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(54) Title: NOVEL DIHYDROXYPYRROLIDINE DERIVATIVES AS ANTI-CANCER AGENTS

(57) Abstract: The present invention provides new dihydroxypyrrolidine derivatives for use as medicaments. The compounds are useful in the treatment in cancer, in particular non-solid neoplasms.

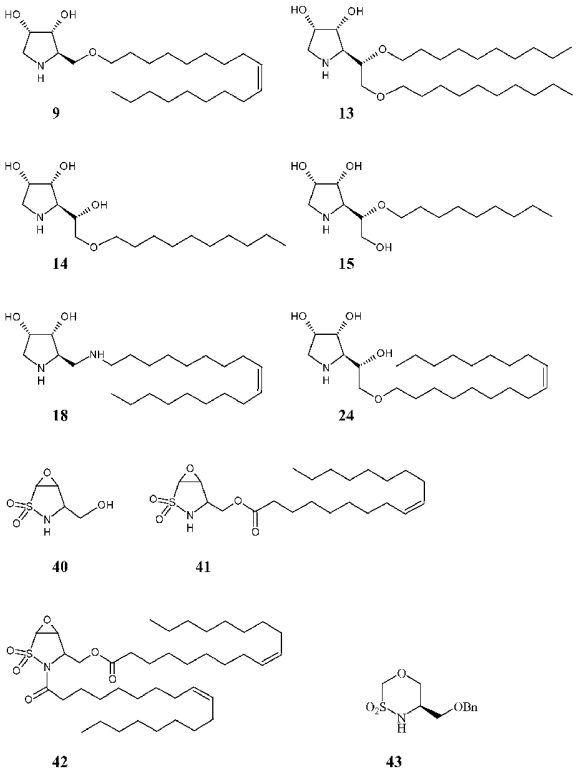

Figure 1

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NOVEL DIHYDROXYPYRROLIDINE DERIVATIVES AS ANTI-CANCER AGENTS

Technical Field

The present invention relates to novel compounds for use as medicaments. More particularly, the novel compounds are toxic to cancer cells and are therefore useful in the treatment of cancer.

Background of the Invention and Problem to be Solved

The specific inhibition of α-mannosidases has already been proposed as an anti-cancer strategy, in particular because catabolic and processing glycosidases were shown to be involved in the transformation of normal cells to cancer cells.

H. Fiaux et al. (J. Med. Chem. 2005, 48, 4237-46) disclose functionalised pyrrolidines that inhibit α-mannosidase and growth of human glioblastoma and melanoma cells. However, several of the dihydroxypyrrolidine derivatives disclosed in this paper actually had high inhibitory effects on α-mannosidase but only little or no anti-cancer effect. Interestingly, swainsonine, an α-mannosidase inhibitor of which anti-tumoral properties were reported previously, had only little inhibitory effect on glioblastoma cell growth.

S. Favre et al. (Heterocycles, Vol. 69, 2006) report 2-benzylamino-3,4-dihydroxypyrrolidines bearing aromatic and aliphatic amido side chains as specific inhibitors of α-mannosidase and of the growth of human glioblastoma cells. While many of the compounds disclosed in this reference show inhibititory effects of α-mannosidase, only one specimen, (N-[(2*R*)-2-({[(2*R*,3*R*,4*S*)-3,4-dihydroxypyrrolidin-2-yl]methyl}amino)-2-phenylethyl]-3-bromobenz-amide) showed convincing inhibition of human glioblastoma cells.

In view of the prior art, it is an objective of the present invention to provide new derivatives of dihydroxypyrrolidines that are useful in the treatment of cancer.

It is a further objective to provide compounds that are capable of attacking at several targets, not only the α-mannosidases. It is a particular objective underlying the present invention to provide derivatives of dihydroxypyrrolidines that inhibit, besides α-mannosidases, also nicotinamide phosphoribosyltransferase.

It is another objective of the present invention to provide new compounds that are suitable to specifically inhibit tumor cells while not or only to a lesser extent affecting healthy cells.

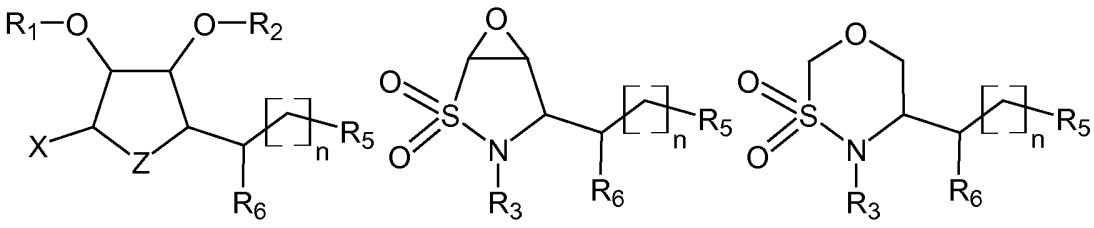
A further objective of the present invention is to provide compounds useful in the treatment of cancer, wherein said compounds show improved internalization by the tumor cells if compared to compounds of the prior art.

It is another objective of the present invention to provide a new anticancer strategy able to overcome resistance to conventional chemotherapeutic agents, for example for the treatment of human glioblastome and metastatic melanoma, for which only very few therapeutic options exist by now.

Summary of the Invention

The present inventors developed new derivatives of dihydroxypyrrolidine, which exhibit high toxicity towards cancer cells.

Accordingly, in a first aspect, the present invention provides an isolated compound of a formula selected from formulae (I), (II) and (III):



(I) (II) (III)

wherein:

in formula (I), Z is selected from –O-, -N(-R_3)-, -N(-O-R_3)-, -N(-C(=O)-R_3)-, -N(SO_2R_3)-, -S-, -S(=O)-, and -S(O_2)-;

R_1, R_2 and R_3 are selected, independently of each other, from H, C1-C26 alkyl, C1-C26 acyl, C2-C26 alkenyl, C2-C26 alkynyl, C6-C26 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms;

R_5 is a C0-C30, preferably C0-C26 hydrocarbon substituent comprising one or more heteroatoms selected from O, N, S, B, P and halogen, in particular F, Cl, I, Br;

n is 0, 1 or 2;

R_6 is H if n = 0; and if n = 1 or 2, R_6 is selected, independently from any other substituent, from H and from substituents as R_5;

X is selected from H, C6-C26 aryl, 5-membered and six membered heterocycle, wherein said aryl and said heterocycle may be further substituted;

wherein the compound of formula (I) , (II) or (III) may be charged or neutral, may be present in the form of a salt and/or an optically resolved enantiomer. For example, the compound may be provided in the form of a pharmaceutically acceptable salt.

Without wishing to be bound by theory, it is believed that the compounds according to the present invention act by a so far un-known mode of action. It is speculated about the

possibility that the compounds act as inhibitors of nicotinamide phosphoribosyltransferase (NMPTRase). However, it is probable that a further cellular target(s) is (are) involved.

Brief Description of the Drawings

In the drawings,

Figure 1 shows chemical structures of specific embodiments of compounds according to the present invention.

Figure 2 schematically illustrates the synthesis of a starting product (compound **6**) used for synthesising the compounds of the present invention.

Figure 3 schematically illustrates the synthesis of compound **9** according to the present invention.

Figure 4 schematically illustrates the synthesis of compound **13** and a mixture of compounds **14** and **15** according to the present invention.

Figure 5 schematically illustrates the synthesis of compound **18** according to the present invention.

Figure 6 schematically illustrates the synthesis of compound **24** according to the present invention.

Figure 7 schematically illustrates the synthesis of compound **40** according to the present invention.

Figure 8 schematically illustrates the synthesis of compounds **41** and **42** according to the present invention.

Figure 9 schematically illustrates the synthesis of compound **43** according to the present invention.

Figure 10 schematically illustrates the synthesis of compounds **48, 49** and **51** according to the present invention.

Figure 11 schematically illustrates the synthesis of compounds **70** and **72** according to the present invention.

Figure 12 schematically illustrates the synthesis of compounds **73-76** according to the present invention.

Figure 13 schematically illustrates the synthesis of compounds **78** and **80** according to the present invention.

Figure 14 schematically illustrates the synthesis of compounds **82** and **84** according to the present invention.

Figure 15 schematically illustrates the synthesis of compounds **85-89** according to the present invention.

Figure 16 schematically illustrates the synthesis of compounds **90-95** according to the present invention.

Figure 17 schematically illustrates the synthesis of compounds and strating materials for compounds according to the present invention.

Figure 18 schematically illustrates the synthesis of compound **104** according to the present invention.

Figure 19 schematically illustrates the synthesis of compound **107** according to the present invention.

Figure 20 schematically illustrates the synthesis of compound **152** according to the present invention.

Figure 21 schematically illustrates the synthesis of compounds **153** and **154** according to the present invention.

Figure 22 schematically illustrates the synthesis of compounds **155** and **156** according to the present invention.

Figure 23 schematically illustrates the synthesis of compound **157** according to the present invention.

Figure 24 schematically illustrates the synthesis of compound **159** according to the present invention.

Figure 25 schematically illustrates the synthesis of compound **160** according to the present invention.

Figure 26 schematically illustrates the synthesis of compounds **162** and **163** according to the present invention.

Figure 27 schematically illustrates the synthesis of compounds **165** and **166** according to the present invention.

Figure 28 schematically illustrates the synthesis of compound **172** according to the present invention.

Figure 29 schematically illustrates the synthesis of compound **176** according to the present invention.

Figure 30 shows the viability of U87 (glioblastoma) tumor cell lines following exposure to different concentrations of CB264, compound **9** of the present invention. CB183 is a a different compound shown for the purpose of comparison.

Figure 31 shows photographs of various cell lines in magnification through a microscope. Cell lines were treated with compounds of the invention or left untreated. CB264 corresponds to compound 9 of the present invention, whereas compounds CB161 and CB183 are different anti-cancer compounds provided for comparison.

Figure 32 A and **B** show a cell cycle analysis following the treatment or not of cell line SKBR3 with CB264 (compound **9**) of the present invention. Treatment with compound **9** resulted in cell cycle arrest in G1-phase upon exposure to low compound concentrations (2 μM for this cell line)

Figure 33 A-D shows a cell cycle analysis following exposure of cell line SKBR3 to various concentrations of CB264 (compound **9**) of the present invention. It can be seen that higher CB264 concentrations led to cell demise with DNA fragmentation and appearance of hypodyploid cell nuclei.

Detailed Description of the Preferred Embodiments

The present invention provides an isolated compound according to formula (I), (II) and (III). Accordingly, the present invention provides a compound selected from formula (I), (II) and (III), but also mixtures of compounds comprising two or more of compounds of formula (I), (II) and (III). For the purpose of the present specification, the term "comprises" or "comprising" is intended to mean "includes amongst other", it is not intended to mean, "consists only of".

