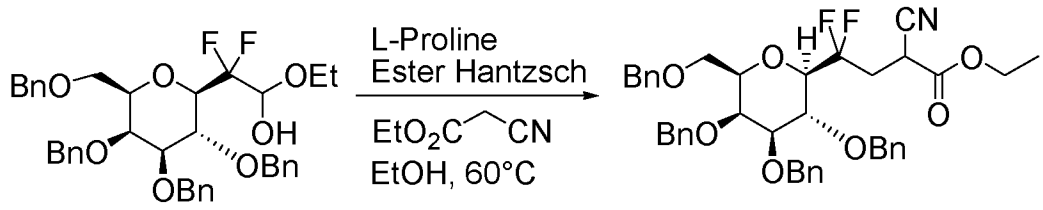
Mass (ESI$^+$): 742.20=$[M+Na]^+$

Compound **5(b)α**: This compound (3.55 g, 5.27 mmol, yield 47 %) was prepared from compound **2(b)α** (6.96 g, 11.29 mmol) following the same procedure as for compound **5(a)α**.

5(b)α: $C_{35}H_{41}F_2NO_{10}$ M=673.70g.mol^{-1}

Mass (ESI$^+$): 691.13($M+H_2O$)

Synthesis of compounds **5(c)β**



2β **5(c)β**

Compound **5(c)β**: This compound (yield=43 %) was prepared from compound **2β** (213 mg) and ethylcyanoacetate (52 µL, 0.49 mmol) following the same procedure as for compound **5(a)α**

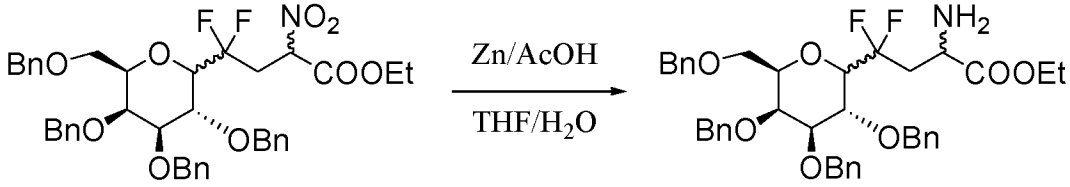
5(c)α: $C_{41}H_{43}F_2NO_7$ M=699.78 g.mol^{-1}

Mass (ESI$^+$): 700.29$[M+H]^+$; 722.27$[M+Na]^+$.

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -103.3 (d, J=256Hz, 1F, CF_2); -103.6 (d, J=256Hz, 1F, CF_2); -107.1 (d, J=256Hz, 1F, CF_2); -108.1 (d, J=256Hz, 1F, CF_2).

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -102.8/ -104.1 (4m, 2F, CF_2); -106.6/ -108.5 (3m, 2F, CF_2).

***Synthesis of compounds* <u>6β</u> *(*<u>6βd1+6 βd2</u>*),* <u>6(a)α and 6(b)α (6(b)αd1/6(b)αd2</u>



<u>5β</u> (R=Bn) <u>6β</u> (R=Bn)

<u>5(a)α</u> (R=Bn) <u>6(a)α</u> (R=Bn)

<u>5(b)α</u> (R=MOM) <u>6(b)α</u> (R=MOM)

<u>Compound 6β</u>: To a solution of compound <u>5β</u> (1.53 g; 2.13 mmol) in THF (7 mL), water (10 mL) and acetic acid (10 mL), was added Zn dust (2.9 g; 44 mmol; 20 eq.). The resultant mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through Celite and concentrated. A solution of NH_4OH was added to adjust the pH of the aqueous layer to pH8, and the resultant aqueous layer was then extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90/10 to 20/80) to give compounds <u>6β</u> (6βd1/6βd2 (50/50)) (0.91 g; 1.32 mmol, yellow oil) 62 % yield. Each diastereomer (6βd1 and 6βd2) was obtained separately.

<u>6βd1+6 βd2</u>: $C_{40}H_{45}F_2NO_7$ M=689.78 g.mol^{-1}

Mass (ESI^+): 690.53(M+H)

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

<u>6βd1</u>: -103.2/-104.2 (2m, 1F); -104.2/ -105.2 (2m, 1F).

<u>6βd2</u>: -102.6/ -103.7 (2m, 1F); -105.0/ -106.0 (2m, 1F).

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled):

<u>6βd1</u>: -103.8 (d, J=256Hz, 1F); -104.7 (d, J=256Hz, 1F).

<u>6βd2</u>: -103.1 (d, J=255Hz, 1F); -105.5 (d, J=255Hz, 1F).

<u>Compound 6(a)α</u>: This compound (m= 44.9 mg, n=0.065 mmol, yield= 47 %) was prepared from compound <u>5(a)α</u> (100 mg, 0.139 mmol, 1 eq) following the same procedure as for compound <u>6β</u>.

<u>6(a)α</u>: $C_{40}H_{45}F_2NO_7$ M= 689.78 g/mol

Mass (ESI^+): 690.33=$[M+H]^+$

<u>Compound 6(b)α</u>: This compound was obtained as a mixture of diastereomer in a proportion 50/50 from compound <u>5(b)α</u> (3.55 g, 5.27 mmol, 1 eq) following the same

procedure as for **6β**. Each diastereomer has been isolated **6(b)αd1** (m = 1.03 g, n = 1.60 mmol, yield = 30 %) and **6(b)αd2** (m = 1.06 mg, n = 1.60 mmol, yield = 31 %).

6(b)αd1/ 6(b)αd2: $C_{35}H_{43}F_2NO_8$ M= 643.71 g/mol

6(b)α d1

Mass (ESI^+): 644.5 $[M+H]^+$, 666.5 $[M+Na]^+$

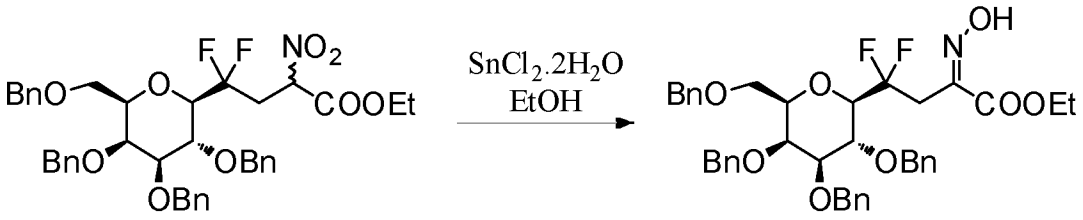
NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -101.1 (1F; d; *J*=258Hz); -106.2 (1F; d; *J*=258Hz)

6(b)α d2

Mass (ESI^+): 644.5 $[M+H]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -99.4 (1F; d; *J*=256Hz); -106.1 (1F; d; *J*=256Hz)

Synthesis of compound 7β



5β **7β**

To a solution of compound **5β** (54 mg; 0.075 mmol) in ethanol, $SnCl_2.2H_2O$ (170 mg; 0.75 mmol; 10 eq.) was added. The mixture was then stirred for 24 h and concentrated. The residue was then diluted in ethyl acetate and a solution of KOH (2M) was added. The aqueous layer was further extracted with portions of ethyl acetate and the combined organic phase was washed with brine and water, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by chromatography (cyclohexane/ethyl acetate 90/10 to 40/60) to give compounds **7β** in 56 % yield.

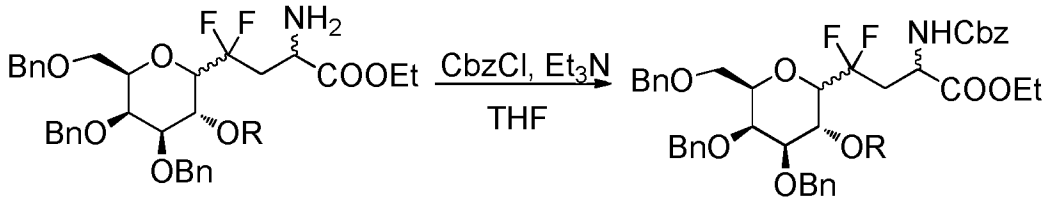
7β: $C_{40}H_{43}F_2NO_8$ M=703.77g.mol^{-1}

Mass (ESI^+): 721.47($M+H_2O$); 726.46(M+Na)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -100.0/ -101.0 (2m, 1F); -103.8 /-104.6 (2m, 1F).

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -100.5 (d, J=253Hz, 1F); -104.2 (d, J=253Hz, 1F).

***Synthesis of compounds* 8β (8βd1/8βd2), 8(a)α and 8(b)α (8(b)αd1/8(b)αd2)**



6βd1/6βd2 (R=Bn) **8βd1/8βd2**(R=Bn)

6(a)α (R=Bn) **8(a)α** (R=Bn)

6(b)αd1/6(b)αd2 (R=MOM) **8(b)αd1/8(b)αd2** (R=MOM)

Compound **8β**: To a chilled (0°C) solution of compound **6βd1** (810 mg; 1.18 mmol) in THF (15 mL) was added benzyl chloroformate (420 µL; 2.95 mmol; 2.5 eq.) and triethylamine (247 µL; 1.77 mmol; 1.5 eq.). The resultant mixture was stirred for 12 h and thenextracted with ethyl acetate, washed with a saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by chromatography (cyclohexane/ethyl acetate 90/10 to 40/60) to give compound **8βd1** (792 mg; 0.96 mmol) as a yellowish solid 81 % yield.

Compound **8βd2** (773 mg; 0.94 mmol) in the form of yellow oil, was prepared following the same procedure but starting from compound **6βd2** (718 mg; 1.04 mmol).

8βd1+8 βd2: $C_{48}H_{51}F_2NO_9$ M=823.92g.mol^{-1}

Mass (ESI^+):824.27(M+H); 841.47(M+H_2O); 846.47(M+Na)

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

8βd1: -102.0/ -103.0 (2m, 1F); -103.5/ -104.6 (2m, 1F).

8βd2: -101.0/ -102.1 (2m, 1F); -104.0/ -105.1 (2m, 1F).

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled):

8βd1: -102.5 (d, J=257Hz, 1F); -104.1 (d, J=257Hz, 1F).

8βd2: -101.5 (d, J=258Hz, 1F); -104.6 (d, J=258Hz, 1F).

Compound **8(a)α**: This compound (m= 27 mg, n = 0.033 mmol, yield = 52 %) was prepared from compound **6(a)α** (44 mg, 0.064 mmol, 1 eq) following the same procedure as for compound **8β**.

8(a)α: $C_{48}H_{51}F_2NO_9$ M=823.92g.mol^{-1}

Masse (ESI^+): 846.3 (M+Na); 862.3 (M+K)

Compound **8(b)α**: The compound **8(b)αd1** (m = 847 mg, n = 1.09 mmol, yield = 100 %) was prepared from compound **6(b)αd1** (700 mg, 1.09 mmol, 1 eq) following the same procedure as for compound **8β**.

The compound **8(b)αd2** (m = 847 mg, n = 1.09 mmol, yield = 100 %) was prepared from compound **6(b)αd2** (700 mg, 1.09 mmol, 1 eq) following the same procedure as for compound **8β**.

8(b)αd1/8(b)αd2: $C_{43}H_{49}F_2NO_{10}$ M=777.85 g.mol^{-1}

8(b)αd1

Mass (ESI$^+$): 778.4 $[M+H]^+$; 795.4 $[M+H_2O]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -100.5/-101.8 (1F; 2m); -104.9/-106.2 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -101.1 (1F; d; *J*=258Hz); -105.6 (1F; d; *J*=258Hz)

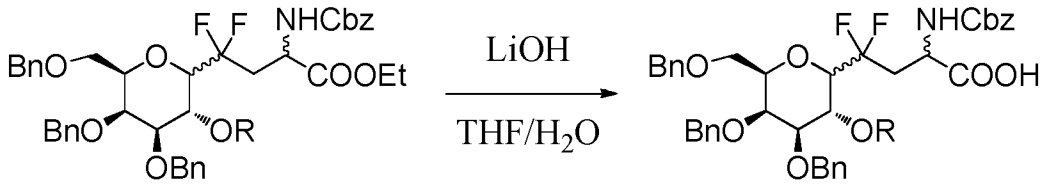
8(b)αd2

Mass (ESI$^+$): 778.3 $[M+H]^+$, 795.4 $[M+H_2O]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -98.0/-99.2 (1F; 2m); -106.2/-107.6 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -98.5 (1F; d; *J*=259Hz); -106.9 (1F; d; *J*=259Hz)

***Synthesis of compounds* 9β (9βd1/9βd2) and 9(b)α (9(b)αd1/9(b)αd2)**



8βd1/8βd2 (R=Bn) **9βd1/9βd2** (R=Bn)

8(b)αd1/8(b)αd2 (R=MOM) **9(b)αd1/9(b)αd2** (R=MOM)

Compound **9β**: To a solution of compound **8βd1** (800 mg; 0.97 mmol) in THF (30 mL) and water (1.7 mL) was added LiOH (70 mg; 2.91 mmol). The solution was stirred for 12 hours then quenched with 1N HCl aqueous solution. The reaction mixture was then extracted with dichloromethane,dried over sulfate magnesium, filtered and evaporated to give compound **9βd1** (680 mg; 0.86 mmol, yellow oil) in89 % yield.

Compound **9βd2** (703 mg; 0.88 mmol) was prepared in 97 % yield from compound **8βd2** (750 mg; 0.91 mmol) following the same procedure as for compound **9βd1**.

9βd1/9 βd2: $C_{46}H_{47}F_2NO_9$ M=795.86 g.mol^{-1}

Mass (ESI$^+$): 796.04(M+H); 818.39(M+Na)

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

9βd1: -98.3/ -99.3 (2m, 1F); -100.4/ -101.4 (2m, 1F).

9βd2: -100.0/ -101.3 (2m, 1F); -103.4/ -104.7 (2m, 1F).

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled):

9βd1: -98.8 (d, J=262Hz, 1F); -100.9 (d, J=262Hz, 1F).

9βd2: -100.8 (d, J=259Hz, 1F); -104.0 (d, J=259Hz, 1F).

Compound **9(b)α**: The compound **9(b)αd1** (m = 818 mg, n =1.09 mmol, yield= 100 %) was prepared from compound **8(b)αd1** (847 mg, 1.09 mmol, 1 eq) following the same procedure as for compound **9βd1**.

The compound **9(b)αd2** (m = 818 mg, n = 1.09 mmol, yield= 100 %) was prepared from compound **8(b)αd2** (847 mg, 1.09 mmol, 1 eq) following the same procedure as for compound**9βd1**.

9(b)αd1/9(b)αd2: $C_{41}H_{45}F_2NO_{10}$ M=749.79g.mol^{-1}

9(b)αd1

Mass (ESI$^+$): 750.3 $[M+H]^+$, 767.3 $[M+H_2O]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -99.9/-101.1 (1F; 2m); -103.6/-105.0 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -100.4 (1F; d; *J*=258Hz); -104.2 (1F; d; *J*=258Hz)

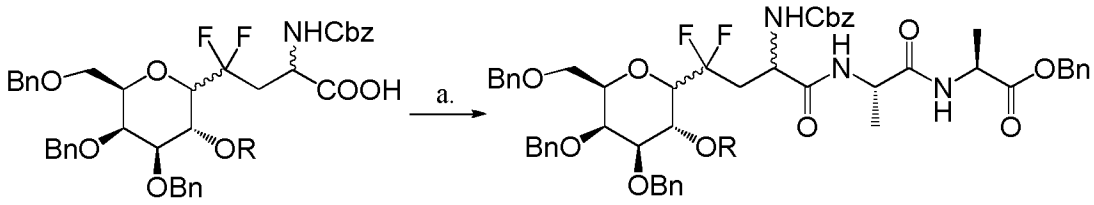
9(b)αd2

Mass (ESI$^+$): 750.3 $[M+H]^+$, 767.3 $[M+H_2O]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -96.5/-97.7 (1F; 2 m); -105.6/-107.0 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.1 (1F; d; *J*=261Hz); -106.3 (1F; d; *J*=261Hz)

Synthesis of compounds 10β (10βd1/10βd2) and 10(b)α (10(b)αd1/10(b)αd2)



a. CF_3CO_2-$^+H_3$N-Ala-Ala-OBn; PyBOP/NMM; DMF

9βd1/9βd2 (R=Bn) **10βd1/10βd2** (R=Bn)

9(b)αd1/9(b)αd2 (R=MOM) **10(b)αd1/10(b)αd2** (R=MOM)

Compound **10β**: To a solution of compound **9βd1** (672 mg; 0.85 mmol) in DMF (9 mL) was added CF_3COO^- $^+H_3$NAlaAlaOBn (340 mg; 1.10 mmol), PyBOP (953 mg; 1.83 mmol) and N-methylmorpholine (284 µL; 2.58 mmol). The reaction mixture was stirred for 48 h. Brine was then added and the reaction mixture was extracted with ethyl acetate. The combined organic phase was washed with an aqueous acid citric (10 %) solution, water and aqueous $NaHCO_3$ (5 %) solution. The organic layer was then dried over magnesium sulfate, filtered and evaporated. The crude residue was purified by chromatography (cyclohexane/ethyl acetate 90/10 to 40/60) to give compound **10βd1** (630 mg; 0.61 mmol), in 72 % yield as a yellowish oil.

Compound **10βd2** (594 mg; 0.58 mmol) was prepared from compound **9βd2** (686 mg; 0.86 mmol) in 67 % yield as a white solid, following the same procedure as for compound **10βd1**.

10βd1/10βd2: $C_{59}H_{63}F_2N_3O_{11}$ M=1028.14g.mol^{-1}

Mass (ESI^+):1028.19(M+H); 1050.44(M+Na)

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

10βd1: -101.4/ -102.3 (2m, 1F); -102.4/ -103.5 (2m, 1F).

10βd2: -98.5/ -99.5 (2m, 1F); -102.9/ -104.0 (2m, 1F).

NMR^{19}F ($CDCl_3$, 282.5MHz) (without H coupled):

10βd1: -102.0 (d, J=258Hz, 1F); -103.0 (d, J=258Hz, 1F).

9βd2: -99.0 (d, J=258Hz, 1F); -103.4 (d, J=258Hz, 1F).

Compound **10(b)α**: The compound **10(b)αd1** (m = 910 mg, n = 0.93 mmol, yield = 85 %) was prepared from compound **9(b)αd1** (818 mg, 1.09 mmol, 1 eq) following the same procedure as for compound **10βd1**.

The compound **10(b)αd2** (m= 845 mg, n= 0.86 mmol, yield= 79 %) was prepared from compound **9(b)αd2** (818 mg, 1.09 mmol, 1 eq) following the same procedure as for compound **10βd1**.

10(b)αd1/10(b)αd2: $C_{54}H_{61}F_2N_3O_{12}$ M=982.07g.mol^{-1}

10(b)αd1

Mass (ESI$^+$): 982.4 $[M+H]^+$, 999.5 $[M+H_2O]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.9/-99.2 (1F; 2m); -103.4/-104.6 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -98.6 (1F; d; *J*=261Hz); -104.0 (1F; d; *J*=261Hz)

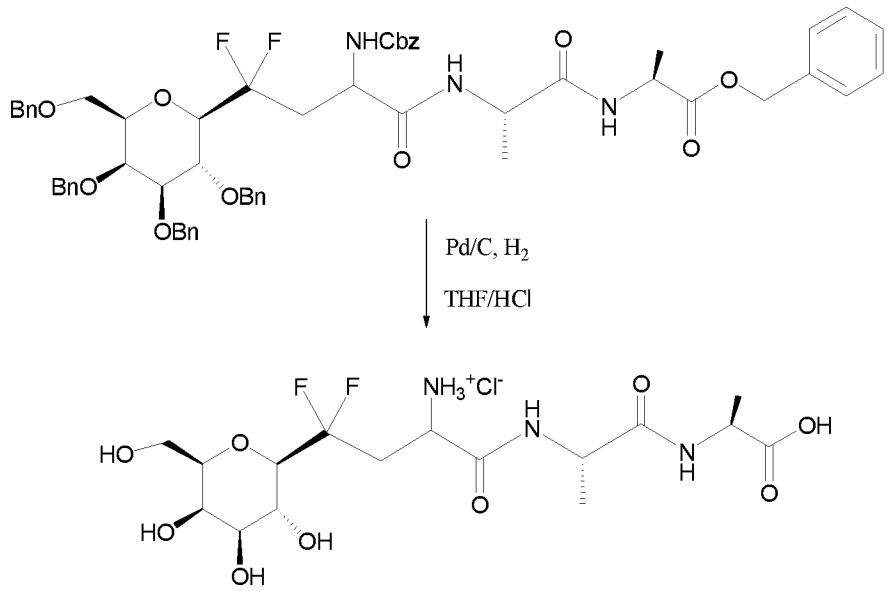
10(b)αd2

Mass (ESI$^+$): 982.4 $[M+H]^+$, 999.5 $[M+H_2O]^+$, 1004.4 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.5/-98.8 (1F; 2m); -104.4/-105.6 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -98.1 (1F; d; *J*=260Hz); -105.0 (1F; d; *J*=260Hz)

Synthesis of compounds 11β (11βd1/11βd2)



Compound **10βd1** (395 mg; 0.38 mmol) dissolved in a mixture of THF (12 mL) and HCl 1N (1,4 mL) and in the presence of Pd/C 10 % was placed under a hydrogen

atmosphere. The mixture was stirred for 48 h, then Millipore-filtered and evaporated to give compound **11βd1** (182 mg, 0.38 mmol, yield 100 %) quantitatively as a white solid.