According to an embodiment, substituents R_1, R_2 and R_3 are selected, independently of each other, from H, C1-C26 alkyl, C1-C26 acyl, C2-C26 alkenyl, C2-C26 alkynyl, C6-C26 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms.

More preferably, the substituents R_1, R_2 and R_3 are selected from H and C1-C20 compounds, more preferably H and C1-C15, and most preferably H and C1-C10 compounds. Of course, if R_1, R_2 and R_3 is an alkenyl, it comprises at least 2 carbons and if it is an aryl at least 6 (phenyl).

An "alkyl", for the purpose of the present specification, may be linear or, if it comprises 3 or more carbons, branched and/or cyclic. For example, an alkyl may thus be branched and cyclic, if it is, for example, a cyclic alkyl in which a hydrogen atom of a ring carbon is substituted by a linear alkyl. Preferably, however, the alkyl is linear. A substituted alkyl may be, for example an aralkyl (= arylalkyl = arylated alkyl), where an H of the basic alkyl is substituted with an aryl.

An "alkenyl", for the purpose of the present specification, may be linear or, if it comprises 3 or more carbons, branched and/or cyclic may. In analogy to the alkyl as defined above, the alkenyl may be cyclic and branched. The alkenyl comprises one or more double bonds.

An "alkynyl" for the purpose of the present specification, may be linear or, if it comprises 5 or more carbons, branched and/or comprise a cylce. The alkynyl comprises one or more triple bonds. If the alkynyl is branched and/or cyclic, the branching and/or the cycle does, of course, not involve a carbon that is connected by way of a triple bond to another carbon.

An "acyl" for the purpose of the present invention, also known as an alkanoyl, could also be regarded as a hydrocarbon comprising an oxygen heteroatom (carbonyl group) at the

C1 carbon of the substituent. The acyl is of the general formula –C(=O)-Rx, wherein Rx is a linear, cyclic and/or branched hydrocarbon optionally comprising one or more heteroatoms and optionally further substituted, for example, Rx is an alkyl, alkenyl, alkynyl or aryl as defined herein. The acyl group is usually derived from a carboxylic acid, but may be also derived from other types of acids, such as sulfonic acids, phosphonic acids, for example.

An "aryl", for the purpose of the present invention, is a substituent comprising a aromatic ring, which is connected by way of a single bond to the basic structure, for example to the structure of formula (I), (II) and (III). A benzyl is also considered as an aryl, but substituents having a bridge of more than one carbon between the aromatic ring and the basic structure comprising the substituent would no longer be aryls. For illustrating this principle, an example of an arylated alkyl is taken: e.g. the substituent -1-ethyl-2-phenyl is an arylated alkyl, and therefore a substituted alkyl as defined above, and not an aryl. Besides phenyl, the term "aryl" also encompasses substituents based on condensed aromatic systems, such as naphthalin, anthracen, phenanthren, pentalene, indene, azulen, chrysen, tetracen, for example. The aromatic ring may comprise heteroatoms, for example nitrogen. Examples are pyridine, pyrazin, pyrimidin, pyridazine, purine, an example of a condensed system with N-heteroatoms is chinnoline. Other aromatic rings with heteroatoms are thiophene, furane, benzofurane, for example.

The aryl according to the present invention may be further substituted, for example by an alkyl, alkenyl, acyl, alkynyl, aryl and/or heteroatoms as defined herein.

The alkyl, alkenyl, alkynyl, acyl and aryl as defined above may comprise one or more heteroatoms. Heteroatoms may be selected from any atom that replaces a carbon atom in the basic structure of the alkyl, alkenyl, acyl and aryl, or may be present in the form of a functional group. Preferably, the heteroatom is selected from O, N, S, P, halogen, B, more preferably, from O, N, and halogen, in particular F, Cl, and Br.

Preferably, in formula (I), Z is selected from –N(-R_3)-, with R_3 being defined as R_1 and R_2, but independently of the latter. Most preferably, R_3 is H.

More preferably, R_1, R_2 and R_3 are independently selected from:

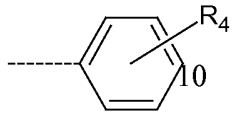
- H;
- C1-C5 acyl (optionally substituted, for example by halogen (for example: -C(=O)CH_3 (acetyl), -C(=O)CH_2Cl (2-chloro-acetyl), -C(=O)CH_2F (2-fluoro-acetyl));
- any aminoacid, which is linked by her carboxyl group to form an acyl with the compound of formula (I). Preferably, the amino acid is an α-aminoacid. Preferably, the aminoacid is selected from proteinogenic amino acids. for example, α-glycin, α-alanin, α-phenylalanin, α-glycine, serine, just to mention a few.

R_1 and R_2 may be the same or may be different. They may also form an acetal, such as an acetal connecting the two oxygen groups by –$CR_{1X}R_{2X}$-, wherein R_{1X} R_{2X} are independently selected from H, C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl and C6-C12

aryl as defined above. Specific examples are $-CH_2-$ (methylene), -CHMe-, (methylmethylene), -CHPh-, (phenylmethylene), $-CMe_2-$ (dimethylmethylene), and so forth.

If, in a compound of formula (I) above, X is a C6-C30 aryl, it may be selected, for example, from unsubstituted and substituted phenyl. If X is a substituted phenyl, it preferably is only once substituted, preferably 3-substituted (para position). Substituents in ortho and meta position are, however, also possible.

According to a preferred embodiment, X is a substituent of formula (VII)



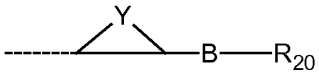
(VII)

wherein R_4 is C1-C24 hydrocarbon optionally comprising one or more heteroatoms and optionally being substituted.

R_4 may be selected from a C1-C24 alkyl, C2-C24 alkenyl, C2-C24 alkynyl, C1-C24 acyl, as defined above. It may comprise one or more heteroatoms.

Particular examples of R_4 are:

$-CO-R_{20}$, $-COO-R_{20}$, $-CONH-R_{20}$, $-C(S)NHR_{20}$, $-CH_2CO-R_{20}$, $-CH_2COO-R_{20}$, $-CH_2CON-R_{20}$ (carboxamides), $-CH_2C(S)NH-R_{20}$ (thionocarboxamides), $-CH_2NHCONH-R_{20}$ (ureas), $-CH_2NHCSNH-R_{20}$, (thioureas), (E)- and (Z)-CH=CHCO-R_{20}, (E)- and (Z)-CH=CHCONH-R20 , (E)- and (Z)-CH=CHCOO-R20, -CH2-CH2CO-R20, -CH2-CH2-CONH-R20, -CH2-CH2-COO-R20, a substituent of formula (VIII),



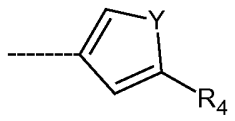
(VIII), wherein Y is selected from $-CH_2-$ and –O-; and B is selected, independently, from –CO-, -CONH-, -COO-; wherein further examples of R_4 are:

-NH, -N-(C1-C10 alkyl), -N-(C1-C10 acyl) (e.g. acetamide, formamide), and $-O-CH_2CO-R_{20}$.

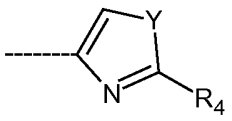
R_{20} may be selected from the same substituents as R_{10} as defined further below, with the proviso that R_{20} comprises not more than 20 carbons. Preferably, R_{20} is selected amongst a C1-C20 alkyl, as well as from alk-m-enyl, alk-m,o-dienyl, alk-m-ynyl, alk-m-en-o-ynyl, a alk-o-en-m-ynyl, wherein each m and o is defined, respectively, as with R_{10} below (with the proviso that R_{20} does not comprise more than 20 carbons). Regarding the (E) and (Z) configuration, the same as with R_{10} applies.

In substituent (VII) above, R_4 is preferably in the para position.

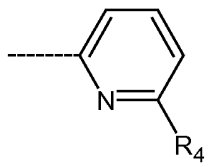
In case that, in a compound of formula (I) above, X is a C5-C26 five-membered or six-membered heterocycle, which may be substituted, the heterocycle may be selected, for example from substituents (IX), (X), (XI), (XII), and (XIII) shown below:



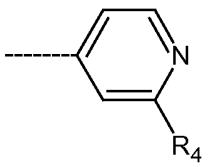
(IX)



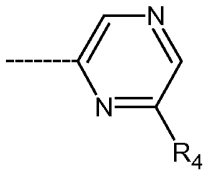
(X)



(XI)



(XII)



(XIII)

wherein R_4 is defined as above.

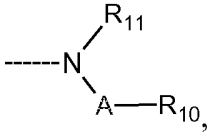
Preferably, X is –H.

According tom an embodiment, R_5 is a C7-C30, preferably a C8-C30, more preferably a C9 or C10 to C30 hydrocarbon. According to a more specific embodiment, R_5 is a C7-C26, a C8-C26, a C9-C26 and more preferably a C10-C26 hydrocarbon comprising one or more heteroatoms selected from O, N, S, B, P and halogen, in particular F, Cl, I, Br.

Preferably, R_5 comprises a hydrophobic tail comprising at least 7, 8, 9, and more preferably at least 10 carbons, in which a polar heteroatom, such as oxygen, nitrogen or sulphur is absent. Preferably, said heteroatom, if present in R_5, is provided close to the attachment of R_5 to the general structure of formula (I), (II) or (III). Preferably, R_5 is selected from substituents of formula –A-R, wherein a is a heteroatom containing group, for example –NH-, -O-, -S-, and other examples as provided below, and R is said hydrocarbon as defined above, or as R_{10} defined below, preferably devoid of any further heteroatom, unless, but less preferred, said heteroatom is a halogen. Preferably, said R is free of any heteroatom.