Compound **11βd2** (187 mg, 0.39 mmol, yield 100 %) was prepared as a white solid in quantitative yield from compound **10βd2** (399 mg; 0.39 mmol) following the same procedure as forcompound **11βd1**.

11βd1/11βd2: $C_{16}H_{28}ClF_2N_3O_9$ M=479.86g.mol^{-1}

Mass (ESI$^-$): 442.1(M-HCl)

NMR ^{19}F (D_2O, 282.5MHz) (with H coupled):

11βd1: -102.2/ -103.3 (m, 1F); -108.4/ -109.5 (m, 1F).

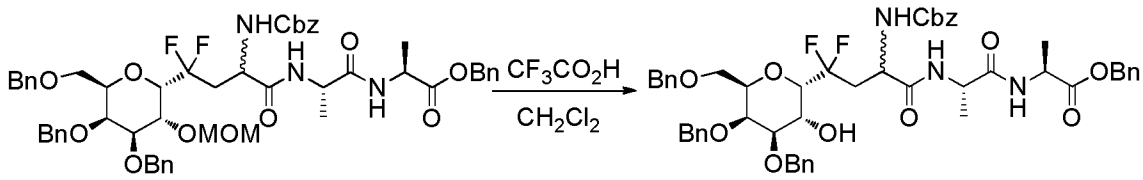
11βd2: -102.8/ -103.7 (m, 1F); -107.4/ -108.4 (m, 1F).

NMR ^{19}F (D_2O, 282.5MHz) (without H coupled):

11βd1: -102.7 (d, J=258Hz, 1F); -108.9 (d, J=258Hz, 1F)

11βd2: -103.3 (d, J=257Hz, 1F); -107.9 (d, J=257Hz, 1F).

Synthesis of compounds **12(b)α (12(b)αd1/12(b)αd2)**



Compound **12(b)α**: Trifluoroacetic acid (3.4 mL, 45.6 mmol) was added dropwise to a solution of compound **10(b)αd1** (675 mg, 0.687 mmol, 1 eq) in dichloromethane (3.4 mL) under inert atmosphere. The reaction mixture was stirred for 3 h and was then poured into a $NaHCO_3$ saturated aqueous solution. The obtained solution was extracted two times with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification of the crude residue by flash column chromatography (cyclohexane/AcOEt 65/35 to 25/75) afford.compound **12(b)αd1** (m = 385 mg, n = 0.41 mmol, yield = 60 %) as a white solid.

The compound **12(b)αd2** (m = 368 mg, n = 0.39 mmol, yield = 60 %) was prepared from compound **10(b)αd2** (642 mg, 0.654 mmol, 1 eq) following the same procedure as for compound **12(b)αd1**.

12(b)αd1/12(b)αd2: $C_{52}H_{57}F_2N_3O_{11}$ M=938.02g.mol^{-1}

12(b)αd1

Mass (ESI$^+$): 938.4 $[M+H]^+$, 955.4 $[M+H_2O]^+$, 960.4 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.3/-98.6 (1F; 2m); -101.6/-102.7 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.9 (1F; d; *J*=262Hz); -102.1 (1F; d; *J*=262Hz

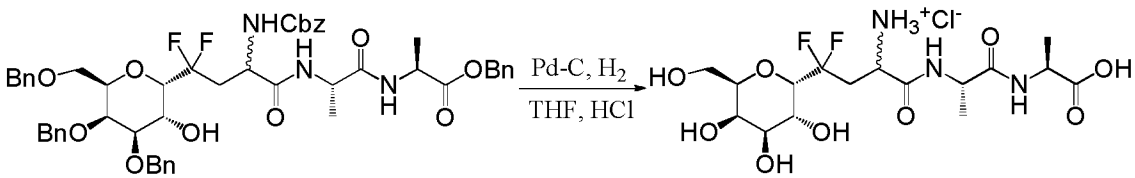
12(b)αd2

Mass (ESI$^+$): 938.4 $[M+H]^+$ 955.4 $[M+H_2O]^+$, 960.4 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): 97.3/-98.5 (1F; 2m); -103.6/-104.7 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.9 (1F; d; *J*=259Hz); -104.1 (1F; d; *J*=259Hz)

Synthesis of compounds **13(b)α (13(b)αd1/13(b)αd2)**



Compound **13(b)α**: Compound **12(b)αd1** (395 mg, 0.42 mmol, 1 eq) dissolved in a mixture of THF (13.2 mL) and HCl 1N (1.5 mL) and in the presence of Pd/C 10 % (112 mg, 0.25 eq) was placed under a hydrogen atmosphere. The mixture was stirred for 24 h, then Millipore-filtered and evaporated to give compound **13(b)αd1** (m = 197 mg, n = 0.41 mmol, yield = 97 %)

The compound **13(b)αd2** (m = 172 mg, n = 0.36 mmol, yield = 100 %) was prepared from compound **12(b)αd2** (338 mg, 0.36 mmol, 1 eq) following the same procedure as for compound**13(b)αd1**.

13(b)αd1/13(b)αd2: $C_{16}H_{28}ClF_2N_3O_9$ M=479.86 g.mol$^-$

13(b)αd1

Mass (ESI$^+$): 444.2 $[M-HCl+H]^+$, 466.2 $[M-HCl+Na]^+$, 482.1 $[M-HCl+K]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.2/-98.4 (1F; 2m); -101.8/-103.0 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.8 (1F; d; *J*=256Hz); -102.4 (1F; d; *J*=256Hz)

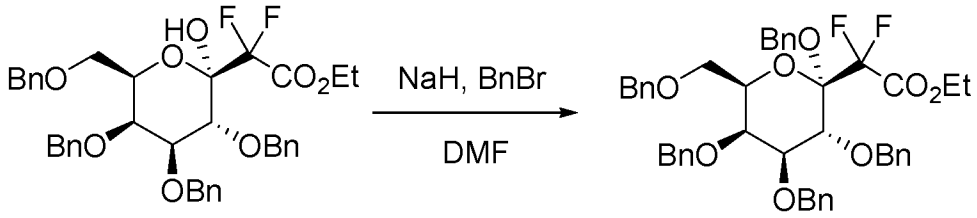
13(b)αd2

Mass (ESI^+): 444.2 $[M\text{-}HCl+H]^+$, 466.2 $[M\text{-}HCl+Na]^+$, 482.1 $[M\text{-}HCl+K]$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.7/-98.8 (1F; 2m); -100.5/-101.8 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -98.2 (1F; d; *J*=257Hz); -101.0 (1F; d; *J*=257Hz)

***Synthesis of compounds* 15**



14 **15**

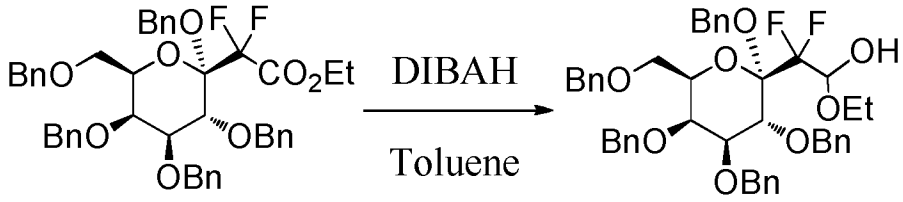
Compound **15**: Compound **14** (3g, 4.50 mmol, 1 eq) obtained from a process described in *Synlett 2005, 17, 2627-2630* – see also WO 2004/014928, WO 2007/125203 and WO 2007/125194 was dissolved in anhydrous DMF (45 mL). The solution was cooled to 0°C and sodium hydride (129 mg, 5.40 mmol, 1.2 eq) was added portion wise. After 45 min. stirring at 0°C, benzyl bromide (1.1 mL, 9 mmol, 2 eq.) was added drop wise. The reaction mixture was warmed to room temperature and stirred 5 h 30. A saturated aqueous solution of ammonium chloride was added and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water, then with brine before being dried and evaporated. Purification by chromatography (cyclohexane/ethyl acetate 98/2 to 75/25) afford compound **15** (m = 2.61 mg, n = 3.47 mmol, yield = 77 %).

15: $C_{45}H_{46}F_2O_8$ $M=752.84 g.mol^{-1}$

Mass (ESI^+): 775.4 $[M+Na]^+$, 791.3 $[M+K]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -111.4 (1F; d; *J*=265Hz); -116.1 (1F; d; *J*=265Hz) ; -112.0 (1F; d; *J*=263Hz); -115.3 (1F; dd; *J*=265Hz ; *J*=3Hz

***Synthesis of compounds* 16**



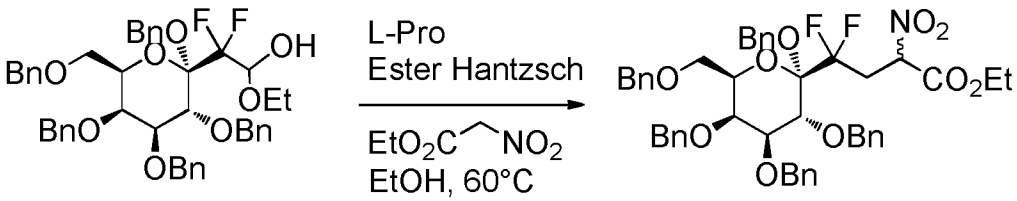
15 **16**

To a cooled (-78°C) solution of Compound **15** (1.34 g, 1.78 mmol, 1 eq) in anhydrous toluene (18 mL) was added a solution of diisobutylaluminium hydride (1.2M in toluene; 2.15 mL; 2.58 mmol; 1.45 eq.) and the resultant mixture was stirred for 5 h at this temperature. The reaction was then quenched with methanol (4 mL) and the solution was warmed to -20°C for 10 min. A Rochelle's salt solution (20 %) was then added and the solution was vigorously stirred for 1 h. The reaction medium was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to give compound **16** (m = 1.3 g, yellow oil). Compound **16** was used in the next step without further purification.

16: $C_{45}H_{48}F_2O_8$ M=754.85g.mol^{-1}

Mass (ESI$^+$): 777.4 $[M+Na]^+$, 793.3 $[M+K]^+$

***Synthesis of compounds* 17d1/17d2**



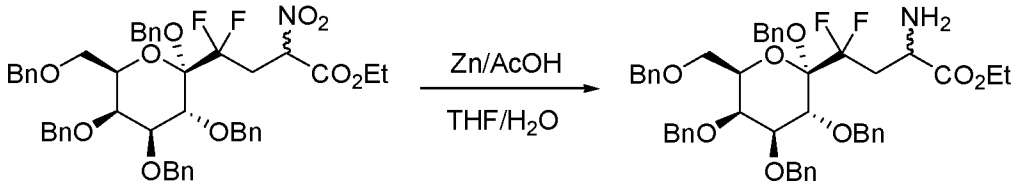
16 **17d1/17d2**

Compound **17**: To a mixture of compound **16** (1.56 g, 2.07 mmol, 1 eq), L-proline (L-Pro) (119 mg, 1.04 mmol, 0.5 eq) and Hantzsch ester (70 mg, 2.69 mmol, 1.3 eq) in ethanol (20 ml) was added ethyl nitroacetate (0.3 mL, 3.11 mmol, 1.5 eq). The reaction mixture was stirred 20 hours at 60°C. Ether was added and the organic phase was washed three times with water, dried over sodium sulfate, filtered and evaporated. The residue was then purified by chromatography (cyclohexane/ethyle acetate 80/20) to give compound **17** **(17d1/17d2 60/40)** (m = 1.3 g, 1.57 mmol, yield = 75 %, yellow solid) as a mixture of diastereomer.

17d1/17d2: $C_{47}H_{49}F_2NO_{10}$ M=825.89g.mol^{-1}

Mass (ESI$^+$): 843.4 $[M+H_2O]^+$, 848.3 $[M+Na]^+$, 864.3 $[M+K]^+$

Synthesis of compounds **18d1/18d2**



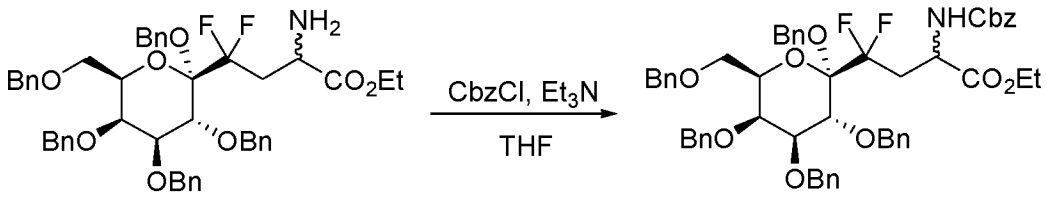
17d1/17d2 **18d1/18d2**

Compound **18**: To a solution of compound **17d1/17d2** **(17d1/17d2 60/40)** (1.23 g, 1.55 mmol, 1 eq) in THF (4.9 mL), water (7.3 mL) and acetic acid (7.3 mL), was added Zn dust (2.1 g; 32.5 mmol; 21 eq.). The resultant mixture was stirred at room temperature for 5 hours. The reaction mixture was filtered through Celite and concentrated. A solution of $NaHCO_3$ was added to adjust the pH of the aqueous layer to pH8, and the resultant aqueous layer was then extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by chromatography on silica gel (cyclohexane/ethyl acetate 80/20) to give compound **18** **(18d1/18d2 60/40)** (m = 780 mg, n = 0.98 mmol, yield = 63 %).

18d1/18d2: $C_{47}H_{51}F_2NO_8$ M=795.91g.mol^{-1}

Mass (ESI$^+$): 796.4 $[M+H]^+$, 818.4 $[M+Na]^+$, 834.4 $[M+K]^+$

Synthesis of compounds **19d1/19d2**



18d1/18d2 **19d1/19d2**

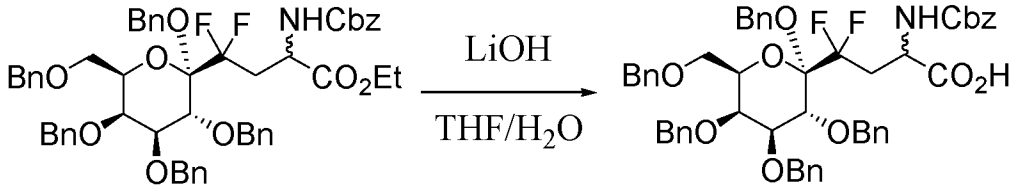
Compound **19**: To a chilled (0°C) solution of compound **18** **(18d1/18d2 60/40)** (658 mg, 0.827 mmol, 1 eq) in THF (8 mL) was added benzyl chloroformate (300 µL; 2.07 mmol; 2.5 eq.) and triethylamine (290 µL; 2.07 mmol; 2.5 eq.). The resultant mixture was stirred for 24 h and then extracted with ethyl acetate, washed with a saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered and evaporated. The crude

residue was purified by chromatography (cyclohexane/ethyl acetate 2/98 to 80/20) to give compound **19** (**19d1/19d2 60/40**) (m = 592 mg, n = 0.637 mmol, yield = 77 %).

19d1/19d2: $C_{55}H_{57}F_2NO_{10}$ M=930.04g.mol^{-1}

Mass (ESI$^+$): 947.44 $[M+NH_4]^+$, 953 $[M+Na]^+$, 968.37 $[M+K]^+$

Synthesis of compounds **20d1/20d2**



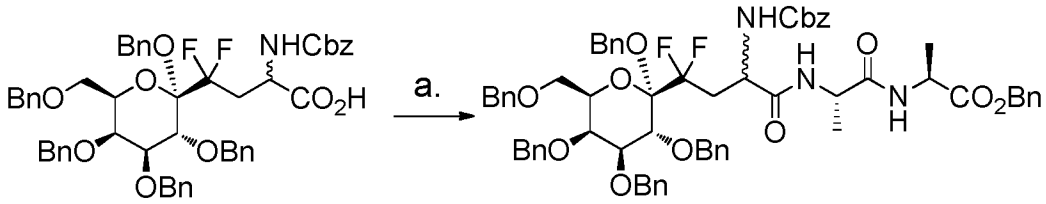
19d1/19d2 **20d1/20d2**

Compound **20**: To a solution of compound **19** (**19d1/19d2** 60/40) (575 mg, 0.618 mmol, 1 eq) in THF (6 mL) was added LiOH 2N solution (0.93 mL; 1.85 mmol, 3 eq.). The solution was stirred for 12 hours then quenched with 1N HCl aqueous solution. The reaction mixture was then extracted with ethyl acetate, dried over sodium sulfate, filtered and evaporated to give compound **20** (**20d1/20d2** 55/45) as a white solid (m = 526 mg, n =0.583 mmol, yield = 94 %).

20d1/20d2: $C_{53}H_{53}F_2NO_{10}$ M=901.99g.mol^{-1}

Mass (ESI$^+$): 919.4 $[M+H_2O]^+$, 924.4 $[M+Na]^+$, 940.3 $[M+K]^+$

Synthesis of compounds **21d1/21d2**



a. CF_3CO_2-$^+{}_3$HN-Ala-Ala-OBn; PyBOP/NMM; DMF

20d1/20d2 **21d1/21d2**

Compound **21**: To a solution of compound **20** (**20d1/20d2** 55/45) (432 mg, 0.477 mmol, 1 eq) in DMF (4.6 mL) was added CF_3COO^- $^+H_3$NAlaAlaOBn (223 mg; 0.612 mmol, 1.3 eq.), PyBOP (510 mg; 1 mmol, 2.1 eq.) and N-methylmorpholine (160 µL; 1.43 mmol, 3eq.). The reaction mixture was stirred for 18 h. Brine was then added and the reaction mixture was extracted with ethyl acetate. The combined organic phase was

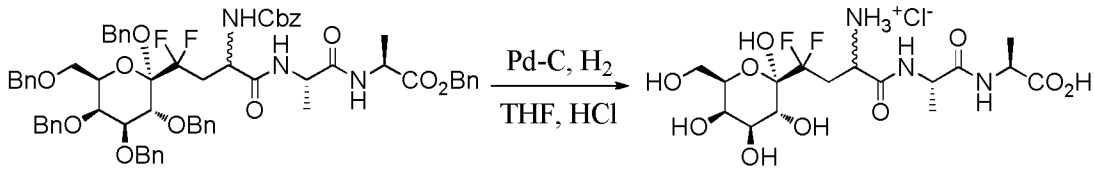
washed with an aqueous acid citric (10 %) solution, water and aqueous $NaHCO_3$ (5 %) solution. The organic layer was then dried over sodium sulfate, filtered and evaporated. The crude residue was purified by chromatography (cyclohexane/ethyl acetate 4/96 to 60/40) to give compound **21** (**21d1/21d2** 55/45) as a colourless oil (m= 453mg, n=0.4mmol, yield= 84%).

21d1/21d2: $C_{66}H_{69}F_2N_3O_{12}$ M=1134.26g.mol^{-1}

Mass (ESI$^+$): 1134.5 $[M+H]^+$, 1151.5 $[M+H_2O]^+$, 1156.5 $[M+Na]^+$, 1172.5 $[M+K]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -102.9 (1F ; d ; *J*=259Hz) ; -103.2 (1F ; d ; *J*=259Hz), -104.6 (1F ; d ; *J*=259Hz) ; -104.8 (1F ; d ; *J*=259Hz)

***Synthesis of compounds* 22d1/22d2**



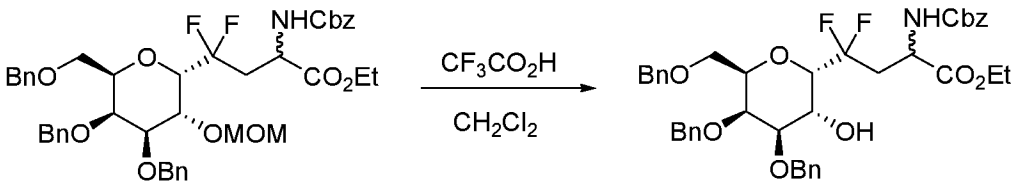
21d1/21d2 **22d1/22d2**

Compound **22**: Compound **21** (**21d1/21d2** 55/45) (51 mg; 0.045 mmol) dissolved in a mixture of THF and HCl 1N (590 µL) and in the presence of Pd/C 10 % was placed under a hydrogen atmosphere. The mixture was stirred for 48h, then Millipore-filtered and evaporated to give compound **22** (m = 22 mg, n = 0.044 mmol, yield = 99 %).