According to an embodiment of the present invention, $–R_5$ is selected from:

-O-A-R_{10},



-S-R_{10},

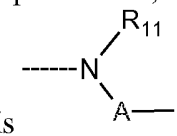
-S(=O)-R_{10},

-S(O_2)- R_{10} and,

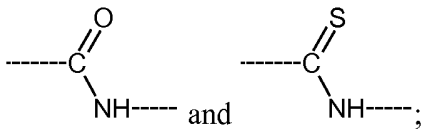
-O-(α or β) glycopyranosyl;

wherein:

A is optional and, if present, is selected from –C(=O)- , -S(-O)-, -S(=O)-, and, if

$–R_5$ is 

, and R_{11} = H, A may also be selected from:



R_{11} is defined as R_{10} below, and/or is selected from: H, -OH, C1-C10 alkyl, C1-C10 alkoxyl, C1-C10 acyl, said alkyl, alkoxyl and acyl optionally being substituted and optionally comprising 1 or more heteroatoms;

R_{10} is selected from H, C1-C30 alkyl, C1-C30 acyl, C2-C30 alkenyl, C2-C30 alkynyl, C4-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms (a C4 and C5 aryl comprises at least one heteroatom, thereby providing an aromatic ring of at least 5 atoms). Preferably, said heteratoms are halogen, more preferably, there are no heteroatoms. Preferably, R_{10} is selected from C8-C30 alkyl, C8-C30 acyl, C8-C30 alkenyl, C8-C30 alkynyl, C8-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms, as indicated above. More preferably, R_{10} is selected from C9-C30 alkyl, C9-C30 acyl, C9-C30 alkenyl, C9-C30 alkynyl, C9-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms, as indicated above. Most preferably, R_{10} is selected from C10-C30 alkyl, C10-C30 acyl, C10-C30 alkenyl, C10-C30 alkynyl, C10-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms, as indicated above. According to an embodiment, said embodiments of alkyl, acyl, alkenyl, alkynyl, and aryl may have up to 26 carbons.

According to a preferred embodiment, R_{10} is selected from H, C1-C26 alkyl, C1-C26 acyl, C2-C26 alkenyl, C2-C26 alkynyl, C6-C26 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms.

According to an embodiment of R_5, A is absent.

According to a preferred embodiment, R_5 is selected from $-O-R_{10}$ and $-NH-R_{10}$.

Preferably, n = 0.

According to preferred embodiment, R_{10} is selected from:

a C2- C30, preferably C8-C30, a C9-C30, a C10-C30, most preferably a C8-C26 alk-m-enyl, wherein m indicates the position of a single double bond and is an integer from 2-16;

a C5-C30, preferably C8-C30, a C9-C30, a C10-C30, most preferably a C8-C26 alk-m,o-dienyl, with m being as defined above, o indicates the position of a second double bond and o = m+i, with i being an integer of 2-16;

a C3-C30, preferably C8-C30, a C9-C30, a C10-C30, most preferably a C8-C26 alk-m-ynyl, with m being as defined above;

a C5-C30, preferably C8-C30, a C9-C30, a C10-C30, most preferably a C8-C26 alk-m-en-o-ynyl, with m and o being as defined above, but with o indicating the position of a triple bond;

a C5-C30, preferably C8-C30, a C9-C30, a C10-C30, most preferably a C8-C26 alk-o-en-m-ynyl, with m and o being as defined above, but with o indicating the position of the double bond and m indicating the position of a triple bond.

According to an embodiment,

if R_{10} comprises a single double bond, R_{10} may have a (Z) or and (E) configuration,

if R_{10} is a dienyl, it may have (E,E), (E,Z), (Z,E), or (Z,Z) configuration,

if R_{10} is alkenynyl, it may have a (Z) or and (E) configuration.

According to another embodiment, R_{10} is selected from:

a C2- C26 alk-m-enyl, wherein m indicates the position of a single double bond and is an integer from 2-16;

a C5-C26 alk-m,o-dienyl, with m being as defined above, o indicates the position of a second double bond and o = m+i, with i being an integer of 2-16;

a C3-C26 alk-m-ynyl, with m being as defined above;

a C5-C26 alk-m-en-o-ynyl, with m and o being as defined above, but with o indicating the position of a triple bond;

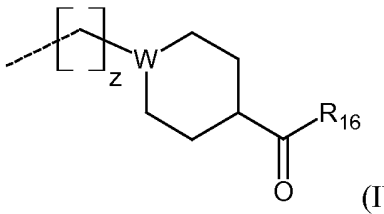
a C5-C26 alk-o-en-m-ynyl, with m and o being as defined above, but with o indicating the position of the double bond and m indicating the position of a triple bond;

otherwise as being defined above in terms of (Z) and (E) configuration.

According to an embodiment, R_{10} is selected from (1) and (2) as defined below:

(1) $-CH_2CH_2O-(CH_2CH_2O)_i-R_{15}$, wherein i is 0 or an integer of 1-6;

(2) a substituent of formula (IV):



(IV), wherein Z is an integer of 1-5 and W is selected, independently, from CH and N;

wherein R_{15} is selected, independently from other substituents, from H, C1-C10 alkyl, C2-C10 alkenyl and from a substituent of formula (IV);

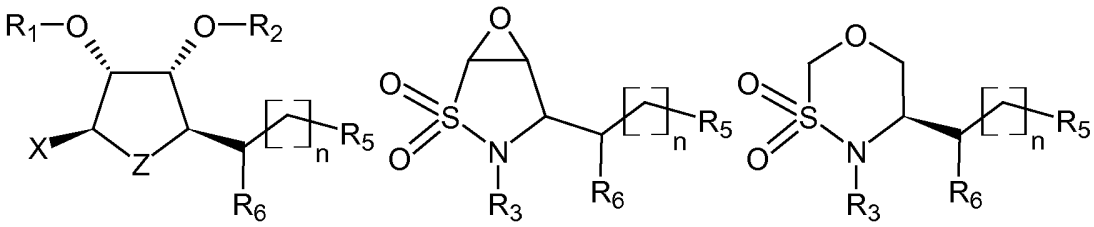
wherein R_{16} is selected from H, C1-C10 alkyl, C2-C10 alkenyl, C6-C12 aryl, -OH, -O-R_{17}, -NH-R_{17}, -NMe-R_{17};

wherein -R_{17} is selected from H, C1-C10 alkyl, C2-C10 alkenyl, C6-C12 aryl.

According to an embodiment, R_{10} is a C8-C26, preferably C9-C26, more preferably a C10-C26 alkenyl, which may optionally be further substituted.

. Most preferably, R_{10} is $(CH_2)_8CH=CH(CH_2)_7-CH_3$.

According to a preferred embodiment, R_3 in the compound of formula (VIII) is H. According to an embodiment, the compound of the invention is selected from a compound of formula (V), (VI) and (VII):



(V) (VI) (VII)

compounds of any one of the preceding claims, wherein:

n=0,

R_5 and R_6 is selected from H, -O-R_{10} and –NH-R_{10}, with R_{10} being as defined in Claims 3-6;

with the proviso that one of R_5 or R_6 is H and the other, R_6 or R_5, respectively, is selected from -O-R_{10} and –NH-R_{10}.

According to an embodiment, the compound is selected from:

(2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol,

(2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-ylamino]methyl}pyrrolidine-3,4-diol, and,

(2R,3R,4S)-2-{(1S)-1-hydroxy-2-[(9Z)-octadec-9-en-1-yloxy]ethyl} pyrrolidine-3,4-diol.

According to an embodiment, the compound of the invention is selected from any one of compounds 9 (=47), 48, 49, 51, 18, 20, 24, 24-is, 67, 68, 74, 75, 76, 80, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 104, 164, 165, 172 as more specifically defined in the examples and the figures, wherein said compounds may be charged or neutral, and which may be present in the form of a salt and/or an optically resolved enantiomer.

According to an embodiment, R_6 is H, n=0 and R_5 is selected from R_5 is as defined above, and preferably selected from –O-R_{10} and –NH-R_{10}.

According to another embodiment, n = 1, and R_5 and R_6 are not H.

According to another embodiment, n=1, R_5 is selected from –OH and –NH_2, and R_6 is as defined above, and preferably selected from –O-R_{10} and –NH-R_{10}.

According to another embodiment, if R_5 is does not contain any carbon, R_6 is different from H.

According to an embodiment, at least one but optionally both selected from R_5 and R_6 contains at least 6, preferably at least 10 carbons. Preferably, at least one but optionally both selected from R_5 and R_6 comprise(s) a hydrophobic part.

According to an embodiment, especially concerning compounds (II) and (III), R_5 is selected from (a) a C1-C26 acyl, said acyl optionally comprising at least one double bond and said acyl preferably being free of any further heteroatom besides the oxygen atoms of the acyl group, (b) C1-C26 alkoxyl, (c) C1-C26 alkenoxyl, (d) C6-C26 aroxyl (said aroxyl including phenoxyl and benzyloxyl, for example), wherein said acyl, alkoxyl, alkenoxyl, aroxyl may further substituted. Said further substituents being selected, preferably, from halogen and hydrocarbons free of heteroatoms other than halogen. Preferably, in compound (II), n = 0 and R_6=H.

Optically pure enantiomers, mixures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form, as well as pharmaceutically acceptable salts, solvent complexes and morphological forms of the compounds disclosed herein are also encompassed by the present invention.

The expression pharmaceutical acceptable derivatives and derivatives also encompasses, but is not limited to, salts.

According to a preferred embodiment of the present invention, the compounds of the present invention are used as medicaments.

The invention provides compounds as defined above, or prodrugs or solvates thereof ("active compounds"), for use in a method of treatment of the human or animal body. A method of treatment may comprise administering to such an individual a therapeutically effective amount of the compound of the present invention, preferably in the form of a pharmaceutical composition. The term treatment as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or animal (e.g. in veterinary applications), in which some therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of the progress, a halt in the rate of the progress, amelioration of the condition, and cure of the condition. The condition usually is associated with suffering, from psychological and/or physical pain, with the individual being in need of a treatment. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The compound of the invention or pharmaceutical composition comprising the active compound may be administered to an individual by any convenient route of administration, whether systemically /peripherically or at the site of desired action, including but not limited to, oral (e.g. by ingestion), topical (including e.g. transdermal, intranasal, ocular, buccal and sublingual), pulmonary (e.g. by inhalation or insufflation therapy using an aerosol, e.g. through mouth or nose), rectal, vaginal, parenteral, for example by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, subcuticula, subcapsular, intraorbital, intraperitoneal, intratracheal, subarachnoid, and intrasternal, by implant of a depot (e.g. subcutaneously or intramuscularly).

More particularly, according to a preferred embodiment, the compound according to the invention is used in the treatment and/or prevention of cancer and/or metastasis. With many cancers, tumors may be removed surgically, with the occurrence of metastasis remaining the principle problem to which so far no convincing remedy has been found.

More particularly, the compounds of the present invention are useful in the treatment of a non-solid neoplasm.

Accordingly, the present invention relates to the use of the compounds comprising a structure as defined above in therapeutic cancer treatment. The invention also relates to the use of these compounds in the treatment of inflammatory and/or immune disorders.

The present invention is described more concretely with reference to the following examples, which, however, are not intended to be understood as any kind of restriction of the scope of the present invention.