22d1/22d2: $C_{16}H_{28}ClF_2N_3O_{10}$ M=495.86g.mol^{-1}

Mass (ESI$^+$): 459.2$[M\text{-}HCl+H]^+$, 477.2 $[M\text{-}HCl+H_2O]^+$

***Synthesis of compounds* 23d1/23d2**



22d1/22d2 **23d1/23d2**

Compound **23d1** (174 mg, 0.24 mmol, yield 52 %) was prepared from compound **8(b)αd1** (m = 355 mg, n = 0.46 mmol) following the same procedure as for compound **12(b)α**.

Compound **23d2** (228 mg, 0.31 mmol, yield 60 %) was prepared from compound **8(b)αd2** (m = 402 mg, n = 0.52 mmol) following the same procedure as for compound **12(b)α**.

23d1/23d2: $C_{41}H_{45}F_2NO_9$ M=733.79g.mol^{-1}

23d1

Masse (ESI$^+$): 756.4 $[M+Na]^+$, 772.4 $[M+K]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -102.3/-103.5 (1F; 2m); -103.5/-104.7 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -102.9 (1F; d; *J*=259Hz); -104.2 (1F; d; *J*=259Hz)

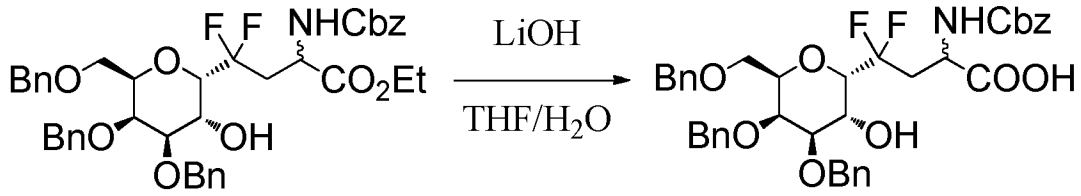
23d2

Mass (ESI$^+$): 756.4 $[M+Na]^+$, 772.4 $[M+K]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -99.3/-100.6 (1F; 2m); -104.9/-106.2 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -99.9 (1F; d; *J*=254Hz); -105.5 (1F; d; *J*=254Hz)

***Synthesis of compounds* 24d1/24d2**



23d1/23d2 **24d1/24d2**

Compound **24d1** (77 mg, 0.11 mmol, yield 100 %) was prepared from compound **23d1** (m = 80 mg, n = 0.11 mmol) following the same procedure as for compound **9(b)αd1**.

Compound **24d2** (77 mg, 0.11 mmol, yield 100 %) was prepared from compound **23d1** (m = 80 mg, n = 0.11 mmol) following the same procedure as for compound **9(b)αd1**.

24d1/24d2: $C_{39}H_{41}F_2NO_9$ M=705.74g.mol^{-1}

24d1

Masse (ESI$^+$): 706.3 $[M+H]^+$, 723.3 $[M+H_2O]^+$, 728.3 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -100.8/-101.9 (1F; 2m); -102.2/-103.4 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -101.3 (1F; d; *J*=262Hz); -102.9 (1F; d; *J*=262Hz)

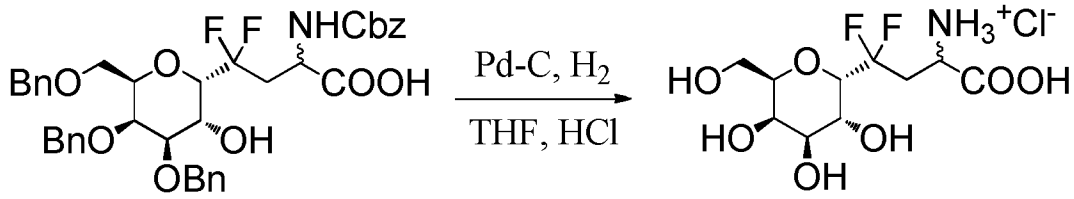
24d2

Mass (ESI^+): 706.3 $[M+H]^+$, 723.3 $[M+H_2O]^+$, 728.3 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -98.2/-99.3 (1F; 2m); -104.4/-105.7 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -98.7 (1F; d; *J*=260Hz); -105.0 (1F ; d ; *J*=260Hz)

***Synthesis of compounds* 25d1/25d2**



24d1/24d2 **25d1/25d2**

Compound **25d1** (35 mg, 0.11 mmol, yield 100 %) was prepared from compound **24d1** (m = 74 mg, n = 0.11 mmol) following the same procedure as for compound **13(b)α**.

Compound **25d2** (32 mg, 0.09 mmol, yield 93 %) was prepared from compound **24d1** (m = 72 mg, n = 0.10 mmol) following the same procedure as for compound **13(b)α**.

25d1/25d2: $C_{10}H_{18}ClF_2NO_7$ M=337.70g.mol^{-1}

25d1

Masse (ESI^+): 302.1 $[M-HCl+H]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -97.2/-98.3 (1F; 2m); -101.9/-103.0 (1F; 2m)

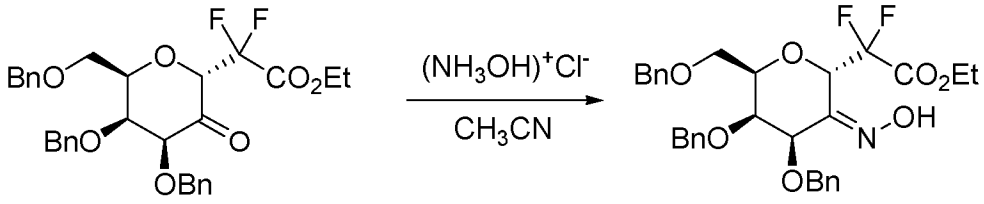
NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.7 (1F; d; *J*=256Hz); -102.4 (1F; d; *J*=256Hz)

25d2

Mass (ESI^+): 302.1 $[M-HCl+H]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -97.9 (1F; d; *J*=257Hz); -100.9 (1F; d; *J*=257Hz)

***Synthesis of compounds* 27**



26 **27**

Compound **26** (24.2 g, 43.6 mmol, 1 eq) obtained from a process described in *Org. Lett. 2007, 9, 2477-2480* was dissolved in acetonitrile (58 mL) and the obtained solution was added to a solution of hydroxylamine hydrochloride (5.46 g, 78.5 mmol, 1.8 eq) and sodium acetate (7.15 g, 87.2 mmol, 2 eq) in water (58 mL). The reaction mixture was stirred at room temperature overnight before being evaporated and purified by chromatography (cyclohexane/ethyl acetate 100/0 to 70/30) to give compound **27** (m = 11.59 g, n = 20.3 mmol, yield = 47 %) as a yellow oil.

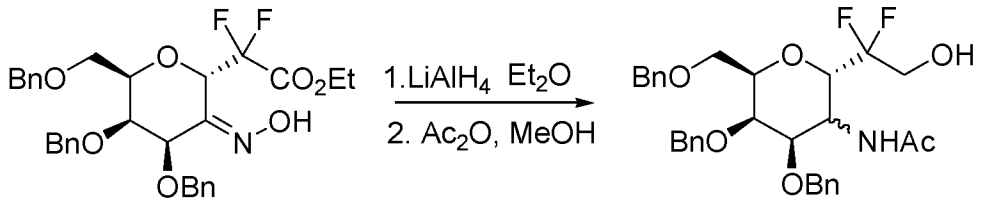
27: $C_{31}H_{33}F_2NO_7$ M=569.59g.mol^{-1}

Mass (ESI$^+$): 570.2 $[M+H]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -109.5 (1F; dd; *J*=255Hz; *J*=9Hz); -113.1 (1F; dd; *J*=255Hz; *J*=23Hz)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -109.5 (1F; d; *J*=255Hz); -113.1 (1F; d; *J*=255Hz)

***Synthesis of compounds* 28G/28T**



27 **28G/28T**

A solution of compound **27** (5.5 g, 9.66 mmol, 1 eq) in diethyl ether (250 mL) was added drop wise to a suspension of lithium aluminium hydride (3.67 g, 96.6 mmol, 10 eq) in diethyl ether (150 mL) under inert atmosphere. The suspension was stirred for 10min at room temperature and then refluxed overnight before being cooled to 0°C. A Rochelle's salt aqueous solution was carefully added drop wise. The mixture was then warmed to room temperature and filtered through a pad of Celite. The pad was washed

with diethyl ether. The layers were separated and the aqueous one was extracted with diethyl ether. The combined organic layers were washed with water, dried over sodium sulfate and evaporated. The yellow crude residue obtained was dissolved in methanol (700 mL) and acetic anhydride (10.8 mL, 115 mmol, 12 eq) was added. The reaction mixture was stirred at room temperature for 1.5 h, then evaporated to give a mixture of two diastereomers (**28T/28G 70/30**). Each diastereomer has been isolated by chromatography (cyclohexane/ethyl acetate 60/40 to 35/65) of the crude residue **28T** (m = 1.65 g, n = 2.97 mmol, yield = 31 %) and **28G** (m = 516 mg, n = 0.93 mmol, yield = 10 %).

28T/28G: $C_{31}H_{35}F_2NO_6$ M=555.61g.mol^{-1}

28T

Mass (ESI$^+$): 562.3 $[M+Li]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -109.5/-110.7 (1F; 2m); -112.9/-114.6 (1F, 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -110.1 (1F; d; *J*=261Hz); -113.7 (1F; d; *J*=261Hz)

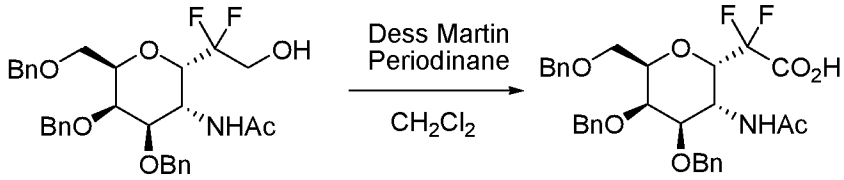
28G

Mass (ESI$^+$): 562.3 $[M+Li]^+$ 578.2 $[M+Na]^+$

NMR ^{19}F ($CDCl_3$, 282.5MHz) (with H coupled): -112.2/-113.7 (1F; 2m); -120.3/-121.7 (1F; 2m)

NMR ^{19}F ($CDCl_3$, 282.5MHz) (without H coupled): -112.8 (1F; d; *J*=269Hz); -120.8 (1F; d; *J*=269Hz)

***Synthesis of compounds* 29G**



28G **29G**

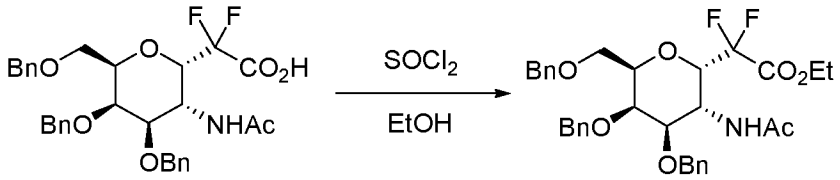
Compound **28G** (200 mg, 0.36 mmol, 1 eq) was dissolved in dichloromethane (1 mL) under inert atmosphere and Dess Martin periodinane (458 mg, 1.08 mmol, 3 eq) was added. The reaction mixture was stirred at room temperature overnight. Dichloromethane and water were added and the layers separated. The aqueous layer was

extracted with dichloromethane and the combined organic layers were dried over sodium sulfate. Evaporation and purification by chromatography (dichloromethane/methanol 90/10 to 85/15) afford compound **29G** (m = 45 mg, n = 0.079 mmol, yield = 22 %)

29G: $C_{31}H_{33}F_2NO_7$ M=569.59g.mol^{-1}

Mass (ESI$^+$): 570.2 $[M+H]^+$, 592.2 $[M+Na]^+$, 608.1 $[M+K]^+$

***Synthesis of compounds* 30G**



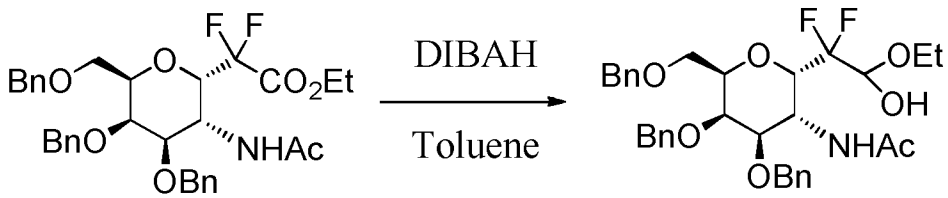
29G **30G**

Thionyl chloride (21 µL, 0.278 mmol, 3.6 eq) was added to a solution of compound **29G** (44 mg, 0.077 mmol, 1 eq) in ethanol (510 µL). The reaction mixture was refluxed 1 h, then cooled and slowly added to an aqueous saturated solution of sodium hydrogenocarbonate. The solution was extracted two times with diethyl ether and the combined organic layers were dried over sodium sulfate. Evaporation and purification by chromatography afford compound **30G** (m = 6 mg, n = 0.01 mmol, yield = 13 %)

30G: $C_{33}H_{37}F_2NO_7$ M=597.65g.mol^{-1}

Mass (ESI$^+$): 598.3 $[M+H]^+$, 620.2 $[M+Na]^+$, 636.2 $[M+K]^+$

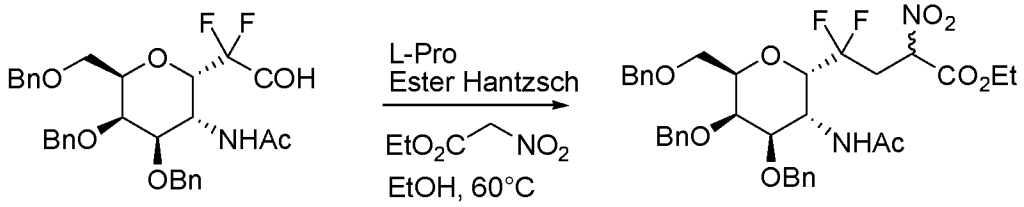
***Synthesis of compounds* 31G**



30G **31G**

The compound **31G** (m = 702 mg, n = 1.17 mmol, yield = 89 %) was prepared from compound **30G** (790 mg, 1.32 mmol, 1 eq) following the same procedure as for compound **16.** The crude mixture containing compound **31G** is used in the next step without further purification and without characterization.

Synthesis of compounds **32Gd1/32Gd2**



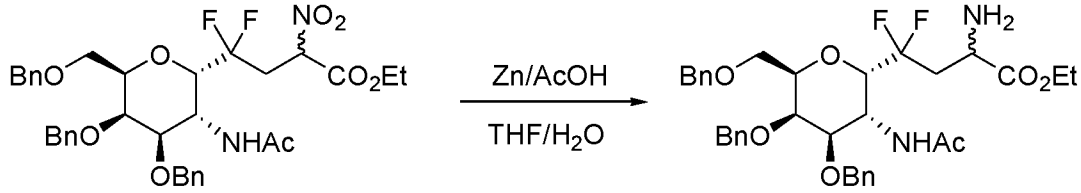
31G **32Gd1/32Gd2**

The compound **32Gd1/32Gd2** (m = 365 mg, n = 0.54mmol, yield = 47 %) was prepared from compound **31G** (702 mg, 1.17 mmol, 1 eq) following the same procedure as for compound **17**.

32Gd1/32Gd2: $C_{35}H_{40}F_2N_2O_9$ M=670.70g.mol^{-1}

Mass (ESI$^+$): 693.3 $[M+Na]^+$, 709.3 $[M+K]^+$

Synthesis of compounds **33Gd1/33Gd2**



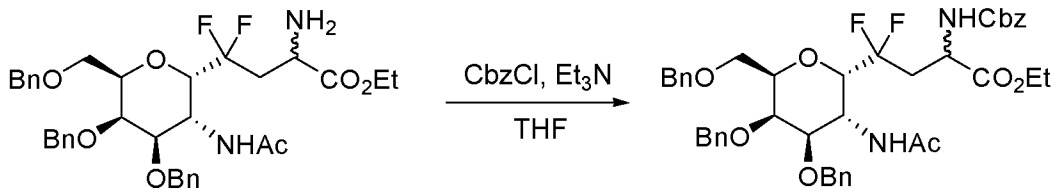
32Gd1/32Gd2 **33Gd1/33Gd2**

The compound **33Gd1/33Gd2** (m = 332 mg, n = 0.52 mmol, yield = 96 %) was prepared from compound **32Gd1/32Gd2** (362 mg, 0.54 mmol, 1 eq) following the same procedure as for compound **18**. At this stage, both diastereomers could be isolated by purification on chromatography.

33Gd1/33Gd2: $C_{35}H_{42}F_2N_2O_7$ M=640.71g.mol^{-1}

Mass (ESI$^+$): 641.4 $[M+H]^+$, 663.4 $[M+Na]^+$, 679.4 $[M+K]^+$

Synthesis of compounds **34Gd1/34Gd2**



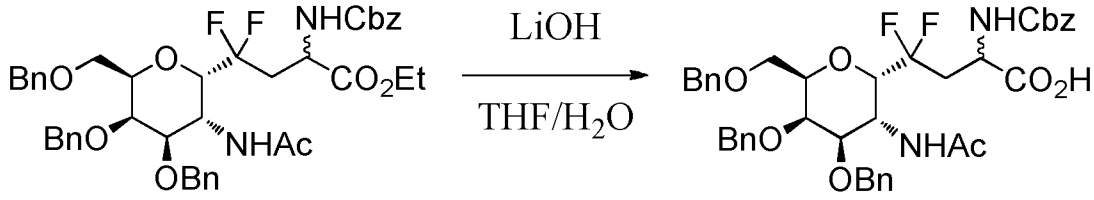
33Gd1/33Gd2 **34Gd1/34Gd2**

The compound **34Gd1/34Gd2** (m = 51 mg, n = 0.066 mmol, yield = 28 %) was prepared from compound **33Gd1/33Gd2** (150 mg, 0.23 mmol, 1 eq) following the same procedure as for compound **19**.

34Gd1/34Gd2: $C_{43}H_{48}F_2N_2O_9$ M=774.85g.mol^{-1}

Mass (ESI$^+$): 775.3 $[M+H]^+$, 792.3 $[M+H_2O]^+$, 797.3 $[M+Na]^+$, 813.3 $[M+K]^+$

Synthesis of compounds **35Gd1/35Gd2**



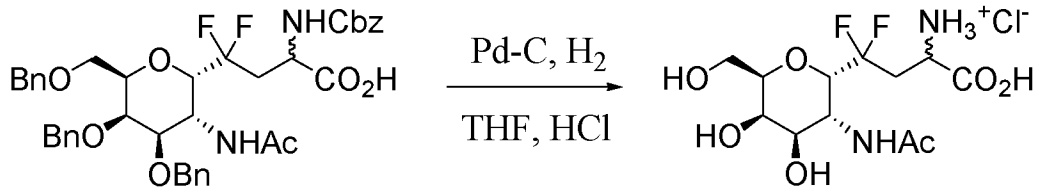
34Gd1/34Gd2 **35Gd1/35Gd2**

The compound **35Gd1/35Gd2** (m = 48 mg, n = 0.065 mmol, yield = 100 %) was prepared from compound **34Gd1/34Gd2** (50 mg, 0.65 mmol, 1 eq) following the same procedure as for compound **20**.

35Gd1/35Gd2: $C_{41}H_{44}F_2N_2O_9$ M=746.79g.mol^{-1}

Mass (ESI$^+$): 747.3 $[M+H]^+$, 764.3 $[M+H_2O]^+$, 769.3 $[M+Na]^+$, 785.3 $[M+K]^+$

Synthesis of compounds **36Gd1/36Gd2**



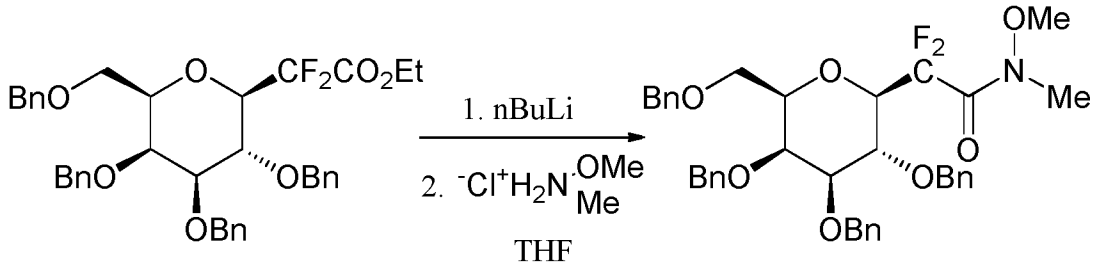
35Gd1/35Gd2 **36Gd1/36Gd2**

The compound **36Gd1/36Gd2** (m = 24 mg, n = 0.065 mmol, yield = 100 %) was prepared from compound **35Gd1/35Gd2** (48 mg, 0.065 mmol, 1 eq) following the same procedure as for compound **13(b)α**.

36Gd1/36Gd2: $C_{12}H_{21}ClF_2N_2O_7$ M=378.75g.mol^{-1}

Mass (ESI$^+$): 343.2 $[M-HCl+H]^+$, 360.2 $[M+NH_4]^+$, 365.2 $[M+Na]^+$

***Synthesis of compound* 38**



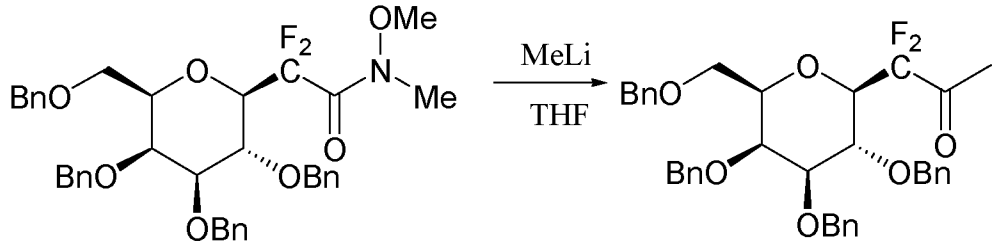
37 **38**

Into a round-bottom flask, under an inert atmosphere, BuLi (1,5 M, 1.6 mL, 5.7 eq.) is added carefully at -78°C to a solution of Weinreb amine (122 mg; 1.25 mmol; 3 eq) in THF anhydrous (2.5 mL). The mixture is left under agitation for 20 minutes, with the media put back at room temperature. The compound **37** (271 mg; 0.420 mmol; 1 eq.) in THF (0.5 mL) is then added at -78°C. Then the media is allowed to get back to room temperature, and stirred for 30 minutes. The mixture is hydrolyzed with HCl 1N to obtained pH 7, extracted three times with Et_2O, dried over magnesium sulfate, filtered and then evaporated. The crude mixture containing compound **38** is used in the next step without further purification.

38: $C_{38}H_{41}F_2NO_7$ M=661.73g.mol^{-1}

Mass (ESI^+): 684.4 (M+Na).

***Synthesis of compound* 39**



38 **39**

Into a round-bottom flask, under an inert atmosphere, MeLi (1.6 M solution in Et_2O, 0.9 mL, 4 eq.) was added at -78°C to a solution of crude compound **38** (226 mg) in THF (5 mL). The mixture was stirred for 30 minutes. Then, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic layers were dried over magnesium sulfate, filtered and evaporated. Then the residue was

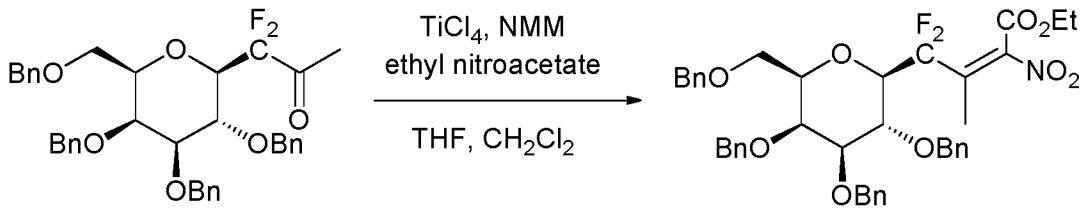
purified by chromatography (cyclohexane/ethyl acetate 93/7 to 40/60) to give compound **39** (120 mg, 0.20 mmol).

39: $C_{37}H_{38}F_2O_6$ M=616.69g.mol^{-1}

Mass (ESI$^+$): 634.3 $[M+H_2O]^+$, 639.3 $[M+Na]^+$, 655.2 $[M+K]^+$.

NMR^{19}F ($CDCl_3$, 282.5MHz): -115.5 (1F, dd, J=257Hz, J=11Hz); -119.6 (1F, ddd, J=257Hz, J=11Hz, J=3Hz).

***Synthesis of compound* 40**



39 **40**

Under an inert atmosphere, a solution of ethyl nitroacetate (0.036 mL, 0.32 mmol) and compound **39** (100 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) was added to a stirred solution of $TiCl_4$ (1M solution in CH_2Cl_2, 0.3 ml, 0.3 mmol) in anhydrous THF (2 mL) at 0°C. The mixture was stirred for 15 min at 0°C and a solution of N-methyl morpholine (NMM) (0.071 mL, 0.65 mmol) in THF (1 mL) was added. Then the reaction mixture was stirred for an additional time of 15 min. at 0°C, allowed to warm to room temperature for 15 h and heated at 60°C for 15 h. Then H_2O was added and the mixture was extracted with Et_2O. The combined organic layers were dried over magnesium sulfate, filtered and evaporated.

40: $C_{41}H_{43}F_2NO_9$ M=731.78g.mol^{-1}

Mass (ESI$^+$): 732.28 $[M+H]^+$; 749.33$[M+H_2O]^+$.

II – Stability of pseudo glycosidic bond

Compound **11βd1**, **11βd2**, **12(b)αd1**, **12(b)αd2**, **25d1** and **25d2** have all been neutralized using the following process before to be used in the stability test described below.

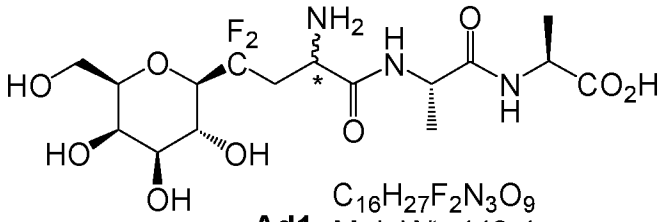
Compound **11βd1** (196 mg, 0.41 mmol) was dissolved in methanol (3 mL). Ion exchange resin (Amberlite IRA-67 weakly basic, previously washed with water, then

with methanol) was added and the suspension thus obtained was stirred for 30 min. The mixture was filtered and the resin washed with methanol (10 mL). Evaporation, dissolution in water (25 mL) and freeze drying afford compound Ad1 (120 mg, 0.27 mmol, yield 66 %) as a white solid.

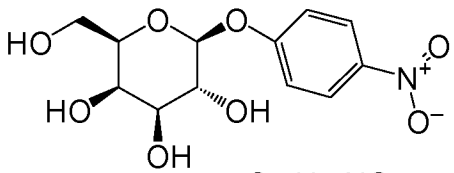
Using the previous process, compound **11βd2** leads to compound **Ad2**, **compound 12(b)αd1** leads to compound **Dd1**, compound **12(b)αd2** leads to compound **Dd2**, compound **25d1** leads to compound **Ed1** and compound **25d2** leads to compound **Ed2**.

- *Stability of β-Gal-CF_2-Ser pseudo-glycosidic bond*

The enzymatic stability has been performed with compound Ad1 and Ad2 according to the invention and compound B used as a reference compound to control the efficacy of the β-galactosidase. Both compounds have been treated with β-galactosidase. The stability of compound Ad1 and Ad2 has been assessed by mass spectrum (MS) analysis after incubation with β-galactosidase. The samples have been injected and ionized by electrospray (ES) (in positive and negative mode). The procedure has been adapted from Maljaars et al. J Comb. Chem. **2006**, 8, 812-819.



$C_{16}H_{27}F_2N_3O_9$
Ad1 Mol. Wt: 443,4
Ad2



$C_{12}H_{15}NO_8$
B Mol. Wt.: 301.25

Test compound Ad1 (12 µmol, 5.3 mg) in 1.5 mL ammonium acetate buffer (10 mM, pH 7) was kept 24h at 37°C in the presence and absence of β-galactosidase (4.5 U, 32 µL of a 1 $mg.mL^{-1}$ solution in ammonium acetate buffer,(48275 sigma, 140 U per mg)). 300 µL of the sample was filtered through a 3-kDa-cutoff centrifugal filter

(Millipore), and the filter was washed with H_2O (2 x 300 μL). The obtained solutions were diluted in water/methanol 1:1 (3 µL in 1mL).

Test compound Ad2 (12 µmol, 5.3mg) has been treated in the presence and absence of β-galactosidase following the same process.

These samples of compound Ad1 and Ad2 in presence of β-galactosidase have been submitted to mass spectra and compared to the mass spectra of compound Ad1 and Ad2 in absence of β-galactosidase. For both compound Ad1 (Figures 1a and 1b) and Ad2 (Figures 2a and 2b), the spectra show that no hydrolysis occurs and that both compounds remain intact.

The two samples were also analyzed by F-NMR to confirm that the test compound Ad1 and Ad2 were not cleaved by the β-galactosidase.

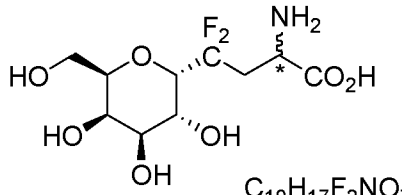
In parallel, p-nitrophenyl-β-galactoside (compound B, 12 µmol, 3.6 mg) in 1.5 mL ammonium acetate buffer (10 mM, pH 7) was kept 24 h at 37°C in the presence and absence of β-galactosidase (4.5 U, 32 µL of a 1 $mg.mL^{-1}$ solution in ammonium acetate buffer (48275 sigma, 140U per mg)).

During the process in the presence of β-Galactosidase, a yellow coloration was observed that underlines the decomposition of compound B.

The optical density (OD) of the two samples was measured at 420 nm to verify that the β-galactosidase is working and that degradation occurs on compound B (OD_{420} with β-galactosidase = 1.5786 / OD_{420} without β-galactosidase = 0.0465).

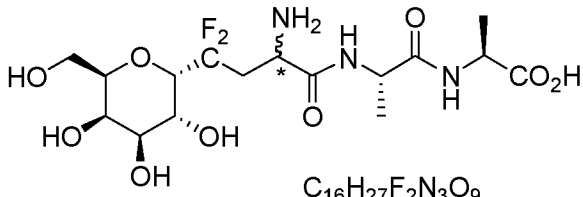
- *Stability of α-Gal-CF_2-Ser pseudo-glycosidic bond*

The enzymatic stability has been performed with compounds Cd1, Cd2, Dd1 and Dd2 according to the invention and compound F was used as a reference compound to control the efficacy of the α-galactosidase. All the compounds have been treated with α-galactosidase. The stability of compounds Cd1, Cd2, Dd1 and Dd2 has been assessed by MS analysis after incubation with α-galactosidase. The procedure has been adapted from Maljaars et al. J Comb. Chem. 2006, 8, 812-819.



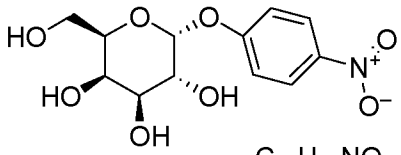
Cd1
Cd2

$C_{10}H_{17}F_2NO_7$
Mol. Wt.: 301.24



Dd1
Dd2

$C_{16}H_{27}F_2N_3O_9$
Mol. Wt.: 443.40



F

$C_{12}H_{15}NO_8$
Mol. Wt.: 301.25

Test compound Cd1 (6 µmol, 1.8 mg) in 0.75 mL ammonium acetate buffer (10 mM, pH 7) was kept 24 h at 37°C in the presence and absence of α-galactosidase (2.25 U, 41 µL of a 3.7 $mg.mL^{-1}$ suspension in ammonium sulphate (G8507 sigma, 14.7 U/mg)). 300 µL of the samples were filtered through a 3-kDa-cutoff centrifugal filter (Millipore) and the filter was washed with H_2O (2 x 300 μL). The resultant solutions were diluted in water/methanol 1:1 (3 µL in 1mL);

Test compound Cd2 (12 µmol, 5.3 mg) has been treated in the presence and absence of α-galactosidase following the same process.

The samples of compound Cd1 and Cd2 in presence of α-galactosidase have been analyzed by mass spectrometry and their spectra compared to the mass spectra of compound Cd1 and Cd2 in absence of α-galactosidase. For both compound Cd1 (Figures 3a and 3b) and Cd2 (Figures 4a and 4b), the spectra underline that no hydrolysis occurs and that both compounds remain intact.

The two samples were also analyzed by F-NMR to confirm that the test compounds Cd1 and Cd2 were not cleaved by α-galactosidase.

The same procedure was applied to compound Dd1 (6 µmol, 2.6 mg) and Dd2 (6 µmol, 2.6 mg).

The samples of compound Dd1 and Dd2 in presence of α-galactosidase have been submitted to mass spectra and compared to the mass spectra of compound Dd1 and Dd2

in absence of α-galactosidase. For both compounds Dd1 (Figures 5a and 5b) and Dd2 (Figures 6a and 6b), the spectra underline that no hydrolysis occurs on both compounds that remain intact.

The two samples were also analyzed by F-NMR to confirm that the test compounds Dd1 and Dd2 were not cleaved by α-galactosidase.

In parallel, p-nitrophenyl-α-galactoside (compound F, 6 µmol, 1.8mg) in 0.75mL of ammonium acetate buffer (10 mM, pH 7) was kept 24h at 37°C in the presence and absence of α-galactosidase 2.25U, 41 µL of a 3.7 $mg.mL^{-1}$ suspension in ammonium sulphate ((G8507 sigma) 14.7 U/mg). The OD of the two samples was measured at 420 nm to verify that the α-galactosidase is working and that degradation occurs on compound F (OD_{420} with α-galactosidase = 1.6303 / OD_{420} without α-galactosidase = 0.0124).

In conclusion, we showed in these experiments that the CF_2 bond is stable and does not undergo hydrolysis in the presence of galactosidase. To the contrary the O-glycosidic bound has been shown to undergo hydrolysis in the presence of galactosidases (vide supra) and as described in the literature (vide infra). Indeed O-glycosidic amino acid such as O-glycosidic serine and threonine can be cleaved by glycosidases (cf Maljaars et al. J Comb. Chem. 2006, 8, 812-819 and Allen et al. Biochem. J. 1978, 171, 665-674).

III – Effect of glycopeptides 13(b)αd1 and 13(b)αd2 on the preservation of neonatal skin fibroblast under starvation conditions

Materials and Methods

Subculturing

- The neonatal human skin fibroblasts (Cell line: CCD-27SK, ATCC number CRL-1475) were grown with DMEM medium supplemented with Fetal Bovine Serum 10 % final, antibiotics (Penicillin/Streptomycin) 1 % final and Amphotericin B 0.1 % final.

- Fibroblasts were grown in 75 cm^2 culture flask to 80 % confluence, in 37°C and 10 % CO_2 incubator. The medium was changed every two days by 37°C preheated fresh medium.

Starvation medium

- This medium was composed of 45 % subculture medium without Fetal Bovine Serum mixed with 55 % of Phosphate Buffer Saline 1X containing EDTA (final concentration of 0.45 mM). This was referred to as serum free or starvation medium.

Product preparation

- The compounds 13(b)αd1 and 13(b)αd2 (M = 479.9 g/mol) were diluted in starvation medium to 5 mg/ml final and pH was adjusted at 7.4 by addition of NaOH 1N.

General Experimental procedure

Assays on 96 well plates

- Fibroblast cells were concentrated to 2.10^5 cells/ml and 100µl of cell suspension was added in wells of a 96-well plate and incubated in 37°C and 10 % CO_2 incubator for 4 hours.
- After cell adhesion the medium was changed and plates were incubated (37°C-10 % CO_2) to perform the assay as follow:
  - 1 plate for each sampling times: days D0, D3, D4, D5, D6, and D7
  - 3 wells for each condition (triplicate count) added with 120µl of culture medium, starvation medium, 13(b)αd1 solution (5 mg/ml) or 13(b)αd2 solution (5 mg/ml)

Viability assay

Cell Viability was evaluated by the *Trypan blue exclusion* technique based on the principle that live cells possess intact cell membranes that exclude the Trypan blue dye. So, only the dead cells are blue at microscopic observation.

For sampling, 110 µl of Trypan Blue (SIGMA T8154) was added to 110 µl of trypsinated cell suspension of matching well for counting.

200 µl of the trypan blue/cell mixture are dropped to a hemacytometer. Cells are counting by using a Neubauer-counting chamber. The unstained (viable) and stained (nonviable) cells are counted separately on 9 area of a large square (1 mm^2) and added to obtain the total number of cells per sample. An average of three counts was used to calculate the viability percentage as:

[number of viable cells / total number of cells]*100

The cell viability percentages from cultures under starvation conditions were compared with control culture for several days after their addition (D0, D3, D4, D5, D6, D7).

Results

The results were plotted in the histogram of figure 7 which represents the evolution of fibroblast viability *in vitro* during a 7 day period while deprived of nutrients.

The viability of 13(b)αd1 and 13(b)αd2 treated cells remained around 95 % up to 7 days of incubation whereas the cell viability in the nutrient deprivation control decreased from 94 % after 4 days to 89 %, 38 % and 8 % after 5, 6 and 7 days, respectively.

Compounds 13(b)αd1 and 13(b)αd2 showed thus a preservative effect on skin fibroblasts since cells have been maintained in a healthy state under unfavorable conditions for growth.

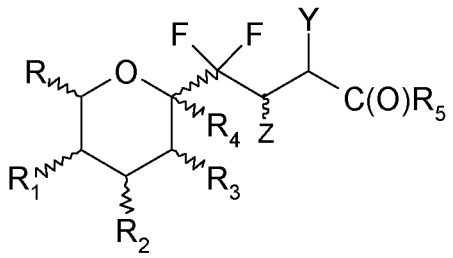
ABBREVIATIONS

Ala	Alanin
Bn	Benzyl
Cbz	Benzyloxycarbonyl
de	Diastereomeric excess
DIBAH	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
eq.	Equivalent
Et	Ethyl
g	Gram
Hz	Hertz
mg	Milligram
MHz	MegaHertz
Min	Minute
mL	Mililitre

mmol	Millimole
µmol	Micromole
MOM	Methoxymethyl
Ms	Mesyl
NMM	N-methylmorpholine
nmol	Nanomole
NMR	Nuclear Magnetic Resonance
PyBOP	(1H-Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
Rf	Retardation factor
THF	Tetrahydrofuran
TLC	Thin Layer chromatography
TMS	Trimethylsilyl

CLAIMS

1. A compound of formula (I):



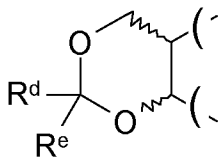
(I)

or a pharmaceutically 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,

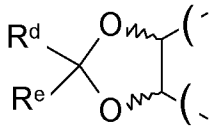
wherein:

- Y represents a CN, NO_2, NR_6R_7 or $CH_2NR_6R_7$ group,
- Z represents H or CH_3,
- R represents a hydrogen or fluorine atom or a CH_3, CH_2F, $CH_2OSiR^{a1}R^{b1}R^{c1}$, CH_2OR_8, $CH_2OC(O)R_9$, $CH_2OCO_2R_{10}$, $CH_2OC(O)NR_{11}R_{12}$, $CH_2OP(O)(OR_{13})_2$ or $CH_2OSO_3R_{14}$ group,
- R_1 and R_2 represent, independently from one another, a fluorine atom or an $OSiR^{a2}R^{b2}R^{c2}$, OR_{15}, $OC(O)R_{16}$, OCO_2R_{17}, $OC(O)NR_{18}R_{19}$, $OP(O)(OR_{20})_2$ or OSO_3R_{21} group,
- R_3 represents a fluorine atom or an $OSiR^{a3}R^{b3}R^{c3}$, OR_{22}, $OC(O)R_{23}$, OCO_2R_{24}, $OCONR_{25}R_{26}$, $OP(O)(OR_{27})_2$, OSO_3R_{28}, N_3, phtalimidyl, $NR_{29}R_{30}$, $NR_{31}C(O)R_{32}$, $NR_{33}C(O)OR_{34}$, $N(C(O)R_{35})C(O)R_{36}$, $N(C(O)R_{37})C(O)OR_{38}$ and $N(C(O)OR_{39})C(O)OR_{40}$ group,
- R_4 represents a hydrogen or halogen atom or an $OSiR^{a4}R^{b4}R^{c4}$, OR_{41}, $OC(O)R_{42}$, OCO_2R_{43}, $OCONR_{44}R_{45}$, $OP(O)(OR_{46})_2$ or OSO_3R_{47} group,

or R and R_1, together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



and/or (R_1 and R_2), (R_2 and R_3), and/or (R_3 and R_4), together with the carbon atoms carrying them, form a cyclic acetal having the following formula:



, and

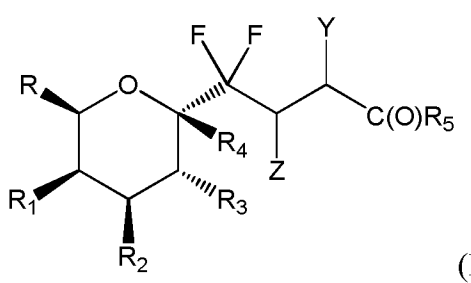
- R_5 represents a hydrogen or halogen atom or a R_{48}, OR_{49} or $NR_{50}R_{51}$ group,

with:

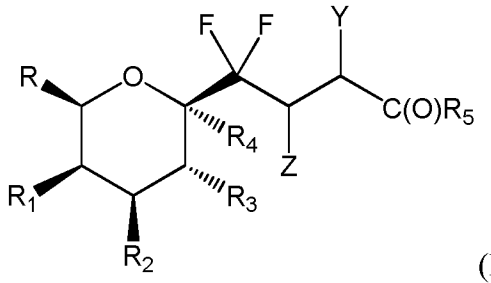
- R_6 representing:
  - a hydrogen atom,
  - a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
  - a $C(O)R_{52}$ group, or
  - a $C(O)OR_{53}$ group,
- R_7 representing:
  - a hydrogen atom,
  - a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
  - a $C(O)R_{52}$ group,
  - a $C(O)OR_{53}$ group, or
  - a N-protecting group,
- R_8, R_{15}, R_{22} and R_{41} representing, independently from one another, a hydrogen atom; an O-protecting group; or a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-aryl, (C_1-C_6)-alkyl-heteroaryl, saccharidic or polysaccharidic group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,

- R_9, R_{10}, R_{16}, R_{17}, R_{23}, R_{24}, R_{32}, R_{34} to R_{40}, R_{42}, R_{43}, R_{48}, R_{52} and R_{53} 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-membered heterocycloalkyl, aryl, heteroaryl, aryl-$(C_1$-$C_6)$alkyl, heteroaryl-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$-alkyl-aryl or $(C_1$-$C_6)$-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
- R_{11}, R_{12}, R_{18}, R_{19}, R_{25}, R_{26}, R_{29} to R_{31}, R_{33}, R_{44}, R_{45}, R_{50} and R_{51} representing, independently from one another, a hydrogen atom or a $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, aryl, heteroaryl, aryl-$(C_1$-$C_6)$alkyl, heteroaryl-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$-alkyl-aryl or $(C_1$-$C_6)$-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among a halogen atom, OH, COOH and CHO,
- R_{13}, R_{14}, R_{20}, R_{21}, R_{27}, R_{28}, R_{46} and R_{47} representing, independently from one another, a hydrogen atom or a $(C_1$-$C_6)$alkyl group,
- R_{49} representing:
  - a hydrogen atom,
  - a $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, 5- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-$(C_1$-$C_6)$alkyl, heteroaryl-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$-alkyl-aryl or $(C_1$-$C_6)$-alkyl-heteroaryl group, this group being possibly substituted with one or more groups chosen among an halogen atom, OH, COOH and CHO, or
  - a O-protecting group,
- R^{a1} to R^{a4}, R^{b1} to R^{b4} and R^{c1} to R^{c4} representing, independently from one another, a $(C_1$-$C_6)$alkyl, aryl or aryl-$(C_1$-$C_6)$alkyl group, and
- R^d and R^e representing, independently from one another, a hydrogen atom or a $(C_1$-$C_6)$alkyl group.