Examples

Example 1: Starting product: *tert*-butyl(3*a*R,4R,6*a*S)-4-formyl-2,2-dimethyltetrahydro-5*H*-[1,3]dioxolo-[4,5-*c*]pyrrole-5-carboxylate (**6**, Figure 2)

D-gulonolactone (25 g, 0.14 mol) was dissolved in acetone / DMP (5 : 1 vol : vol, 750 ml). *p*-toluenesulfonic acid was added until pH 3 and the solution was then stirred at 25°C until the starting material was consumed (control by TLC, AcOEt / petrol ether 4 : 1). The solution was neutralized with solid Na_2CO_3 and, after solvent evaporation *in vacuo*, the residue was poured into water and the aqueous phase was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried with $MgSO_4$. After solvent evaporation *in vacuo*, 2,3:5,6-di-O-isopropylidene-D-gulono-1,4-lactone **1** was obtained as a light yellow solid (24.536 g, 0.095 mol, 68 % yield). (In the Fleet's procedure (Tetrahedron 1988, 44, 2649-2655), once the solution has been neutralized with Na_2CO_3, the mixture was filtered through a Celite pad and then the product was recovered after solvent evaporation *in vacuo*).

The product obtained above **1** (24.536 g, 0.095 mol) was added portionwise to a Red-Al solution in toluene / THF (49 ml of a 3.5 M solution in toluene diluted in 96 ml of anhydrous THF) at 0°C. The solution was stirred at 0°C for 5 h and then methanol was added until the excess of Red-Al was consumed. The solution was poured into a saturated solution of sodium potassium tartrate (150 ml) and the mixture was stirred for 2 h at 25°C. The organic phase was collected and the aqueous phase extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed successively with a saturated solution of $NaHCO_3$ (1 x 30 ml) and brine (1 x 30 ml), then dried ($MgSO_4$). After solvent evaporation *in vacuo*, 5,6-Di-O-isopropylidene-D-gulitol **2** was obtained as a white solid (18.689 g, 0.071 mol, 75% yield) without any further purification.

The subsequent reaction (esterification with methanesulfonyl chloride / pyridine) was performed following Fleet's procedure. The mesylate so obtained was not purified before its reaction with benzylamine forming N-benzyl-1,4-dideoxy-2,3:5,6-di-O-isopropylidene-1,4-imino-D-allitol **3** in 40-55% yield, this also following Fleet's procedure.

The excess of benzylamine was eliminated as its azeotrope with xylene and then the product was purified by flash chromatography (petroleum ether / diethyl ether 3 / 2).

3 was dissolved in acetic acid (80% vol:vol in water) and the solution was stirred at 60°C overnight. After evaporation of the solvent *in vacuo*, the product was purified by flash chromatography using pure ethyl acetate as eluent yielding 45-70% of N-benzyl-1,4-dideoxy-5,6-O-isopropylidene-1,4-imino-D-allitol **4**.

This diol was then dissolved in methanol, Boc_2O (2 equivalent) was added and then $Pd(OH)_2$-C as catalyst under Argon atmosphere. The mixture was stirred under H_2 atmosphere for 3 h. The catalyst was filtered off on a Celite pad and the product was purified by flash chromatography (diethyl ether/ petroleum ether 4 : 1 to diethyl ether 100%) giving N-*tert*-butiloxycarbonyl-1,4-dideoxy-5,6-O-isopropylidene-1,4-imino-D-allitol **5** in 82% yield.

The last step was the oxidation of the diol moiety of **5**.
$NaIO_4$ (0.4083 g, 1.9 mmol, 2.7 eq) was added to a solution of the above product (0.202 g, 0.7 mmol) in methanol / water at 0°C and the solution was stirred for 1 h at 0°C. The solution was poured into water and ethyl acetate was added. The two phases were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo* leading to pure (**6**, 0.1844 g, 0.68 mmol, 97 % yield).

Example 2: Synthesis of (2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol (CB264, **9**, Figure 3)

$NaBH_4$ (0.031 g, 0.8 mmol, 1.6 eq) was added portionwise to a solution of **6** (0.1454 g, 0.5 mmol) in methanol (1.5 ml) at 0°C. The solution was stirred for 1h at 0°C, cold water was added (0.5 ml) and then ethyl acetate (1 ml). The two phases were separated, the aqueous phase was extracted twice with ethyl acetate (2 x 0.5 ml) and the collected organic layers were washed with brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo* to afford *tert*-butyl(3*a*R,4R,6*a*S)-4-hydroxymethyl-2,2-dimethyltetrahydro-5*H*-[1,3]dioxolo-[4,5-*c*]pyrrole-5-carboxylate **7** (0.0994 g, 0,36 mmol, 72 % yield).

7 (0.0994 g, 0.36 mmol) was dissolved in DMF (2 ml), NaH (0.022 g (60% in oil), 1.5 eq) and then oleyl bromide (0.1488 g, 0.45 mmol, 1.25 eq) were added and the mixture was stirred at room temperature, then at 60°C for 18 h. Methanol was added, then water (2 ml) and the solution was extracted with diethyl ether (3 x 2 ml). The combined organic phases were washed successively with water and brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. After flash chromatography (petroleum ether / AcOEt 7:1) the product *tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{[(9Z)-octadec-9-en-1-yloxy]methyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **8** was recovered as a colourless oil (0.0754 g, 0.14 mmol, 40% yield).

Deprotection of Boc and acetonide protecting groups (TFA / H_2O, 4 : 1 vol : vol, 0°C for 3 h) and purification by flash chromatography (CH_3CN / NH_4OH 12 : 1) lead to the pure product **9** (0.0208 g, 0.06 mmol, 43% yield) as a white foam.

$[\alpha]_D^{25} = +13$ $[\alpha]_{577}^{25} = +4$ $[\alpha]_{435}^{25} = +16$ $[\alpha]_{405}^{25} = +24$ (0.076g/ 100ml, MeOH)

IR (solid, cm^{-1}):

3346, 3005, 2960, 2920, 2875, 2851, 2258, 1664, 1624, 1467, 1435, 1407, 1371, 1347, 1316, 1258, 1203, 1185, 1138, 1096, 1064, 1035, 1014, 975, 925, 891, 850, 798, 723, 598,570.

^1H *NMR* (MeOH-d_4, 800 MHz):

δ 0.93 (t, J = 7.1, 3H, C*H*$_3$ (oleyl)) 1.35 (m, 22 H, 11 x C*H*$_2$ (oleyl)) 1.64 (m, 2H, *H*$_2$C(17) (oleyl)) 2.06 (m, 4H, 2 x CH_2 (oleyl)) 3.23 (dd, J = 14.6, 7.4, 1H, *H*HC(5)) 3.27 (dd, J = 14.6, 10.1, 1H, H*H*C(5)) 3.53 (m, 1H, H*H*C(1) (oleyl)) 3.59 (m, 1H , *H*HC(1) (oleyl)) 3.62 (m, 1H, *H*-C(2)) 3.66 (dd, J = 10.5, 6.4, 1H, *H*HC-C(2)) 3.77 (dd, J = 10.5, 2.3, 1H, H*H*C-C(2)) 4.12 (m, 1H, *H*-C(3)) 4.27 (m, 1H, *H*-C(4)) 5.35 (m, 2H, HC=CH (oleyl)).

^{13}C *NMR* (MeOH-d_4, 200MHz):

δ 14.43 (C(18) oleyl) 23.73 (CH_2 (oleyl)) 27.19 (CH_2 (oleyl)) 28.11 (CH_2 (oleyl)) 28.13 (CH_2 (oleyl)) 30.32 (CH_2 (oleyl)) 30.44 (CH_2 (oleyl)) 30.59(CH_2 (oleyl)) 30.60 (CH_2 (oleyl)) 30.62(CH_2 (oleyl)) 30.82(CH_2 (oleyl)) 30.86 (CH_2 (oleyl)) 33.05 (CH_2 (oleyl)) 48.45 (C(5)) 60.93 (H_2C-C(2)) 67.16 (C(2)) 69.77 (C(3)) 71.34 (C(4)) 72.11(C(1) (oleyl)) 130.78 (HC=CH (oleyl)) 130.89 (HC=CH (oleyl)).

MALDI-TOF: calculated 384.3477, found 384.3473 $[M+H]^+$

Example 3: Synthesis of (2R,3R,4S)-2-{(1S)-1,2-bis[decyloxy] ethyl}pyrrolidine-3,4-diol (**13**, Figure 4)

Sodium hydride (0.0140 g, 0.35 mmol, 1.1 eq) was added portionwise to a solution of **5** (0.1020 g, 0.33 mmol) and 1-bromodecane (83 µl, 0.4 mmol, 1.2 eq) in DMF (0.5 ml) and the mixture was stirred at 25°C overnight. Methanol was added dropwise until the excess of NaH was consumed followed by water (4 ml) and ethyl acetate (2 ml). The two phases were separated and the aqueous layer was extracted twice with ethyl acetate (2 x 2 ml). The collected organic phases were washed successively with water and brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. Purification by flash chromathography on silica gel (light petrol / ethyl acetate 7:1 to 1:1) allowed the separation of pure *Tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{(1S)-1,2-bis[decyloxy]ethyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **10** (0.0450g, 0.08 mmol, 24% yield) and a mixture (8:2) of *Tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{(1S)-1-hydroxy-2-[decyloxy]ethyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **11** and *Tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{(1S)-1-[decyloxy]-2-(hydroxy)ethyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **12** (0.0463 g, 0.10 mmol, 31%yield).

Trifluoroacetic acid (0.35 ml) was added to a solution of **10** (0.0450g, 0.08 mmol) in dichloromethane (0.35 ml) at 0°C and the reaction was stirred at 0°C for 1h, then at 25°C for 4h. After solvent evaporation *in vacuo*, the crude product was diluted with CH_2Cl_2 (1 ml) and neutralized with solid $NaHCO_3$ (0.0076 g, 0.09 mmol, 1.1eq). The solvent was evaporated *in*

vacuo and the pure product **13** (0.0157 g, 0.04 mmol, 50% yield) was recovered as a white foam after purification by flash chromatography on silica gel (CH_3CN / NH_3 10:1).

$[\alpha]_D^{25} = +4$ $[\alpha]_{577}^{25} = +2$ $[\alpha]_{435}^{25} = +5$ $[\alpha]_{405}^{25} = +8$ (0.214 g/ 100ml, MeOH)

IR (solid, cm^{-1}):

3247, 3055, 2953, 2917, 2850, 1672, 1578, 1467, 1379, 1313, 1242, 1202, 1122, 1076, 1041, 1008, 939, 908, 874, 833.