2. The compound according to claim 1, characterized in that it corresponds to a compound of formulas (Iα) or (Iβ):



(Iα),



(Iβ),

with R, R_1, R_2, R_3, R_4, R_5, Z and Y as defined in claim 1.

3. The compound according to any of claims 1 and 2, characterized in that R represents a CH_2OR_8 group; R_1 and R_2 represent, independently from one another, an OR_{15} group; and R_3 represents an OR_{22} or $NR_{31}C(O)R_{32}$ group, R_8, R_{15} and R_{22} representing advantageously a hydrogen atom or an O-protecting group, R_{31} representing advantageously a hydrogen atom and R_{32} representing a $(C_1\text{-}C_6)$alkyl group.

4. The compound according to any of claims 1 to 3, characterized in that R_4 represents a hydrogen atom or an OR_{41} group, R_{41} representing advantageously a hydrogen atom or an O-protecting group.

5. The compound according to any of claims 1 to 4, characterized in that Y represents a NR_6R_7 or $CH_2NR_6R_7$ group, with R_6 and R_7 as defined in claim 1 and notably with R_6 representing a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group and R_7 representing:

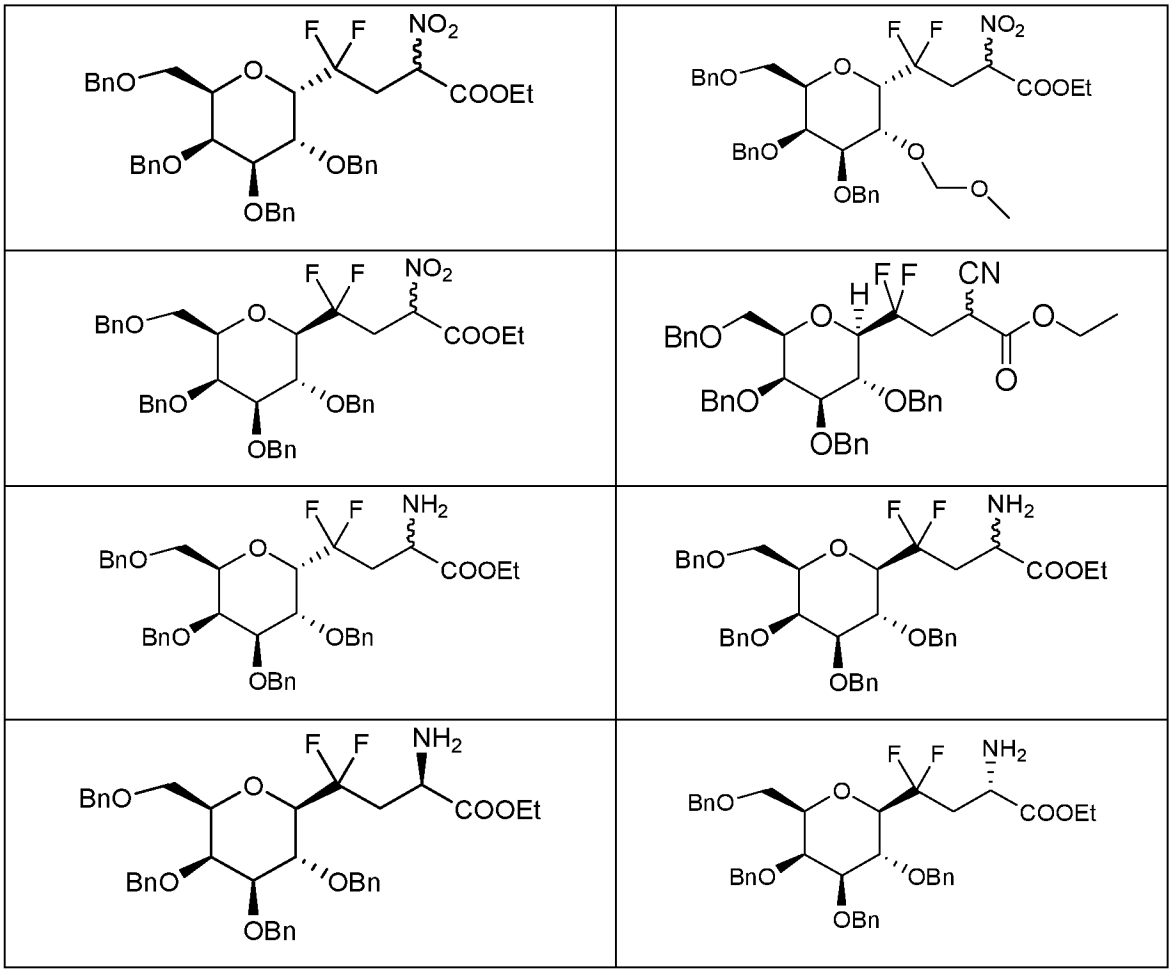
- a hydrogen atom,
- a $(C_1\text{-}C_6)$alkyl, aryl or aryl-$(C_1\text{-}C_6)$alkyl group,
- a $C(O)R_{52}$ group, with R_{52} as defined above and representing in particular a $(C_1\text{-}C_6)$alkyl, aryl or aryl-$(C_1\text{-}C_6)$alkyl group,
- a $C(O)OR_{53}$ group, with R_{53} as defined above and representing in particular a $(C_1\text{-}C_6)$alkyl, aryl or aryl-$(C_1\text{-}C_6)$alkyl group, or
- an N-protecting group.

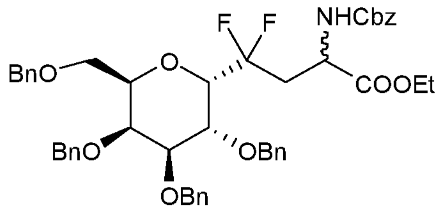
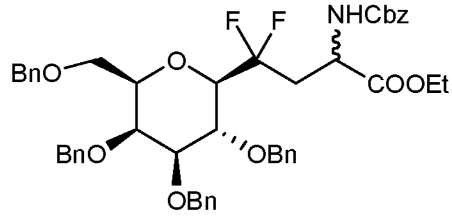
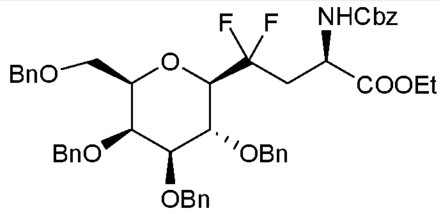
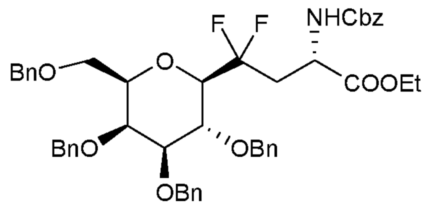
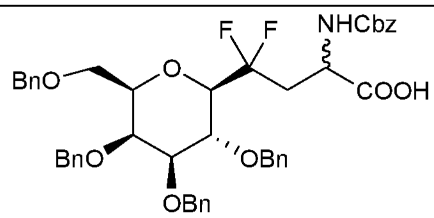
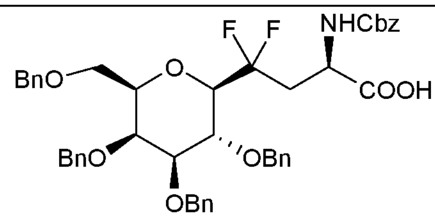
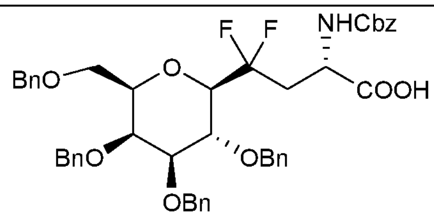
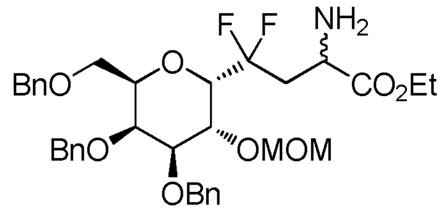
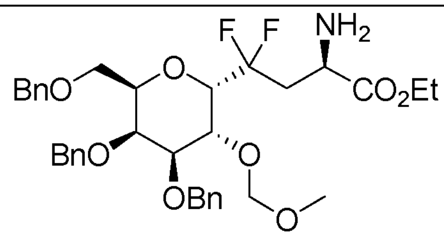
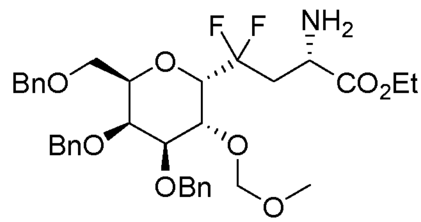
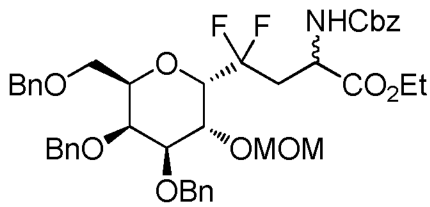
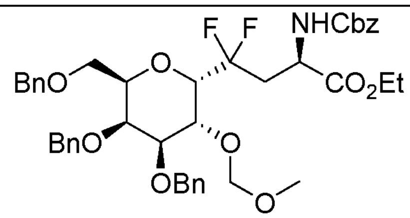
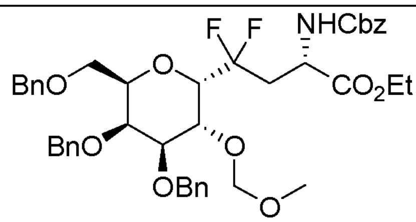
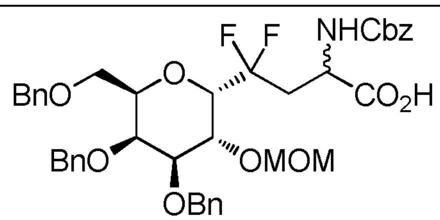
6. The compound according to any of claims 1 to 5, characterized in that R_5 represents an OR_{49} group, with R_{49} as defined in claim 1 and advantageously representing a hydrogen atom, a $(C_1$-$C_6)$alkyl group or an O-protecting group.

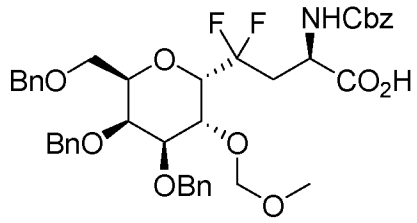
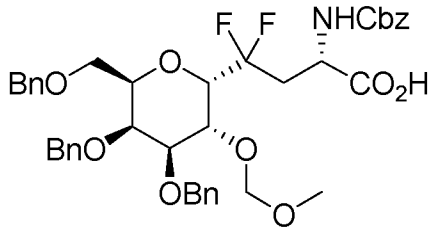
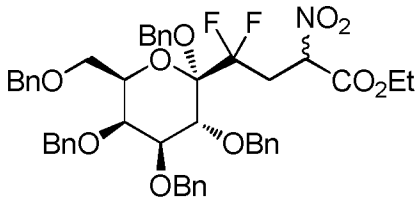
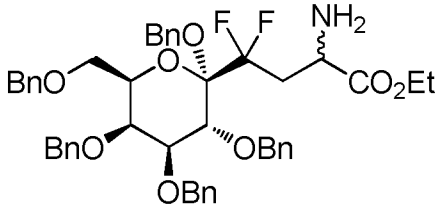
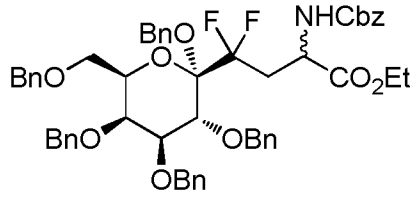
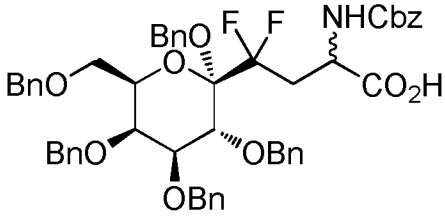
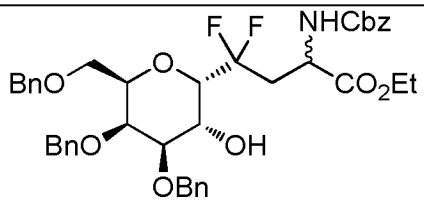
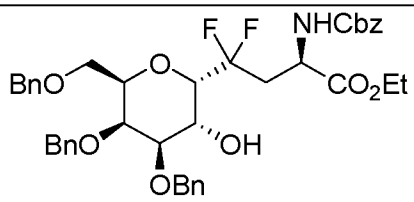
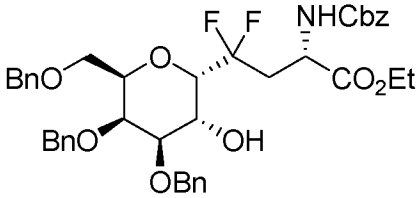
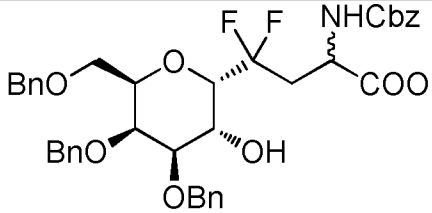
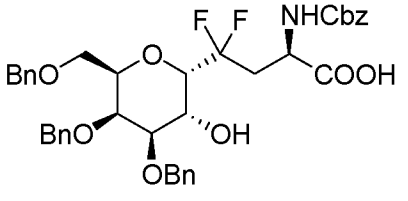
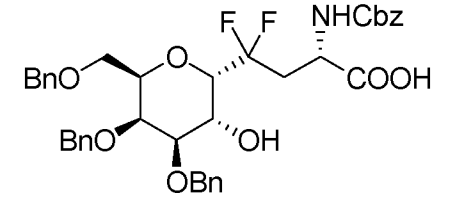
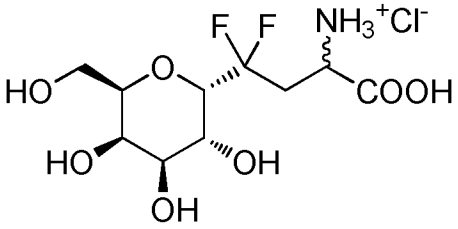
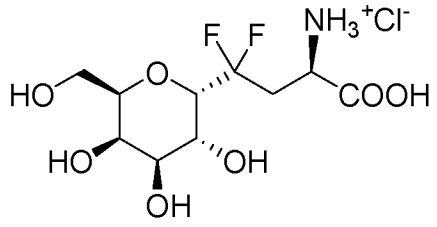
7. The compound according to any of claims 1 to 6, characterized in that Y represents a NR_6R_7 or $CH_2NR_6R_7$ group and R_5 represents an OR_{49} group, with:

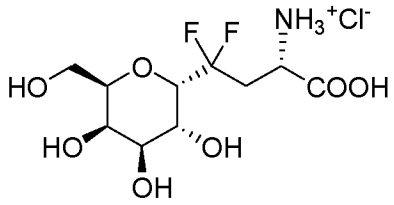
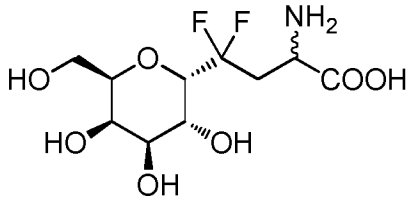
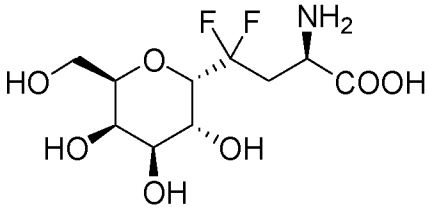
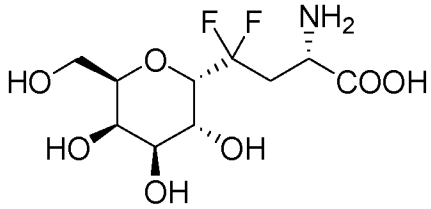
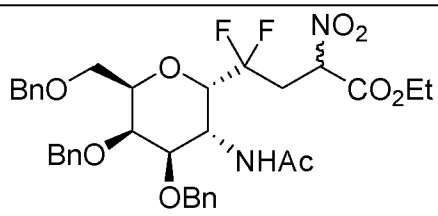
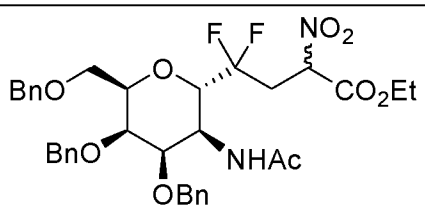
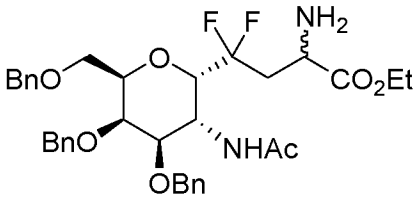
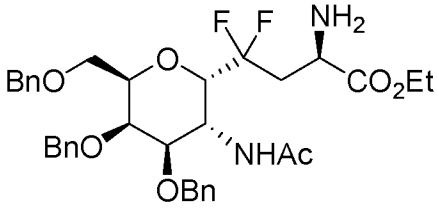
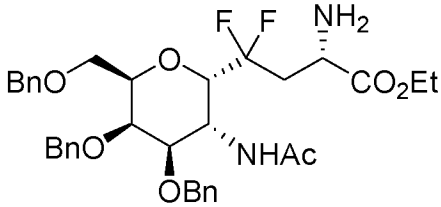
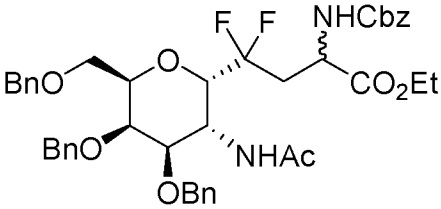
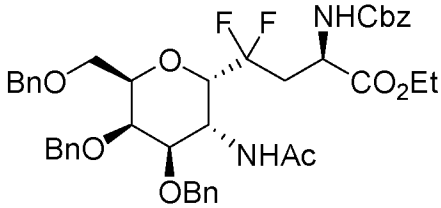
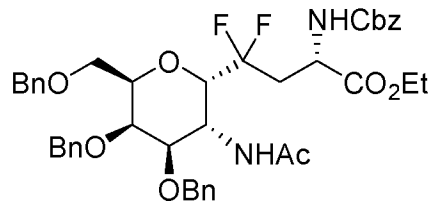
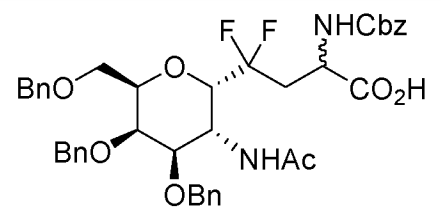
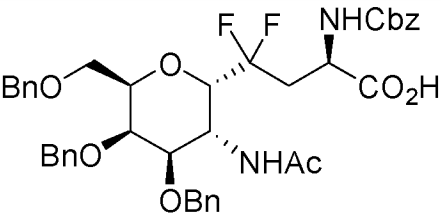
- R_6 and R_7 representing each a hydrogen atom and R_{49} representing an O-protecting group such as a $(C_1$-$C_6)$alkyl group, or
- R_{49} and R_6 representing each a hydrogen atom and R_7 representing a N-protecting group.

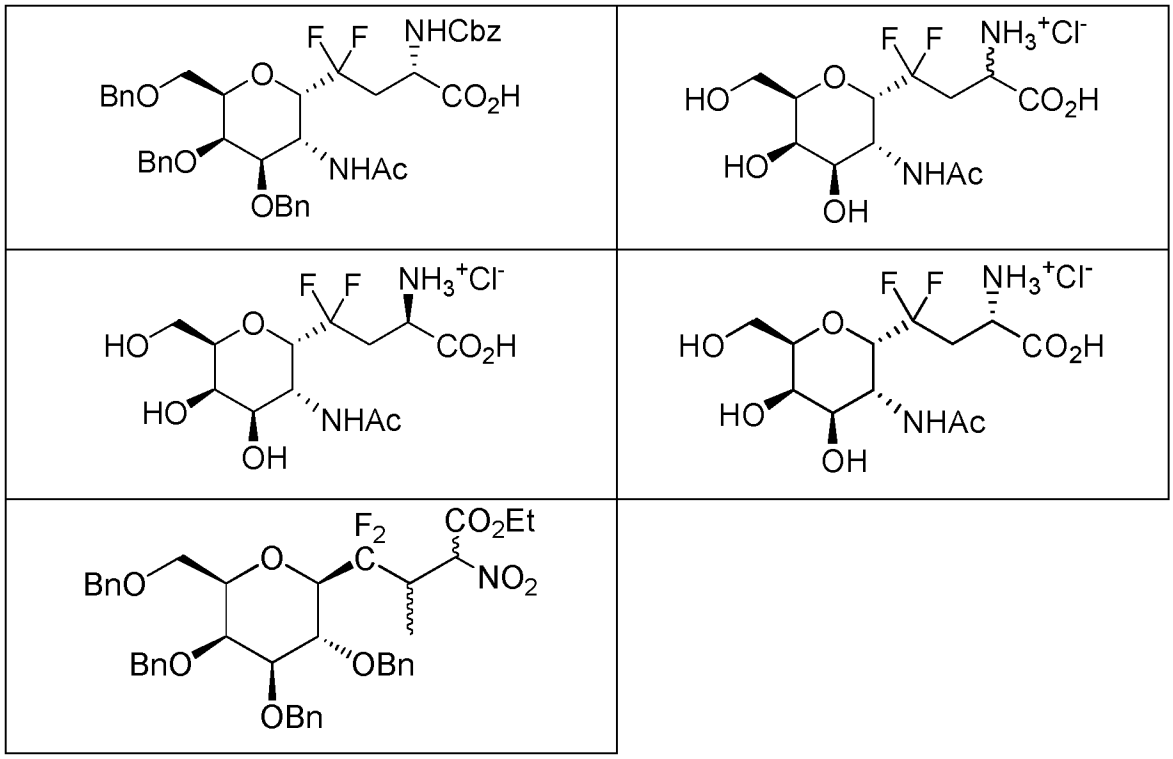
8. The compound according to any of claims 1 to 7, characterized in that it is chosen among the following compounds:



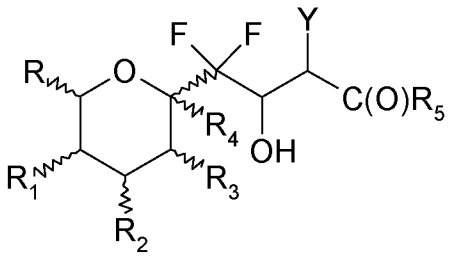
	
	
	
	
	
	
	



9. A process for preparing a compound of formula (I) according to any of claims 1 to 8 with Z = H, comprising the following successive steps:

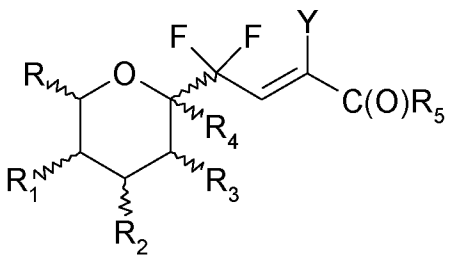
a) dehydration of a compound of formula (II):



(II)

in which R, R_1, R_2, R_3, R_4, R_5 and Y are as defined in claim 1,

to give a compound of formula (III):



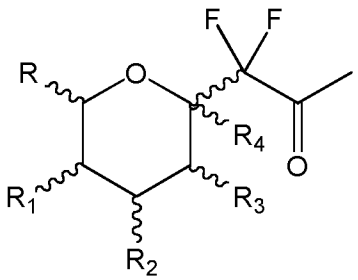
(III)

in which R, R_1, R_2, R_3, R_4, R_5 and Y are as defined in claim 1, and

b) hydrogenation of the compound of formula (III) obtained in the previous step to give a compound of formula (I) with Z = H.

10. A process for preparing a compound of formula (I) according to any of claims 1 to 8 with Z = CH_3, comprising the following successive steps:

i) reaction of a compound of formula (VII):



(VII)

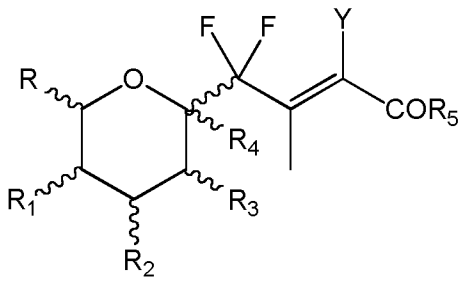
in which R, R_1, R_2, R_3 and R_4 are as defined in claim 1,

with a compound of formula (V):

$$Y\text{-}CH_2\text{-}COR_5 \quad (V)$$

in which R_5 is as defined in claim 1 and Y = NO_2 or CN,

to give a compound of formula (VIII):



(VIII)

in which R, R_1, R_2, R_3, R_4 and R_5 are as defined in claim 1 and Y = NO_2 or CN,

ii) optionally reduction of the compound of formula (VIII) obtained in the previous step i) to give a compound of formula (I) with Z = CH_3 and Y = NO_2 or CN,

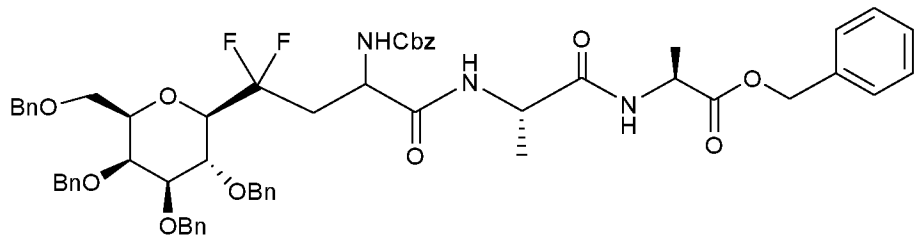
iii) optionally reduction of the NO_2 or CN function of the compound of formula (I) obtained in the previous step ii) to give a compound of formula (I) with Z = CH_3 and Y = NH_2 or CH_2NH_2, and

iv) optionally substitution of the amino function of the compound of formula (I) obtained in the previous step iii) to give a compound of formula (I) with Z = CH_3 and Y = NR_6R_7 or $CH_2NR_6R_7$, with the proviso that at least R_6 or R_7 is not a hydrogen atom.

11. The use of a compound of formula (I) according to claim 1 with Y = NH_2 or CH_2NH_2 and/or R_5 = OH, and in particular a compound of formula (I) according to claim 7, in the synthesis of a peptide, in place of an amino acid such as a serine or a threonine.

12. A peptide (VI) in which at least one amino acid, such as a serine or a threonine, has been replaced with a compound of formula (I) according to claim 1 in which Y = NHR_7 or CH_2NHR_7, and notably NHR_7, and/or R_5 = OH, the Y and/or R_5 group being linked to an amino acid of the peptide by means of peptide bond.

13. The peptide according to claim 12 selected from the following compounds:



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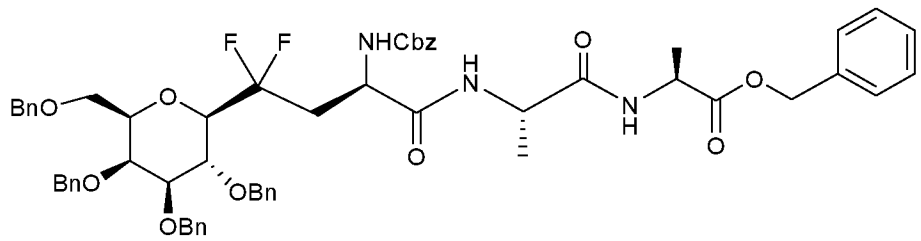

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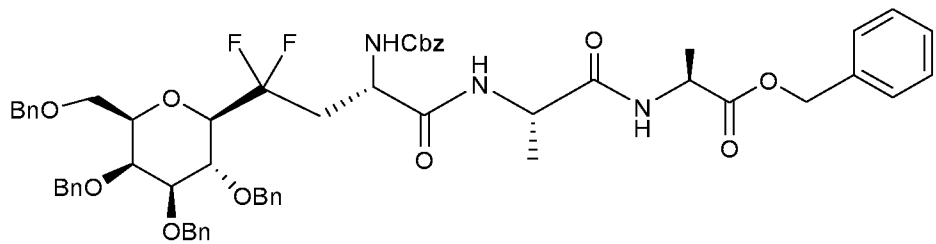

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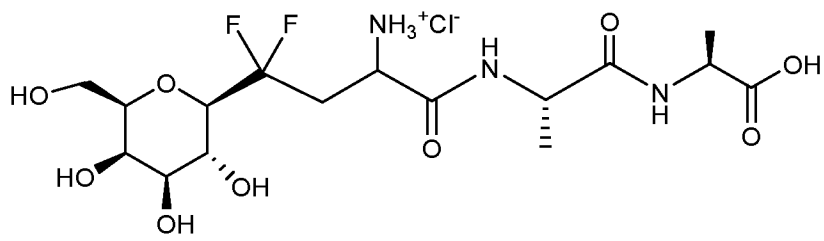

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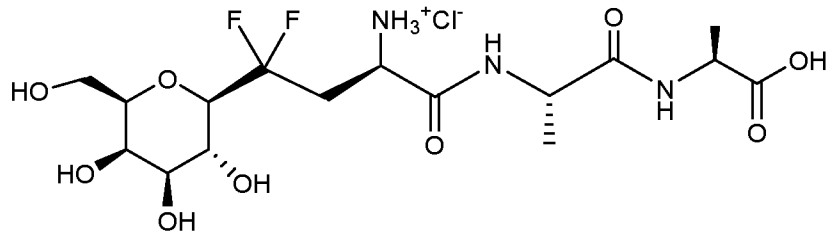

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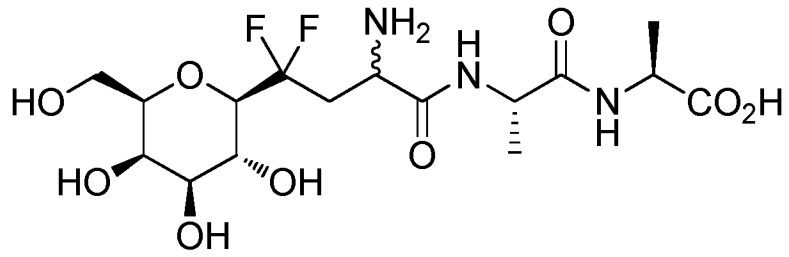

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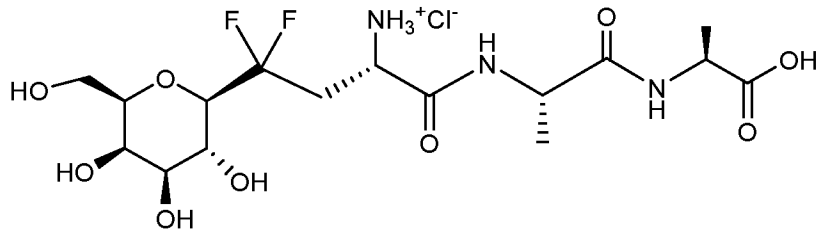

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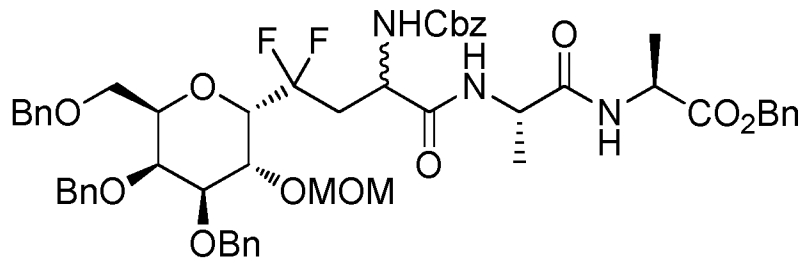

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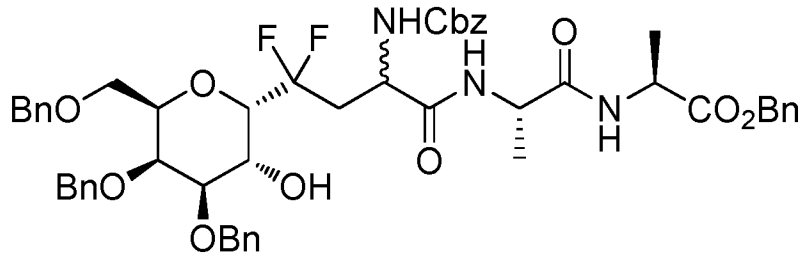

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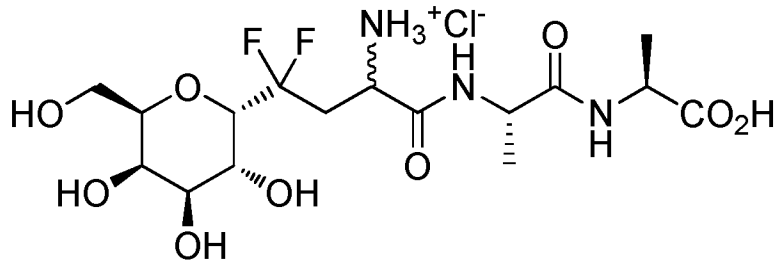

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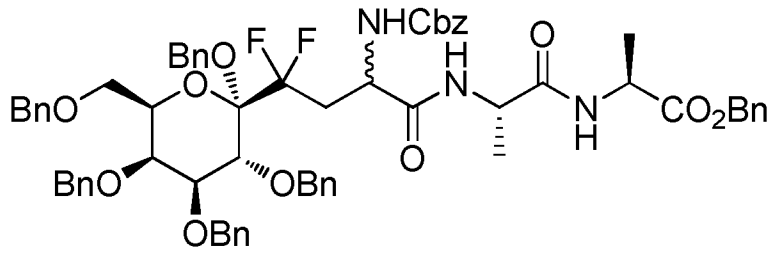

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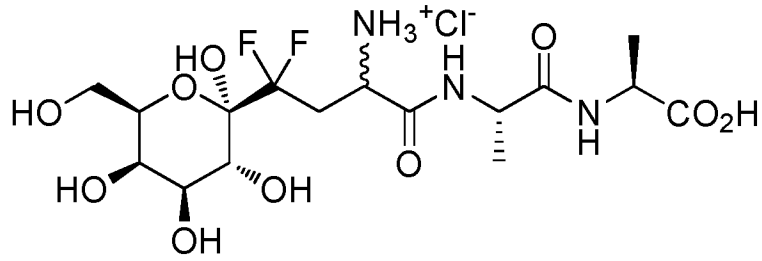


14. A peptide (VI) according to claim 12 for use as medicament.

15. A peptide (VI) according to claim 12 for use as medicament intended for the treatment or the prevention of viral, bacterial or inflammatory diseases or for use as cancer vaccine.

16. A peptide (VI) according to claim 15 for use as cancer vaccine, characterized in that the compound of formula (I) integrated in the said peptide represents a mimic of antigen Tn.

17. The use of a compound of formula (I) according to any of claims 1 to 8 as a mimic of antigen Tn.

18. A pharmaceutical or cosmetic composition comprising at least one peptide (VI) according to claim 12 and a pharmaceutically acceptable carrier, for example a hapten, protein, chemical scaffold or carrier matrix.

19. The use of a peptide (VI) according to claim 12 in preservation of biological materials such as cells, tissues and organs, notably at a temperature below 37°C, such as a temperature below 0°C.

20. The cosmetic use of a peptide (VI) according to claim 12.

21. The cosmetic use according to claim 20 for skin anti-aging applications.

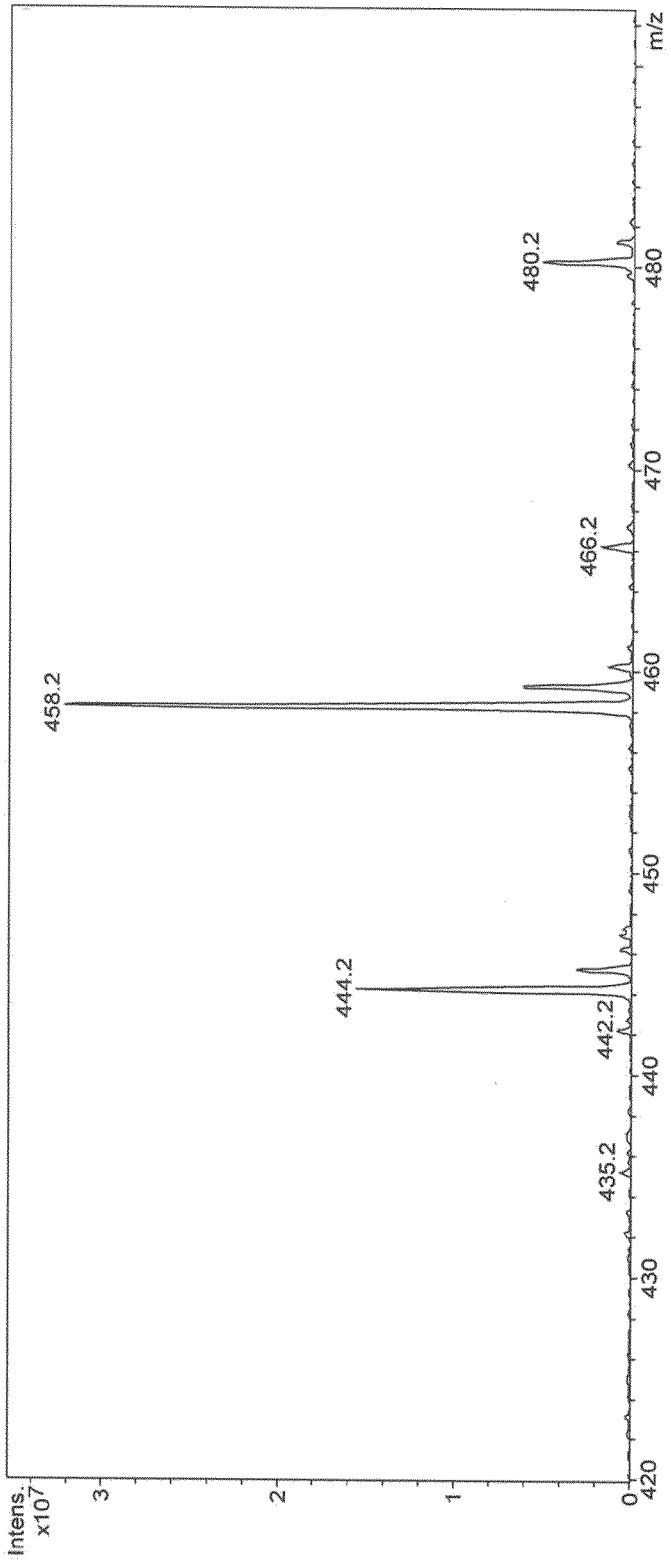
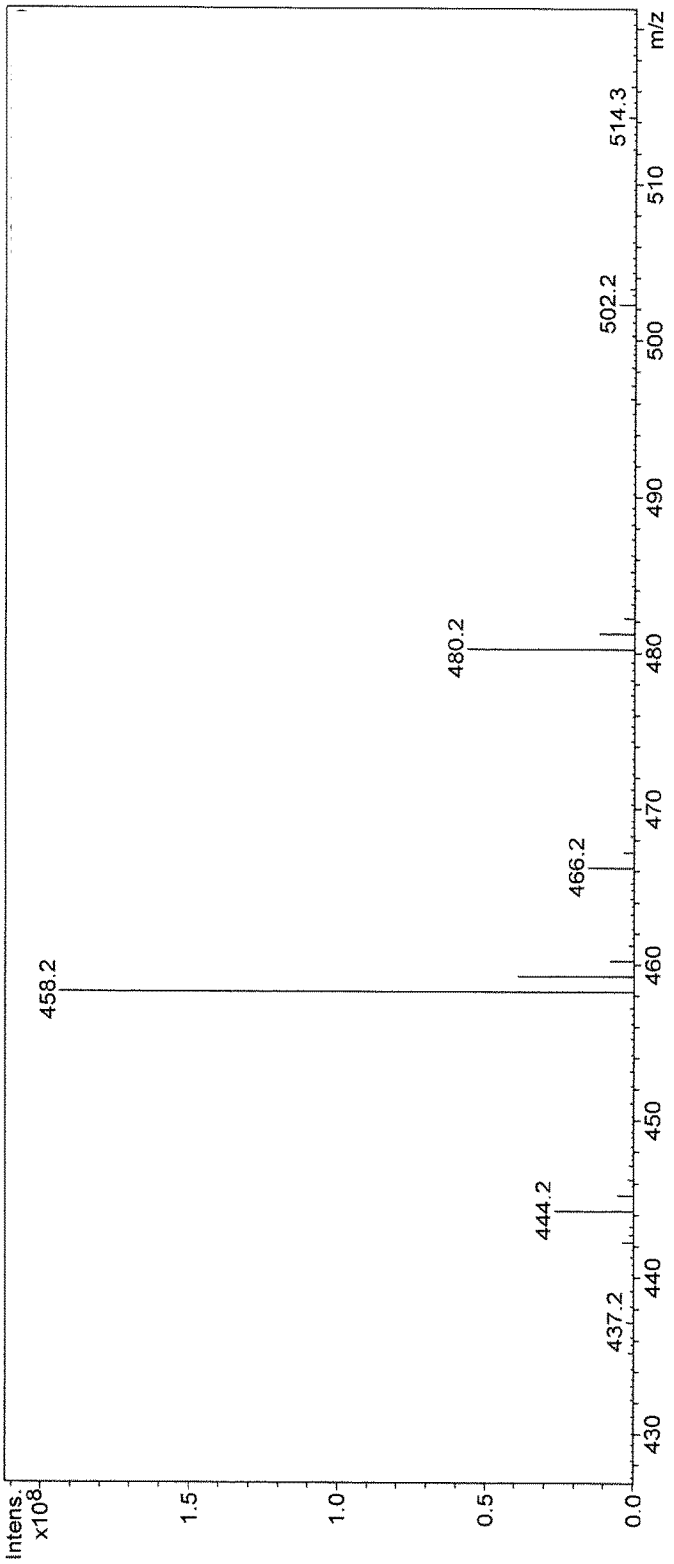