^1H NMR (MeOH-d_4, 400 MHz)

δ 0.92 (t, J = 6.74, 6 H, H_3C(10) (R and R')) 1.32 (m, 28 H, $(CH_2)_7$ (R and R')) 1.61 (m, 4H, H_2C(2) (R and R')) 3.28 (m, 2 H, H_2C(5)) 3.52 (t, J = 6.56, 2 H, H_2C(1) (R)) 3.58 (m, 1 H, C(2)-CH(OR)C*H*HOR') 3.75 (m, 4 H, *H*-C(2), C(2)-CH(OR)CH*H*OR', H_2C(1) (R')) 3.84 (m, 1 H, C*H*(OR)CH_2OR') 4.27 (m, 1 H, *H*-C(4)) 4.34 (dd, J = 7.70, 4.07, 1 H, *H*-C(3)).

^{13}C NMR (MeOH-d_4, 100MHz):

δ 14.44 (C(10) (R and R')) 23.74 (CH_2 (R and/or R')) 27.26 (CH_2 (R and/or R')) 30.49 (CH_2 (R and/or R')) 30.57 (CH_2 (R and/or R')) 30.60 (CH_2 (R and/or R')) 30.74 (CH_2 (R and/or R')) 30.80 (CH_2 (R and/or R')) 31.10 (CH_2 (R and/or R')) 33.09 (CH_2 (R and/or R')) 51.41 (C(5)) 63.79 (C(2)) 70.44 (C(1) (R)) 71.34 (CH(OR)CH_2OR') 71.49 (C(4)) 72.47 (C(3)) 72.92 (C(1) (R')) 76.25 (CH-C(2)).

MALDI-TOF: calculated 443.3975, found 444.4065 ($[M+H]^+$)

Example 4: Synthesis of (2R,3R,4S)-2-{(1S)-1-hydroxy-2-[decyloxy]ethyl} pyrrolidine-3,4-diol (**14**, Figure 4)

(mixture 8:2 with (2R,3R,4S)-2-{-2-hydroxy-(1S)-1[decyloxy]ethyl} pyrrolidine-3,4-diol, **15**)

Trifluoroacetic acid (0.5 ml) was added to a solution of a mixture (8:2) of **11** and **12** (0.0463 g, 0.10 mmol) (see Example 3, synthesis of (13)) in dichloromethane (0.5 ml) at 0°C and the reaction was stirred at 0°C for 1h, then at 25°C for 5h. After solvent evaporation *in vacuo*, the crude product was diluted with CH_2Cl_2 (2 ml) and neutralized with solid $NaHCO_3$ (0.0093 g, 0.11 mmol, 1.1eq). The solvent was evaporated in vacuo and the pure product (**14** and **15**) (0.0287 g, 0.1 mmol, quantitative) was recovered as a white foam after purification by flash chromatography on silica gel (CH_3CN / NH_3 8:1).

$[\alpha]_D^{25} = +3$ $[\alpha]_{577}^{25} = +7$ $[\alpha]_{435}^{25} = +22$ $[\alpha]_{405}^{25} = +26$ (0.282 g/ 100ml, MeOH)

IR (solid, cm^{-1}):

3041, 2922, 2854, 1721, 1651, 1457, 1200, 1173, 1135, 840, 798, 723, 599.

^1H NMR (MeOH-d_4, 400 MHz)

δ 0.90 (t, J = 6.74, 3H, H_3C(10) (R)) 1.30 (m, 14H, $(CH_2)_7$ (R)) 1.60 (m, 2H, H_2C(9) (R)) 3.27 (dd, J = 11.8, 2.3, 1 H, H*H*C(5)) 3.38 (dd, J = 11.8, 3.8, 1H, *H*HC(5)) 3.50 (t, J = 6.5,

2H, H_2C(1) (R)) 3.60 (m, 3H, *H*-C(2), C(2)-CH(OH)CH_2OR) 4.13 (m, 1H, C*H*(OH)CH_2OR) 4.27 (m, 1H, *H*-C(4)) 4.38 (m, 1H, *H*-C(3)).

^{13}C *NMR* (MeOH-d_4, 100MHz):

δ 14.43 (C(10) (R)) 23.71 (CH_2 (R)) 27.15 (CH_2 (R)) 30.43 (CH_2 (R)) 30.60 (CH_2 (R)) 30.61 (CH_2 (R)) 30.67 (CH_2 (R)) 30.72 (CH_2 (R)) 33.04 (CH_2 (R)) 51.36 (C(5)) 64.33 (C(2)) 68.38 (CH(OH)CH_2OR) 71.58 (C(4)) 71.70 (C(3)) 72.43 (C(1) (R)) 72.83 (CH-C(2)).

MALDI-TOF: calculated 303.2410, found 304.2488 ($[M+H]^+$)

Example 5: Synthesis of (2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-ylamino]methyl}pyrrolidine-3,4-diol (**18**, Figure 5)

A solution of oleyl bromide (0.1763 g, 0.53 mmol) and sodium azide (0.0817 g, 1.26 mmol, 2.4 eq) in CH_3CN (4.5 ml) was stirred at 70°C for 36h. After solvent evaporation *in vacuo*, the crude product was purified by flash chromatography on silica gel (100% light ether) affording oleyl azide (0.037 g, 0.13 mmol, 25% yield) as a colourless oil. Triphenylphosphine (0.27 ml, 1M solution in anhydrous THF, 2 eq) was added to a solution of oleyl azide (0.037 g, 0.13 mmol) in anhydrous THF, the solution was stirred at 25°C overnight and then a solution of **6** (0.0528 g, 0.19 mmol, 1.5 eq) in anhydrous THF (0.15 ml) was added dropwise at 0°C. The mixture was stirred at 25°C overnight.

After solvent evaporation *in vacuo* the crude was dissolved in anhydrous methanol (1.4 ml), $NaBH_4$ was added portionwise at 0°C and the solution was stirred for 15 minutes at 0°C, then for 5 h at 25°C. Water was added dropwise until the excess of $NaBH_4$ was consumed. The mixture was poured into water (2 ml), ethyl acetate was added (2 ml) and the two phases were separated. The aqueous layer was extracted three times with ethyl acetate (3 x 2 ml), the collected organic phases were washed successively with water (2 ml) and brine (2 ml), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*.

Purification by flash chromatography on silica gel (CH_2Cl_2 / MeOH 97:3) lead to pure *tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{[(9Z)-octadec-9-en-1-ylamino]methyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **17** (0.039 g, 0.075 mmol, 58% yield) as a colourless oil.

Deprotection of *tert*-butyl carbamate and acetonide protecting groups (TFA /CH_2Cl_2 1:1 vol : vol, 0.8 ml) and purification by flash chromatography (CH_3CN / NH_4OH 10 : 1) lead to pure **18** (0.0291 g, quantitative) as a white foam.

^1H *NMR* (MeOH-d_4, 400 MHz):

δ 0.90 (t, J = 6.7, 3 H, H_3C(18)oleyl) 1.32 (bd, J = 16.0, 22 H, $(CH_2)_6$ and $(CH_2)_5$ oleyl) 1.55 (quint, J = 7.3, H_2C(17) oleyl) 2.04 (m, 4H, H_2CCH=CHCH_2 oleyl) 2.70 (m, 3H, *H*HC(5) and H_2C-C(2)) 2.88 (dd, J = 12.2, 3.0, 3H, H_2C(oleyl)-N) 3.14 (m, 2H, *H*-C(2) and

H*H*C(5)) 3.69 (dd, J = 7.2, 5.2, 1 H, *H*-C(3)) 4.06 (m, 1H, *H*-C(4)) 5.35 (m, 2H, *H*C=C*H* oleyl).

^{13}C *NMR* (MeOH-d_4, 100MHz):

δ 14.48 (*C*(18) oleyl) 23.74 (*C*H_2 (oleyl)) 28.12 (*C*H_2 (oleyl)) 28.14 (*C*H_2 (oleyl)) 28.27 (*C*H_2 (oleyl)) 29.99 (*C*H_2 (oleyl)) 30.31 (*C*H_2 (oleyl)) 30.33 (*C*H_2 (oleyl)) 30.45 (*C*H_2 (oleyl)) 30.58 (*C*H_2 (oleyl)) 30.60 (*C*H_2 (oleyl)) 30.83 (*C*H_2 (oleyl)) 30.86 (*C*H_2 (oleyl)) 33.06 (*C*H_2 (oleyl)) 50.65 (*C*H_2-C(2)) 52.26 (*C*(5)) 53.05 (*C*H_2(oleyl)-N) 61.61 (*C*(2)) 72.48 (*C*(4)) 77.11 (*C*(3)) 130.78 (H*C*=CH (oleyl)) 130.88 (HC=*C*H (oleyl)).

MALDI-TOF: calculated 382.6287, found 383.3659 ($[M+H]^+$)

Example 6: Synthesis of (2R,3R,4S)-2-{(1S)-1-hydroxy-2-[(9Z)-octadec-9-en-1-yloxy]ethyl} pyrrolidine-3,4-diol. (**24**, Figure 6)

Sodium hydride (0.0162 g, 0.39 mmol, 1.1 eq) was added portionwise to a solution of **5** (0.1101 g, 0.36 mmol) and oleyl bromide (0.1281 mg, 0.39 mmol, 1.1 eq) in DMF (0.6 ml) and the mixture was stirred at 25°C overnight. Methanol was added dropwise until the excess of NaH was consumed followed by water (4 ml) and ethyl acetate (2 ml). The two phases were separated and the aqueous layer was extracted twice with ethyl acetate (2 x 2 ml). The collected organic phases were washed successively with water and brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. Purification by flash chromathography on silica gel (petroleum ether / ethyl acetate 100:0 to 1:1) allowed the separation of pure (2R,3R,4S)-2-{(1S)-1,2-bis[(9Z)-octadec-9-en-1-yloxy] ethyl}pyrrolidine-3,4-diol **20** (0.0413 g, 0.06 mmol, 17% yeld) and a mixture (65:35) of (2R,3R,4S)-2-{(1S)-1-hydroxy-2-[(9Z)-octadec-9-en-1-yloxy]ethyl} pyrrolidine-3,4-diol **21** and (2R,3R,4S)-2-{2-hydroxy-(1S)-1-[(9Z)-octadec-9-en-1-yloxy] ethyl} pyrrolidine-3,4-diol **22** (0.0554 g, 0.13 mmol, 36% yield).

Trifluoroacetic acid (0.7 ml) was added to a solution of (21) and (22) (0.0554g, 0.13 mmol) in dichloromethane (0.7 ml) at 0°C and the reaction was stirred at 0°C for 1h, then at 25°C for 4h. After solvent evaporation *in vacuo*, the crude product was diluted with CH_2Cl_2 (2 ml) and neutralized with solid $NaHCO_3$ (0.0118 g, 0.14 mmol, 1.1eq). The solvent was evaporated in vacuo and the pure product (24) (as mixture 65:35 of the two isomers) was recovered quantitatively as a white foam after purification by flash chromatography on silica gel (CH_3CN / NH_3 10:1).