Intens.
x10^7
3
2
1
0
420
430
435.2
440
442.2
444.2
450
458.2
460
466.2
470
480.2
480
m/z

Figure 1a


Intens.
x10^8
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1.0
0.5
0.0
430
437.2
440
444.2
450
458.2
460
466.2
470
480.2
480
490
500
502.2
510
514.3
m/z

Figure 1b

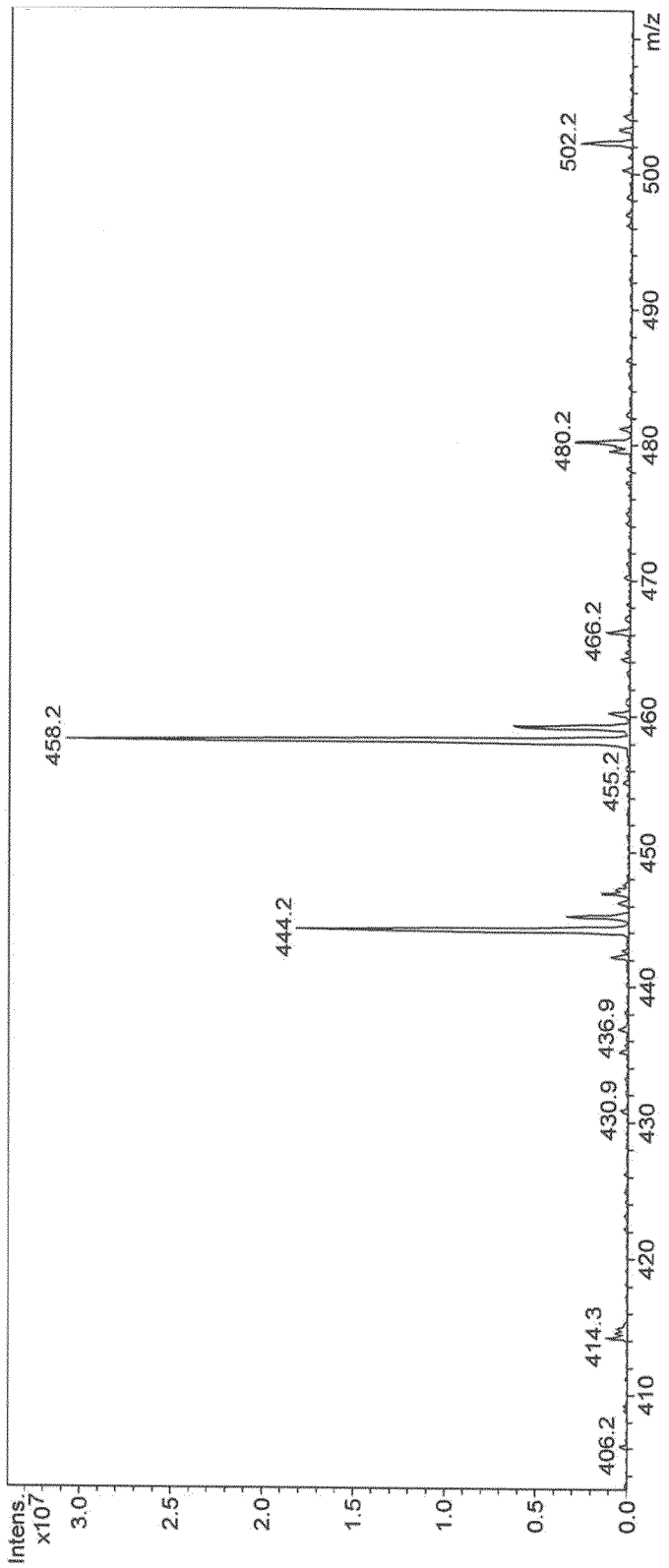
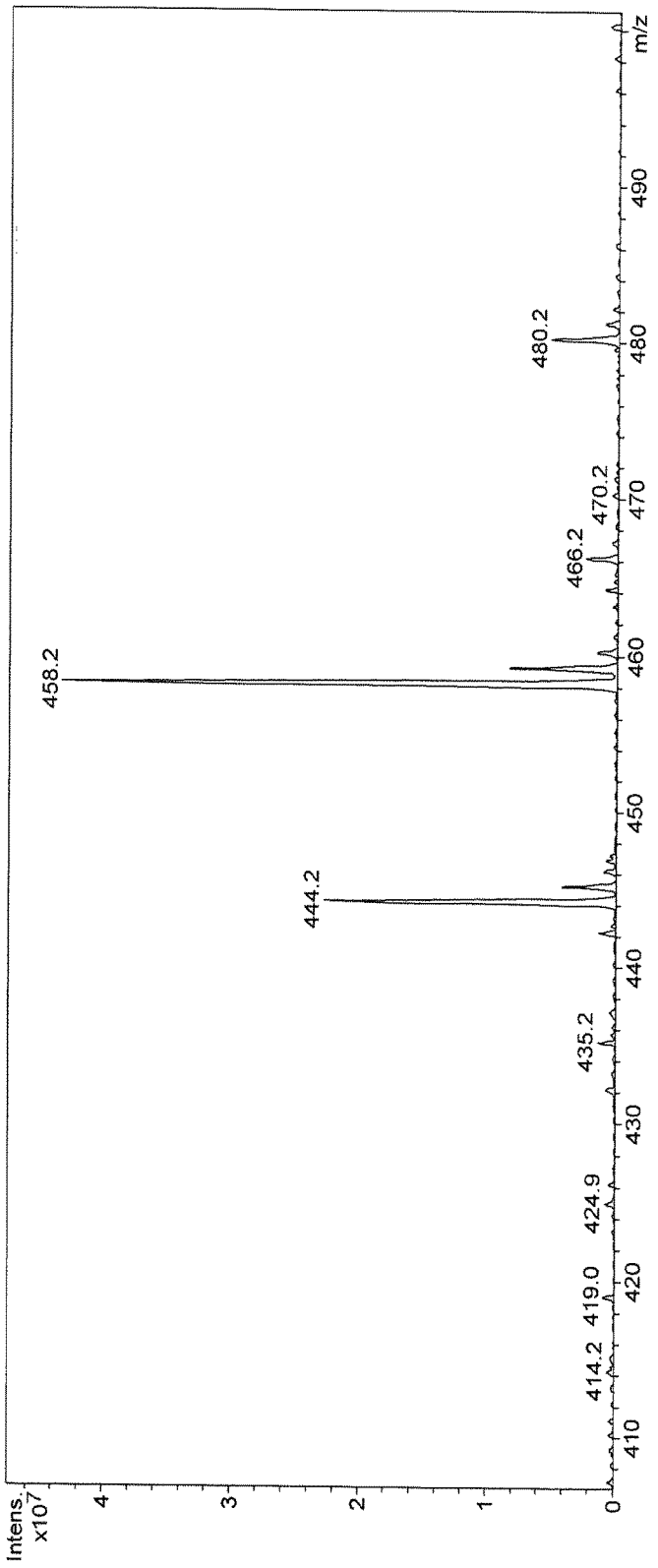

Intens.
x10^7
3.0
2.5
2.0
1.5
1.0
0.5
0.0
406.2
414.3
420
430.9
436.9
440
444.2
450
455.2
458.2
460
466.2
470
480.2
480
490
502.2
500
m/z

Figure 2a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2
1
0
410
414.2
419.0
420
424.9
430
435.2
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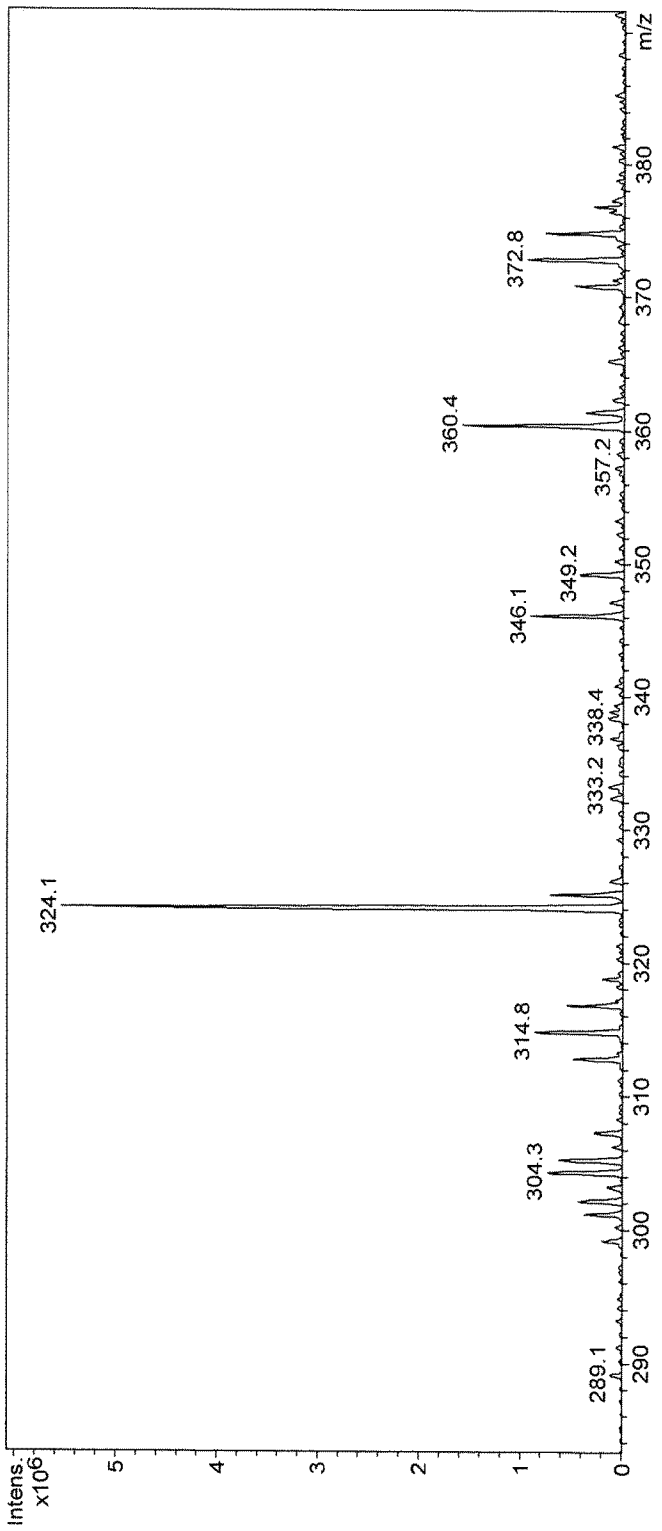
444.2
450
458.2
460
466.2
470.2
470
480.2
480
490
m/z

Figure 2b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3
2
1
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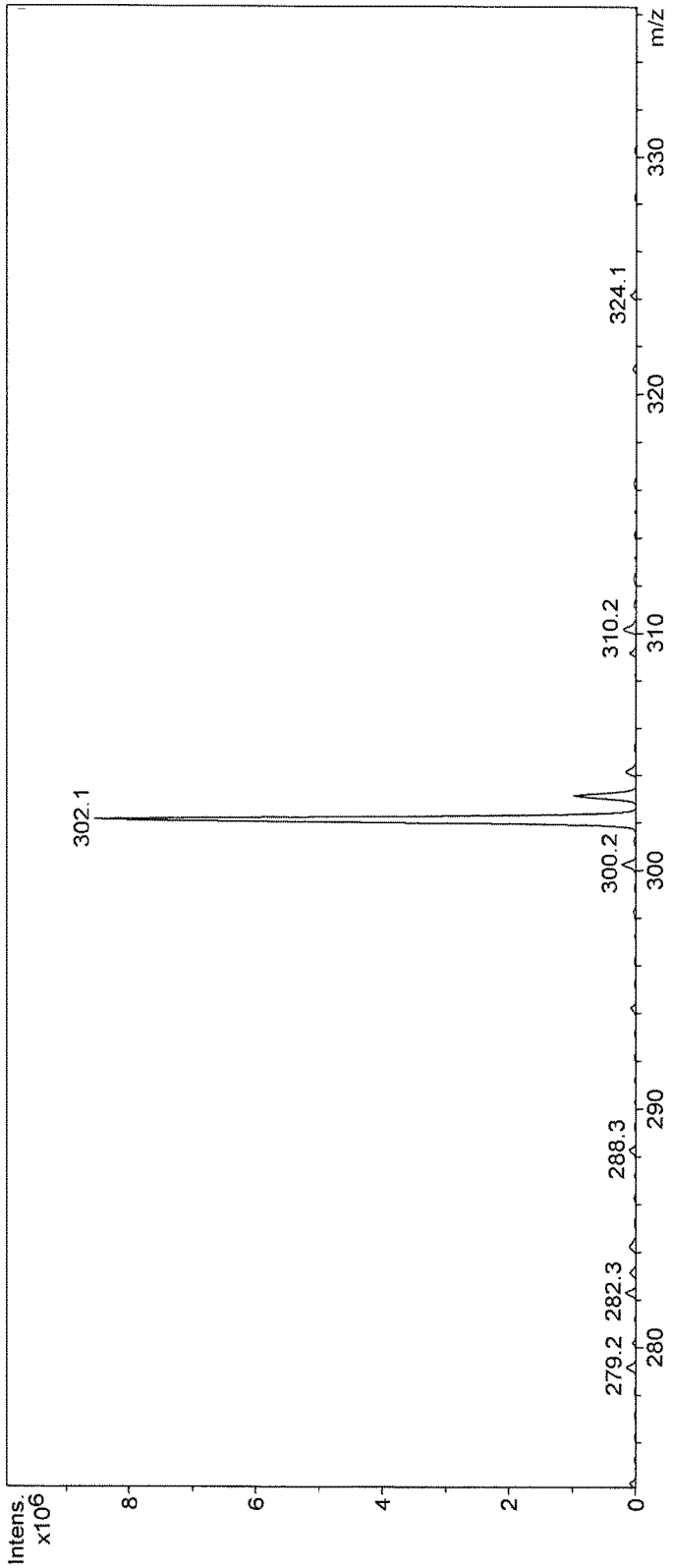
289.1
290
304.3
300
314.8
310
324.1
320
333.2
338.4
330
346.1
349.2
340
357.2
350
360.4
360
372.8
370
380
m/z

Figure 3a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8
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4
2
0
m/z
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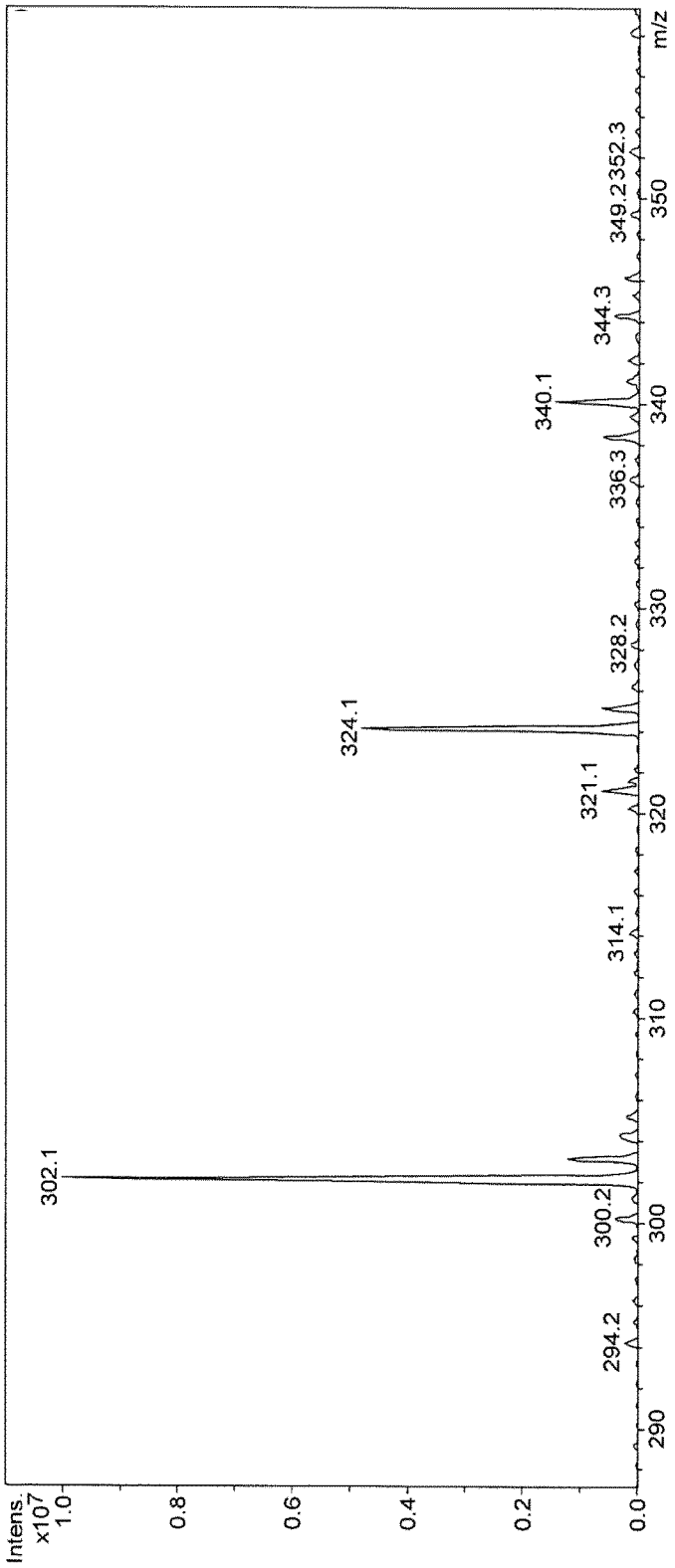
290
300
310
320
330
279.2
282.3
288.3
300.2
302.1
310.2
324.1