MALDI-TOF: calculated 413.3505, found 414.3583 ($[M+H]^+$)

Example 7: Synthesis of 6-oxa-2-thia-3-azabicyclo[3.1.0]hexane-4-methanol 2,2-dioxide (**40**, Figure 7)

[(1*E*)-2-phenylethenyl]sulfonyl chloride **31** (10g, 49.3 mmol) was dissolved in a 25% aqueous solution of ammonium hydroxide (100 ml) and the mixture was warmed to reflux for 30 minutes. After cooling at 0°C, the precipitate was filtered and then dissolved in ethyl

acetate, dried ($MgSO_4$) and the pure [(1*E*)-2-phenylethenyl]sulfonamide **32** was recovered as a white solid (7.39 g, 40.3 mmol, 82% yield) after solvent evaporation *in vacuo*.

A solution of di-*tert*-butyl-dicarboxylate (7.95 g, 36.9 mmol, 1.1 eq) in dichoromethane was addet to a solution of [(1*E*)-2-phenylethenyl]sulfonamide **32** (6 g, 33 mmol), triethylamine (54 ml, 36.3 mmol, 1.1 eq) and DMAP (0.403g, 3.3 mmol, 0.1 eq) in dichloromethane (50 ml) and the solution was stirred at room temperature for 1 hours. A solution of citric acid (0.2 M, 30 ml) was then added, the two phases were separated and the aqueous phase was extracted with ethyl acetate (1x 20 ml). The collected organic layers were washed with brine (1 x 20ml), dried ($MgSO_4$) ad the solvent was evaporated in vacuo leading to the pure *N*-{[(1*E*)-2-phenylethenyl]sulfonyl}carbamic acid *tert*-butyl ester **33** as a white solid (7.85 g, 27.7 mmol, 84% yield).

A solution of *tert*-butyl-dimethylsilylchloride (8.55 g, 56.8 mmol, 1 eq) in dichloromethane (210 ml) was added to a solution of (R,S)-3-butene-1,2-diol **34** (5 g, 56.8 mmol), imidazole (7.8 g, 113.6 mmol, 2 eq) and DMAP (0.05 g, 0.4 mmol, 0.7% mol) in dichloromethane at 0°C. The solution was stirred for 5 hours at 0°C (reaction monitored by TLC, eluent light ether, ethyl acetate 3:2). Water was added (50 ml) and the two phases were separated. The aqueous layer was extracted with diethyl ether (2 x 50 ml), the collected organic layers were washed with brine (1 x 50 ml), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The pure 1-{[(*tert*-butyl)dimethylsilyl]oxy}but-3-en-2-ol **35** was recovered as a colourless oil (10.8 g, 53.4 mmol, 94 % yield) after flash chromatography on silica gel (light ether/ ethyl acetate 9:1).

Diethyl azodicarboxylate (3.17 g, 18.2 mmol, 1.1 eq) was added to a solution of **33** (4.69 g, 16.6 mmol), **35** (3.36 g, 16.6 mmol, 1eq) and triphenylphosphine (4.77 g, 18.2 mmol, 1.1 eq) in anhydrous THF (28 ml) and the mixture was stirred vigorously at 25°C overnight. The crude was purified directly by flash chromatography on silica gel (eluent: 9:1 vol/vol petroleum ether/ diethyl ether) after solvent evaporation *in vacuo* leading to pure *N*-{1-{{[(tert-butyl)dimethylsilyl]oxy}methyl}prop-2-en-1-yl}-*N*-{[(1*E*)-2-phenylethyl]sulfonyl}carbamic acid *tert*-butyl ester **36** (4.11 g, 8.8 mmol, 53% yield).
36 (4.11 g, 8.8 mmol) was dissolved in anhydrous dichloromethane (88 ml), Grubbs II catalyst was added (848 mg, 0.1 eq) in three portions (565 mg, then 142 mg after 18 hours, and 140 mg after 28 h) and the solution was stirred at reflux for 48 h. The solvent was evaporated *in vacuo* and the pure 2,3-dihydro-3-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}isothiazol-2-carboxylic acid *ter*t-butyl ester **37** (2.49 g, 6.9 mmol, 78% yield) was recovered as a colourless oil after flash chromatography on silica gel (eluent 9:1 vol/vol petroleum ether/diethyl ether). Deprotection of sulphonamide and hydroxyl functional groups (trifluoroacetic acid/H_2O 4:1) followed by flash chromatography on silica gel (CH_2Cl_2/ MeOH 10:1 vol:vol) led to 2,2-dihydroisothiazole-3-methanol 1,1-dioxide **38** in 77% yield.

37 (200 mg, 0.55 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (8.4 ml). KOCl (~2M in water, 5.52 ml), KOH (~9.5M in water, 1.2 ml) and tetrabutylamonium hydrogenosulfate (20 mg, 55 µmol, 0.1 equiv.) were added and the resulting mixture was vigorously stirred under argon at rt. The reaction was monitored by TLC and finished after about 4 hours. After dilution with CH_2Cl_2 and water, the phases were separated and the organic one washed with water. The organic phase was dried ($MgSO_4$), concentrated (T < 30°C) and pure 4-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-6-oxa-2-thia-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester 2,2-dioxide **39** was recovered as white solid (192 mg, 92 %) after purification by flash column chromatography on silica gel (eluent 4:1 vol/vol petroleum ether/diethyl ether).

(The solution of KOCl was prepared as follow: a solution of 1.50 g K_2CO_3 and 0.43 g KOH in 2.5 mL warm water was added to a solution of 2.1 g $Ca(OCl)_2$ in 5 mL warm water. The resulting mixture was vigorously stirred until the semi solid gel became liquid. The solid was removed in Büchner and washed with 1 mL warm water => solution obtained ~2 M KOCl in water.)

The deprotected epoxide was obtained by treatment with borontrifluoride etherate: a solution of borontrifluoride etherate (187 mg, 1.32 mmol, 5 equiv.) in CH_2Cl_2 (1.5 mL) was added over 30 minutes at 0°C to a solution of **39** (100 mg, 0.26 mmol, 1 equiv.) and 4Å molecular sieves (0.16g) in CH_2Cl_2 (2.5 mL). The mixture was then let at room temperature and monitored by TLC. After about 5 hours the reaction was finished. Molecular sieves were removed by filtration and washed with ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried with magnesium sulphate and concentrated. The crude product was purified by flash column chromatography (eluent 4:1 vol/vol ethyl acetate/petroleum ether) and the pure **40** was isolated as white foam (30mg, 69% yield) after solvent evaporation *in vacuo*.

^1H *NMR* (MeOH-d_4, 400 MHz)

δ: 4.71 (d, 1 H, J = 2.5 Hz, SO_2CH-**H**), 4.06 (d, 1 H, J = 2.5 Hz, SO_2CH-C**H**), 3.71 (dd, 1 H, J = 8.1, 6.2 Hz, C**H**$_2$OH), 3.62 (dd, 1 H, J = 10.8, 8.4 Hz, C**H**$_2$OH), 3.67 (m, 1 H, J = 11.1, 6.2 Hz, NH-C**H**)

^{13}C *NMR* (MeOH-d_4, 100MHz):

δ: 62.2 (**C**H_2-OH), 60.3 (SO_2-**C**H), 57.6 (NH-**C**H), 56.6 (SO_2-CH-**C**H)

Example 8: Synthesis of (2,2-dioxido-6-oxa-2-thia-3-azabicyclo[3.1.0]hex-4-yl)methyl (9Z)-octadec-9-enoate **41** and {2,2-dioxido-3-[(9Z)-1-oxooctadec-9-en-1-yl]-6-oxa-2-thia-3-azabicyclo[3.1.0]hex-4-yl}methyl (9Z)-octadec-9-enoate **42** (Figure 8)

A solution of the oleic anhydride (209 µl, 0.34 mmol, 1.2 equiv.) in dry CH_3CN (1 ml) was added slowly to a solution of 6-oxa-2-thia-3-azabicyclo[3.1.0]hexane-4-methanol 2,2-

dioxide **30** (50mg, 0.31 mmol) and pyridine (27µl, 0.34 mmol, 1.2 equiv.) in dry CH_3CN at rt. The resulting mixture was stirred at room temperature and monitored by TLC. After completion of the reaction the solvent was removed *in vacuo* and the two products were separated by flash column chromatography on silica gel (7:1 vol/vol ethyl acetate/petroleum ether). After solvent evaporation, **41** was recovered in 15 % yield as a white foam and **42** was recovered in 21 % yield as a colourless oil.

^1H NMR **41** ($CDCl_3$, 400 MHz)

5.29-5.40 (m, 2 H, olefinic **H** oleoyl), 4.60 (d, 1 H, N**H**), 4.54 (d, 1 H, J = 2.5, SO_2-C**H**, 4.34 (dd, 1 H, J = 11.7, 6.3 Hz, NH-CH-C**H**$_2$), 4.25 (dd, 1 H, J = 11.7, 7.8, NH-CH-C**H**$_2$), 3.98 (d, 1 H, J = 2.5, SO_2-CH-C**H**), 2.39 (t, 2 H, J = 7.52, $H_2C(1)$ oleoyl), 2.04 (m, 4 H, CH_2 oleoyl), 1.66 (m, 2H, C**H**$_2$$CH_3$ oleoyl) 1.30 (bd, 22 H, 11 x CH_2 oleoyl), 0.90 (t, 3 H, J = 6.4, CH_3 oleoyl).