Figure 3b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0.6
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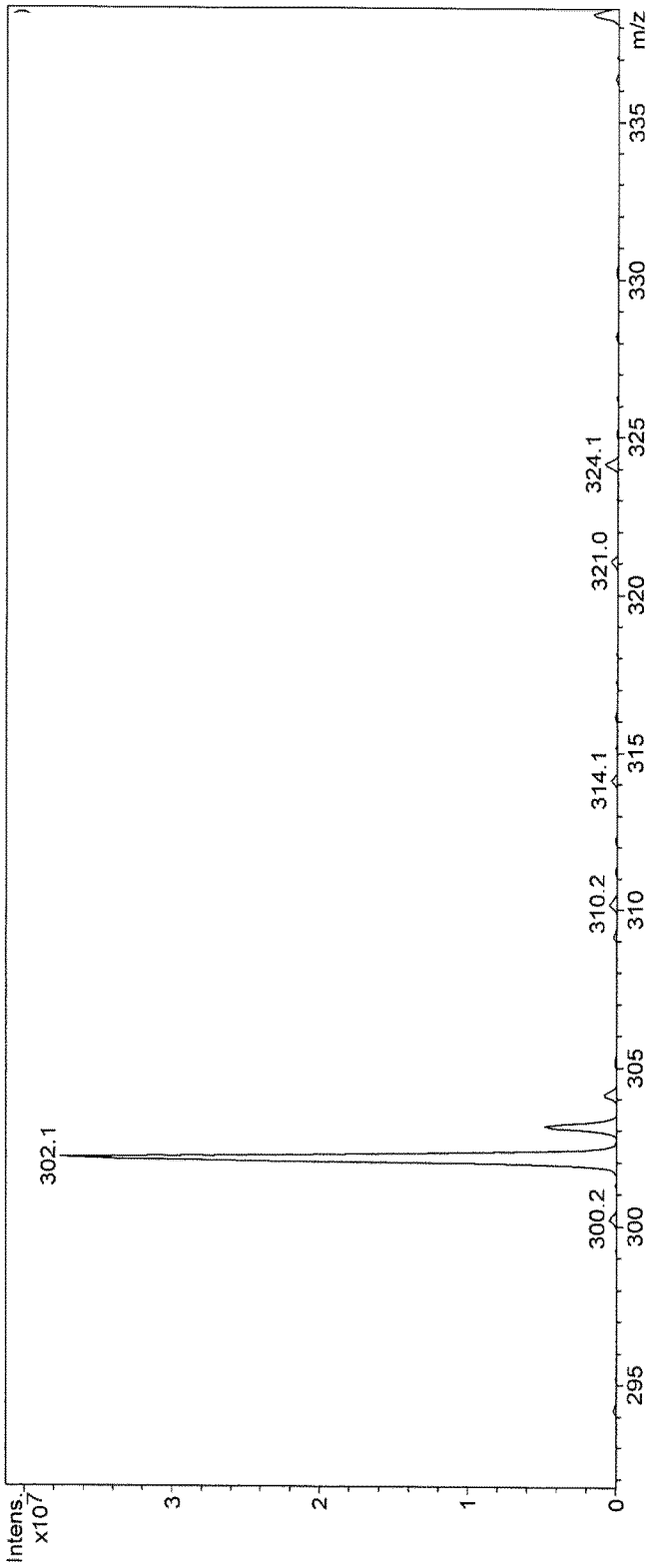
0.2
0.0
290
294.2
300
300.2
302.1
310
314.1
320
321.1
324.1
330
328.2
336.3
340
340.1
344.3
349.2
350
352.3
m/z

Figure 4a


Intens.
x10^7
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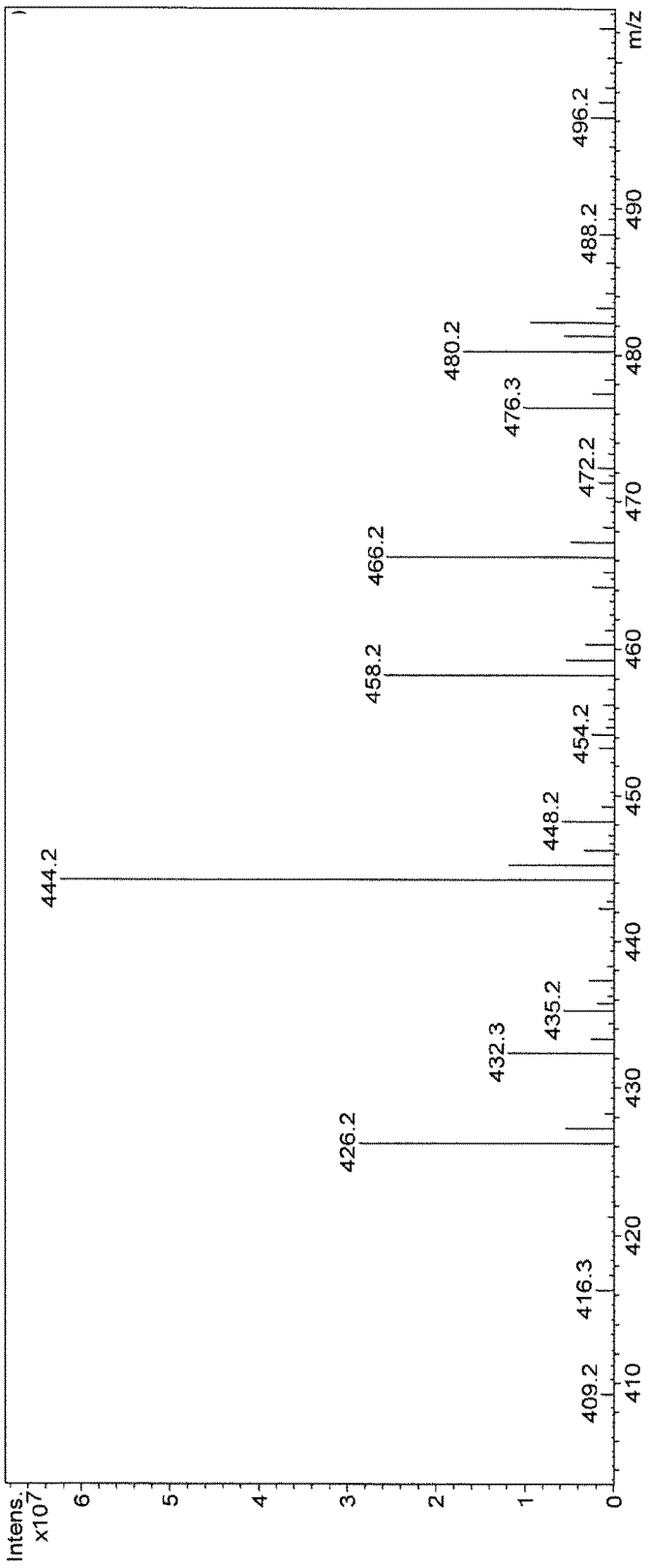
1
0
295
300
305
310
315
320
325
330
335
m/z
300.2
302.1
310.2
314.1
321.0
324.1

Figure 4b


Intens.
x10^7
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4
3
2
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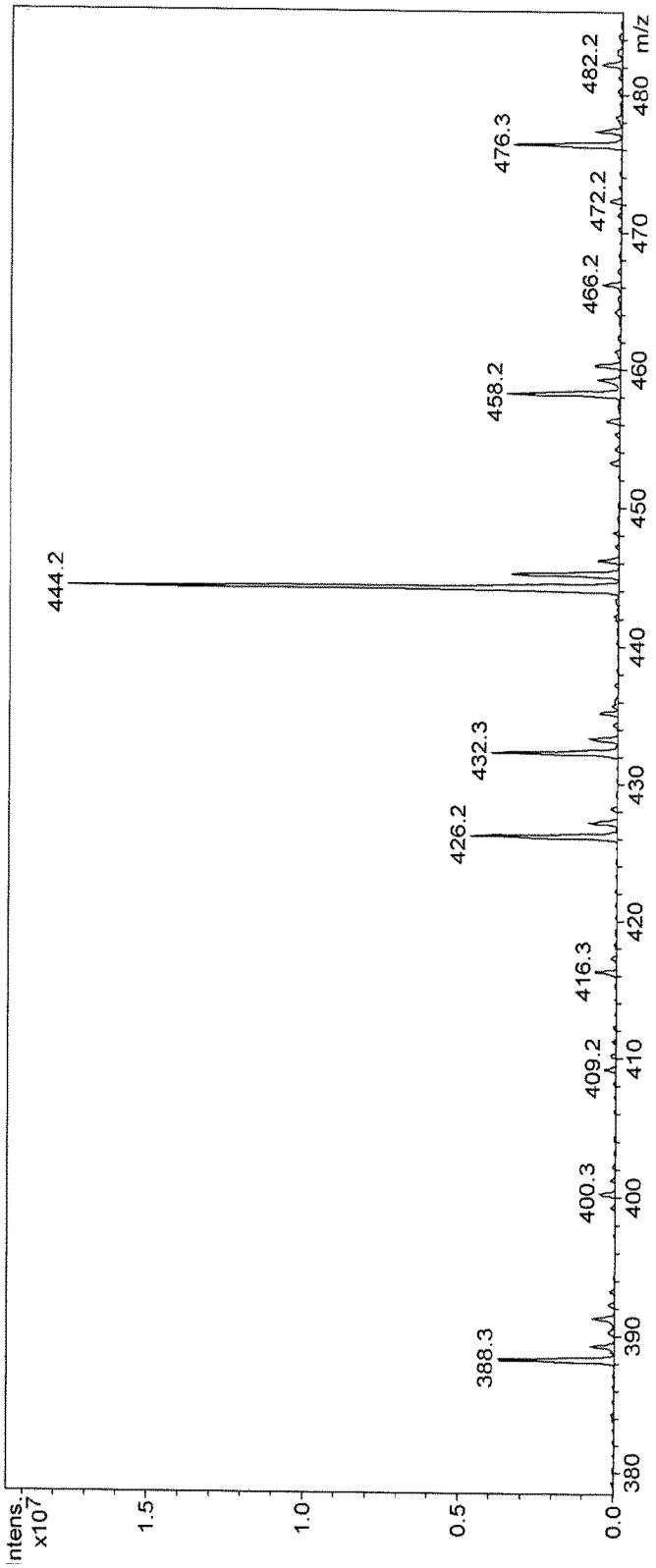
0
409.2
416.3
426.2
432.3
435.2
444.2
448.2
454.2
458.2
466.2
472.2
476.3
480.2
488.2
496.2
410
420
430
440
450
460
470
480
490
m/z

Figure 5a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0.5
0.0
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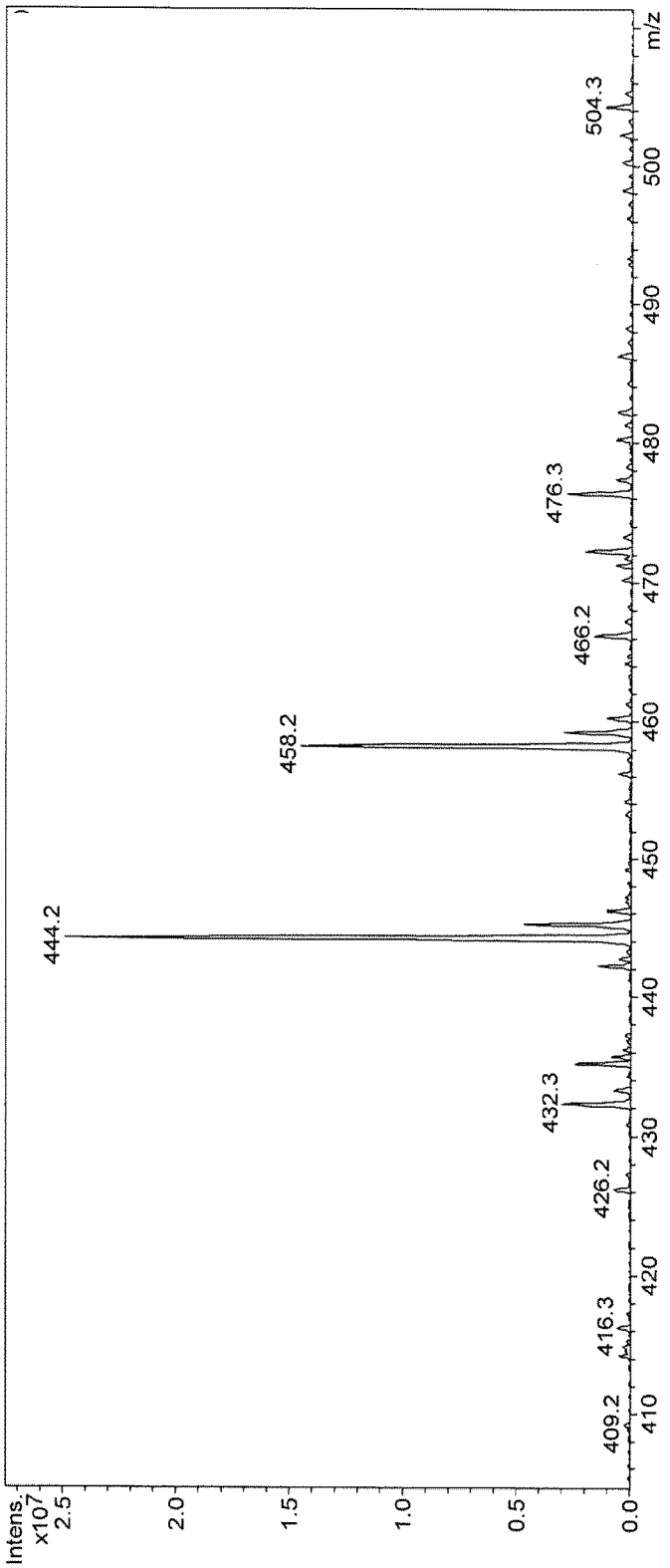
390
400
410
420
430
440
450
460
470
480
m/z
388.3
400.3
409.2
416.3
426.2
432.3
444.2
458.2
466.2
472.2
476.3
482.2

Figure 5b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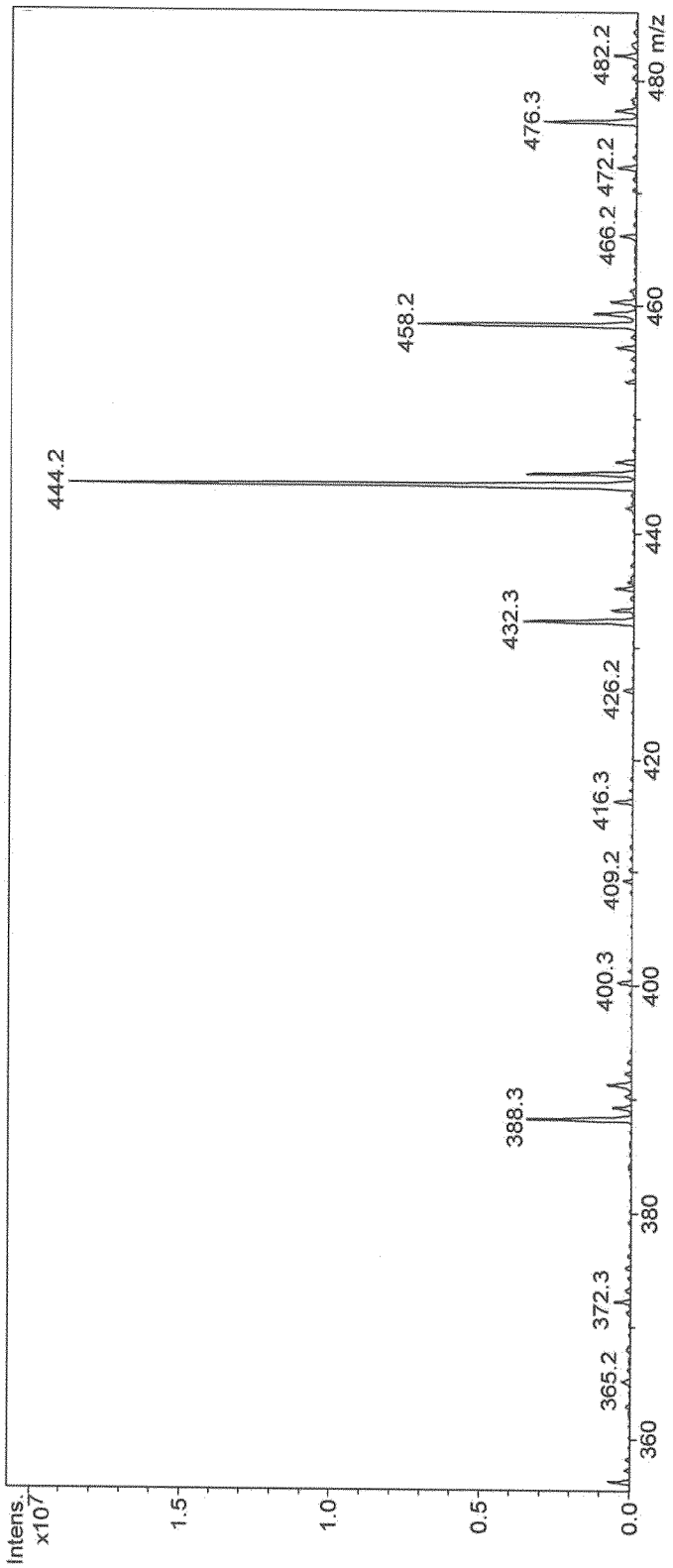
0.5
0.0
409.2
416.3
426.2
432.3
444.2
458.2
466.2
476.3
504.3
410
420
430
440
450
460
470
480
490
500
m/z

Figure 6a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365.2
372.3
380
388.3
400
400.3
409.2
416.3
420
426.2
432.3
440
444.2
460
458.2
466.2
472.2
476.3
482.2
480 m/z

Figure 6b

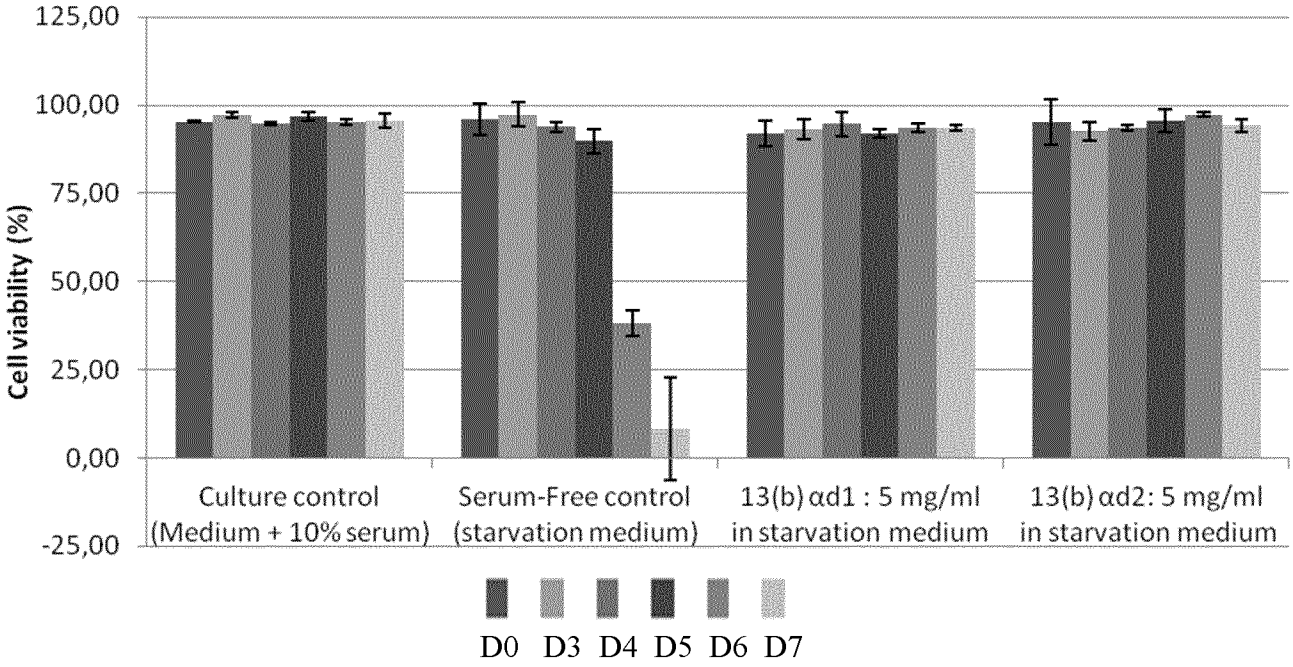
125,00
100,00
75,00
50,00
25,00
0,00
-25,00
Cell viability (%)
Culture control (Medium + 10% serum)
Serum-Free control (starvation medium)
13(b) αd1 : 5 mg/ml in starvation medium
13(b) αd2: 5 mg/ml in starvation medium
D0 D3 D4 D5 D6 D7

Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/073822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D309/10 C07K9/00 A61K38/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/125203 A1 (INST NAT SCIENCES APPLIQ [FR]; CASTELOT DELIENCOURT-GODEFROY [FR]; QUI) 8 November 2007 (2007-11-08) cited in the application	1-21
A	WO 2006/059227 A1 (INSA INST NAT DES SCIENCES APP [FR]; QUIRION JEAN-CHARLES [FR]; CASTEL) 8 June 2006 (2006-06-08)	1-21
A	WO 2004/014928 A2 (INST NAT SCIENCES APPLIQ [FR]; QUIRION JEAN-CHARLES [FR]; PANNECOUCKE) 19 February 2004 (2004-02-19) cited in the application	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2012	20/02/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Klein, Didier

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/073822

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007125203 A1	08-11-2007	BR PI0711156 A2	23-08-2011
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		JP 2006508048 A	09-03-2006
		RU 2369612 C2	10-10-2009
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		WO 2004014928 A2	19-02-2004