^{13}C NMR ($CDCl_3$, 100MHz):

173.6 (-**C**O_2-), 130.5 (HC=CH oleoyl), 130.1 (HC=CH oleoyl), 62.4 (CO_2-**C**H_2), 59.5 (SO_2-**C**H), 55.6 (NH-**C**H), 54.1 (SO_2-CH-**C**H), 23-35 (**C**H_2 oleyls), 14.5 (**C**H_3 oleyls)

MALDI-TOF: calculated 430.2622, found 430.2622 $[M+H]^+$

^1H NMR **42** ($CDCl_3$, 400 MHz)

5.29-5.40 (m, 4 H, olefinic **H** oleoyls), 4.99 (dd, 1 H, J = 4.82, 3.32 Hz, NH-C**H**), 4.63 (d, 1 H, J = 2.98 Hz, SO_2-C**H**), 4.56 (dd, 1 H, J = 12.1, 5.2 Hz, NH-CH-C**H**$_2$), 4.23 (dd, 1 H, J = 12.1, 3.1 Hz, NH-CH-C**H**$_2$), 4.04 (d, 1 H, J = 3.11 Hz, SO_2-CH-C**H**), 2.79 (ddd, 1 H, J = 16.4, 8.1, 6.7 Hz, C**H**$_2$-CO_2), 2.60 (ddd, 1 H, J = 16.4, 7.9, 6.9 Hz, C**H**$_2$-CO_2), 2.29-2.43 (m, 2 H, C**H**$_2$-CON), 1.95-2.06 (m, 8 H, -**H**$_2$CHC=CH-C**H**$_2$ oleoyls), 1.54-1.73 (m, 4 H, H_3C-C**H**$_2$ oleoyls), 1.19-1.38 (m, 40 H, CH_3-CH_2-(C**H**$_2$)$_5$ and (C**H**$_2$)$_5$-CH_2-CO_2 oleoyls), 0.83-0.92 (m, 6 H, C**H**$_3$ oleoyls)

^{13}C NMR ($CDCl_3$, 100MHz):

173.3 (-**C**O_2-), 171.7 (**C**ON), 130.0 (HC=CH oleoyl), 129.9 (HC=CH oleoyl), 129.7 (HC=CH oleoyl), 129.6 (HC=CH oleoyl), 62.0 (CO_2-**C**H_2), 60.1 (SO_2-**C**H), 55.1 (NH-**C**H), 52.4 (SO_2-CH-**C**H), 22-36 (**C**H_2 oleyls), 14.1 (**C**H_3 oleyls)

MALDI-TOF: calculated 694.5075, found 694.5040 $[M+H]^+$

Example 9: Synthesis of (5R)-5-[(phenylmethoxy)methyl]-4*H*-1,3,4-oxathiazine 3,3-dioxide (**43,** Figure 9)

(R)-O-benzyl serine (2 g, 10.2 mmol, 1 eq.) was added to a solution of thionyl chloride (28.7 mmol, 2.8 eq.) in MeOH (20 mL) at 0°C. The mixture was stirred a few minutes at 0°C then heated to reflux overnight. Methanol and $SOCl_2$ were then removed under reduced pressure and AcOEt and saturated aqueous $NaHCO_3$ were added. The two layers were separated and the aqueous phase was extracted several times with AcOEt. The combined

organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used without further purification for the next step.

A solution of $LiAlH_4$ (370 mg, 9.75 mmol, 2 eq.) was prepared in anhydrous THF (23 mL) at 0°C under argon and stirred for 10 minutes. A second solution of O-benzyl serine methyl ester (1.02 g, 4.87 mmol, 1 eq.) in anhydrous THF (23 mL) was added dropwise over 1 hour to solution of the hydride at 0°C. The resulting mixture was stirred at 0°C for 30 minutes then at rt for 2 hours. The reaction was monitored by TLC and supplementary $LiAlH_4$ was added until complete conversion of the starting material. Water (0,4 mL) is then carefully added dropwise at 0°C, then NaOH 1M (0.4 mL) and again water (0,8 mL). The resulting mixture was stirred for a few minutes at room temperature and then dried with $MgSO_4$. Filtration on a Celite pad and several washings with AcOEt, then concentration under reduced pressure give the desired O-benzylserinol (this product if shown in the middle of Figure 9 and is used as a starting material in Figure 20, referred to herein as compound **130**) in 90 % yield. The crude product is used for the next step without chromatographic purification.

Chloromethansulfonyl chloride (0.048 ml, 0.53 mmol, 1.2 eq) was added to a solution of O-benzylserinol (0.08 g, 0.44 mmol) and triethylamine (0.12 ml, 0.88 mmol, 2 eq) in CH_2Cl_2 (5 ml). The mixture was stirred at 25°C until complete consumption of the starting material (monitored by TLC). After solvent evaporation *in vacuo* and flash chromatography on silica gel (eluent 1:1 petroleum ether/ethyl acetate), pure **43** (31.7 mg, 0.12 mmol, 28 % yield) was recovered as a colourless oil.

^1H NMR ($CDCl_3$, 400 MHz)

7.28-7.40 (m, 5 H, Ar**H**), 5.09 (d, 1 H, J = 8.9 Hz, N**H**), 4.56 (s, 2 H, Ar-C**H**$_2$), 4.55 (d, 1 H, J = 12.1 Hz, SO_2-C**H**$_2$), 4.49 (d, 1 H, J = 12.1 Hz, SO_2-C**H**$_2$), 3.90 (m, 1 H, NH-C**H**), 3.76 (m, 3 H, O-C**H**$_2$-CH and CH-CH*H*-OBn) 3.65 (dd, J = 19.70, 6.24, CH-C*H*H-OBn).

^{13}C NMR ($CDCl_3$, 100MHz):

137.41, 128.93 , 128.50 ,128.23, 73.99, 69.53, 56.88, 55.44, 45.19

MALDI-TOF: calculated 258.0795, found 258.0756 $[M+H]^+$

Example 10: (2R,3R,4S)-2-{(9Z,12Z,15Z)octadeca-9,12,15-trien-1-yloxy]methyl}pyrrolidine-3,4-diol **48** (Figure 10)

Tetrabutylammonium iodide (0.13635 g, 0.37 mmol, 1.2 eq) was mixed to linolenylmethanesulfonate (0.5 ml, excess) and the mixture was stirred at 25°C for 20 minutes. *Tert*-butyl(3*a*R,4R,6*a*S)-4-hydroxymethyl-2,2-dimethyltetrahydro-5*H*-[1,3]dioxolo-[4,5-*c*]pyrrole-5-carboxylate **45** (0.08213 g, 0.30 mmol) then NaOH (0.11 ml of a 50% aqueous solution) were added and the solution was stirred at 25°C for 5h (reaction monitored by TLC: ethyl acetate/ petroleum ether 4:1 and 1:7). Ethyl acetate (5 ml) and water (5ml) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 ml), the collected organic layers were washed with brine (5 ml), dried ($MgSO_4$)

and the solvent was evaporated *in vacuo*. The pure product *tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{[(9Z,12Z,15Z)octadeca-9,12,15-trien-1-yloxy]methyl} tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (0.10312 g, 0.2 mmol, 67% yield) was obtained as a colourless oil after flash column chromatography on silica gel (petroleum ether/ ethyl acetate 7:1).The protected product (0.10312 g, 0.2 mmol) was dissolved in cold trifluoroacetic acid (0.34 ml), the solution was stirred for ten minutes at 0°C, then water (0.08 ml) was added and the solution was stirred at 0°C for ten minutes, then at room temperature until consumption of the starting material (monitored by TLC, pertroleum ether/ethyl acetate 7:1 and CH_2Cl_2/MeOH 9:1 with 1% NH_4OH 25% aq). The solvent was evaporated *in vacuo* and the crude was dissolved in dichloromethane, neutralized with NH_4OH (25% aqueous solution)and the solvent was evaporated *in vacuo*. Pure **48** (0.04801 g, 0.13 mmol, 65% yield) was obtained as a white foam after flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1, 1% NH_3 aq).

^1H NMR (400 MHz, $CDCl_3$, lin = linolenyl) δ 5.42-5.28 (m, 6H, H-C(9), H-C(10) H-C(12), H-C(13), H-C(15) and H-C(16) lin) 4.14 (m, 1H, H-C(4)) 3.89 (m, 1H, H-C(3)) 3.73 (bs, 3H, 2 xH-O and H-N) 3.57 (dd, ^2J = 9.7, ^3J = 4.3, 1H, *H*HC(6)) 3.52 (dd, ^2J = 9.7, ^3J = 5.3, 1H, H*H*C(6)) 3.45 (t, ^3J = 13.2, 2H, $H_2C(1)$ lin) 3.23 (dd, ^2J = 12.0, ^3J = 4.9, 1H, *H*HC(5)) 3.18 (m, 1H, H-C(2)) 2.97 (bd, ^2J = 9.7, 1H, H*H*C(5)) 2.80 (m, 4H, $H_2C(11)$ and $H_2C(14)$ lin) 2.11-2.02 (m, 4H, $H_2C(8)$ and $H_2C(17)$ lin) 1.55 (m, 2H, $H_2C(2)$ lin) 1.28 (bs, 10H, C(2)-$(CH_2)_5$-C(8) lin) 0.97 (t, ^3J = 7.5, 3H, $H_3C(18)$ lin).

HR-ESI-TOF-MS: calculated for $C_{23}H_{41}NO_3$: 380.3159, found 380.2331 ($[M+H]^+$)

The same procedure used for the synthesis of product **48** was applied for the preparation of the following compounds:

(2R,3R,4S)-2-{(9Z,12Z)octadeca-9,12-dien-1-yloxy]methyl}pyrrolidine-3,4-diol **49** (Fig. 10), using linoleylmethanesulfonate as alkylating agent,

(2R,3R,4S)-2-{pent-5-en-1-yloxy]methyl}pyrrolidine-3,4-diol **70** (Fig. 11), using 1-bromo-5-pentene as alkylating agent,

(2R,3R,4S)-2-{hept-1-yloxy]methyl}pyrrolidine-3,4-diol **73** (Fig. 12), using heptylmethanesulfonate as alkylating agent,

(2R,3R,4S)-2-{dec-1-yloxy]methyl}pyrrolidine-3,4-diol **74**, (Fig. 12) using decylbromide as alkylating agent,

(2R,3R,4S)-2-{tetradec-1-yloxy]methyl}pyrrolidine-3,4-diol **75** (Fig. 12), using tetradecylmethanesulfonate as alkylating agent,

2R,3R,4S)-2-{(9Z)esadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **76** (Fig. 12), using palmitoleylmethanesulfonate as alkylating agent,

(2R,3R,4S)-2-{benzyloxymethyl}pyrrolidine-3,4-diol **78** (Fig. 13), using benzylbromide as alkylating agent, and,

(2R,3R,4S)-2-{*p*-phenylbenzyloxymethyl}pyrrolidine-3,4-diol **80** (Fig. 13), using *p*-phenylbenzylbromide as alkylating agent.

Example 11: (2R,3R,4S)-2-{octadec-1-yloxy]methyl}pyrrolidine-3,4-diol **51** (Figure 10)

Tert-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{[(9Z)-octadec-9-en-1-yloxy]methyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **46** (0.04321 g, 0.08 mmol) was dissolved in methanol (1ml) and the solution was degassed with argon. Palladium hydroxide on activated charcoal (0.00703 g, 12% mol) was added and the solution was stirred under hydrogen at 25°C for 1h (reaction monitored by ^{1}H-NMR). The suspension was filtered on a Celite pad (eluent: ethyl acetate) in order to eliminate the catalyst, and the solvent was evaporated *in vacuo*, obtaining *tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{[octadec-1-yloxy]methyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **50** quantitatively. The product was dissolved in cold trifluoroacetic acid (0.32 ml) and the solution was stirred at 0°C for 10 minutes. Water (0.08 ml) was added and the solution was stirred at 0°C for 30 minutes, then at 25°C for 1h (reaction monitored by TLC, petroleum ether / ethyl acetate 7:1 and CH_2Cl_2/CH_3OH 9:1 (1% aqueous ammonia)). The solvent was evaporated *in vacuo* and the product was dissolved in CH_2Cl_2 and neutralized with ammonia. After solvent evaporation *in vacuo*, the product was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH 9:1 (1% aqueous ammonia)). Pure **51** (0.0221 mg, 0.06 mmol, 75% yield) was obtained as white foam.

^{1}H NMR (400 MHz, MeOH-d_4, od = octadecyl)
δ 4.06 (m, 1H, H-C(4)) 3.84 (dd, ^{2}J = 7.2, ^{3}J = 5.0, 1H, H-C(3)) 3.56 (dd, ^{2}J = 10.1, ^{3}J = 3.5, 1H, H*H*C-C(2)) 3.52-3.41 (m, 3H, *H*HC(1) od, H-C(2) and *H*H-C(6)) 3.20-3.14 (m, 2H, H*H*C(5) and H*H*C(1) od) 2.88 (dd, ^{2}J = 12.1, ^{3}J = 3.4, 1H, *H*HC(5)) 1.55 (m, 2H, H_2C(2) od) 1.26 (bs, 30 H, C(2)-$(CH_2)_{15}$-C(18) od) 0.87 (t, ^{3}J = 6.7, 3H, H_3C(18) od).

HR-ESI-TOF-MS: calculated for $C_{23}H_{47}NO_3$: 386.3629, found: 386.3492 ($[M+H]^+$)

The same synthetic pathway was used for the preparation of (2R,3R,4S)-2-{pent-1-yloxy]methyl}pyrrolidine-3,4-diol **72** (Figure 11), starting from *tert*-butyl(3*a*R,4R,6*a*S)-2,2-dimethyl-4-{(pent-5-en-1-yloxy)methyl}tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate **69.**

Example 12: Diethyl (*E*)-2-[(2*R*,3*R*,4*S*)-3,4-dihydroxytetrahydro-1*H*-pyrrol-2-yl]ethenylphosphonate **82** (Figure 14)

Methylene-bis-diethylphosphonate (1 ml, 1.163 g, 4.035 mmol, 2.6 eq) was added to a solution of $LiClO_4$ (0.9 ml of a solution 5M in Et_2O) in THF (3 ml) and stirred for 15 minutes at 25°C. After cooling to 0°C, triethylamine (0.62 ml, 0.451 g, 4.46 mmol, 3 eq) was added, the solution was stirred for 30 minutes at 0°C, then a solution of *tert*-butyl(3*a*R,4R,6*a*S)-4-

formyl-2,2-dimethyltetrahydro-5*H*-[1,3]dioxolo-[4,5-*c*]pyrrole-5-car boxylate **16** (0.41789 g, 1.54 mmol) in THF (3 ml) was added dropwise and the solution was stirred at 0°C for 2h, then at 25°C for 1h. The reaction mixture was washed with NH_4Cl (5 ml of a saturated aqueous solution), the aqueous phase was extracted with diethyl ether (3x 5 ml) and the collected organic layers were washed with brine (1 x 5 ml), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Pure product **81** (0.18106 g, 0.45 mmol, 29% yield) was obtained as colourless oil after column chromatography on silica gel (ethyl acetate / petroleum ether 8:1). **81** (0.08056 g, 0.19 mmol) was dissolved in trifluoroacetic acid (0.7 ml, 80% aqueous) and the solution was stirred at 0°C for 1h, then at 25°C overnight. After solvent evaporation *in vacuo* and neutralization with NH_4OH (25% aqueous solution), the product **82** was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 9:1, 1% NH_3 aq) and obtained as a white foam (0.03530 g, 0.13 mmol, 52% yield).

^1H *NMR* (400 MHz, MeOH-d_4)

δ 6.80 (ddd, $^4J_{H\text{-}P}$ = 22.2, ^3J = 17.3, ^3J = 6.5, 1H, H-C(6)) 6.07 (dd, $^2J_{H\text{-}P}$ = 19.9, ^3J = 17.3, 1H, H-C(7)) 4.17-4.08 (m, 5H, 2 x H_2C-O-P and H-C(4)) 3.83 (dd, ^3J = 8.4, ^3J = 4.7, 1H, H-C(3)) 3.75 (m, 1H, H-C(2)) 3.34 (dd, ^2J = 12.3, ^3J = 5.0, 1H, *H*HC(5)) 3.00 (dd, ^2J = 12.3, ^3J = 2.2, 1H, H*H*C(5)) 1.35 (t, ^3J = 7.1, 6H, 2 x CH_3 (Et-O-P)).

HR-ESI-TOF-MS: calculated for $C_{10}H_{20}NO_5P$: 266.1152, found 266.1186 ($[M+H]^+$)

Diethyl 2-[(2*R*,3*R*,4*S*)-3,4-dihydroxytetrahydro-1*H*-pyrrol-2-yl]ethylphosphonate **84** (Fig. 14) was prepared via the same protocol used for product **51**, using phosphonate **81** as starting material.

Example 13: (2R,3R,4S)-1-methyl-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **85** (Figure 15)

(2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **47** (the same as compound 9, see Example 2) (0.17640 g, 0.46 mmol) was dissolved in acetonitrile (6.7 ml), formaldehyde (2.1 ml of a 37% aqueous solution), then acetic acid (0.15 ml) and finally sodium cianoborohydride (0.14202 g, 2.26 mmol, 5 eq) were added and the solution was stirred at 25°C for 1h (reaction monitored by TLC: CH_2Cl_2/MeOH 9:1 with 1% of NH_3 aq). The solvent was evaporated *in vacuo* and the pure product **85** (0.15342 g, 0.39 mmol, 84% yield) was obtained as a white foam after flash column chromatography on silica gel (CH_2Cl_2/MeOH 95:5 with 1% of NH_3aq).

^1H *NMR* (400 MHz, $CDCl_3$, ol = oleyl)

δ 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.15 (m, 1H, H-C(4)) 3.91 (t, ^3J = 6.1, H-C(3)) 3.60 (dd, ^2J = 9.3, ^3J = 4.5, 1H, *H*HC(6)) 3.51-3.43 (m, 3H, H_2C(1) ol and H*H*C(6)) 3.38 (dd, ^2J = 10.2, ^3J = 6.0, 1H, *H*HC(5)) 2.51 (m, 1H, H-C(2)) 2.39 (m, 1H, H*H*C(5)) 2.37 (s, 3H, H_3C-

N) 2.00 (m, 4H, $H_2C(8)$ and $H_2C(11)$ ol) 1.57 (m, 2H, $H_2C(2)$ ol) 1.28 (m, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.88 (t, ^3J = 6.7, 3H, $H_3C(18)$ ol).

HR-ESI-TOF-MS: calculated for $C_{24}H_{47}NO_3$: 398.3634, found 398.3620 ($[M+H]^+$)

(2R,3R,4S)-1-isopropyl-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **86** (Fig. 15) was prepared via the same protocol described for **85** using acetone instead than formaldehyde.

Example 14: (2R,3R,4S)-1-butyl-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **87** (Figure 15)

Solid Na_2CO_3 (13.27 mg, 0.13 mmol, 1.6 eq) was added to a solution of **47** (29.89 mg, 0.08 mmol) in DMF (0.2 ml). After few minutes *n*-butyl iodide (20 µl, 0.17 mmol, 2.1 eq) was added and the mixture was stirred at 0°C until consumption of starting material (TLC CH_2Cl_2/MeOH 8:2). The solid was filtered off and the solvent was evaporated *in vacuo*. After column chromatography on silica gel (CH_2Cl_2/MeOH 85:15) pure **87** was recovered as a with foam (12.9 mg, 0.029 mmol, 38% yield).

^1H NMR (500 MHz, MeOH-d_4, ol = oleyl):

δ 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.05 (m, 1H, H-C(4)) 3.77 (m, 1H, H-C(3)) 3.53 (dd, ^2J = 10.1, ^3J = 4.5, 1H, H*H*C(6)) 3.46 (m, 3H, $H_2C(1)$ ol and *H*HC(6)) 3.27 (m, 1H, *H*HC(5)) 2.94 (m, 1H, *H*HC(1) butyl) 2.71 (m, 1H, H-C(2)) 2.44 (m, 2H, H*H*C(1) butyl and H*H*C(5)) 2.04 (m, 4H, $H_2C(8)$ and $H_2C(11)$ ol) 1.58 (m, 2H, $H_2C(2)$ ol) 1.49 (m, 2H, $H_2C(2)$ butyl) 1.33 (m, 24H, $H_2C(3)$ butyl, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.95 (t, ^3J = 7.5, 3H, $H_3C(4)$ butyl) 0.90 (t, ^3J = 7.2, 3H, $H_3C(18)$ ol)

HR-MALDI-TOF-MS: calculated for $C_{27}H_{53}NO_3$: 440.4098, found 440.5022 $([M+H])^+$

By the same synthetic patways were synthesized:

(2R,3R,4S)-1-benzyl-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **88** (Fig. 15), using benzylbromide as the alkylating agent, and

(2R,3R,4S)-1,1-dimethyl-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **89** (Fig. 15) using methyl iodide as the alkylating agent.

Example 15: (2R,3R,4S)-3,4-dihydroxy-2-{[((9Z)-octadec-9-en-1-yloxy)methyl]tetrahydro-1H-pyrrol-1-yl}-1-ethanone **90** and the mixture of (2R,3R,4S)-1-acetyl-4-hydroxy-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}tetrahydro-1H-pyrrol-3-yl acetate **91** and (2R,3R,4S)-1-acetyl-3-hydroxy-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}tetrahydro-1H-pyrrol-4-yl acetate **92** (Figure 16)

47 (Example 13 compound **47** is compound **9** of Example 2, Figure 3) (0.15052 g, 0.39 mmol) was dissolved in dichloromethane (4 ml) at 0°C, K_2CO_3 (0.06445 g, 0.47 mmol,

1.2 eq) was added, then, dropwise, acetic anhydride (0.074 ml, 0.08044 g, 0.79 mmol, 2 eq) and the solution was stirred at 0°C for 3h (reaction monitored by TLC: CH_2Cl_2/MeOH 93:7 with 1% NH_3 aq). The solution was washed with saturated NH_4Cl aq (1 x 3 ml) and the aqueous phase was extracted with CH_2Cl_2 (3 x 3ml). The collected organic layers were washed with saturated $NaHCO_3$ aq (1 x 5 ml), brine (1 x 5ml), dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Flash column chromatography on silica gel (CH_2Cl_2/MeOH 95:5) allowed the separation of pure **90** (0.07126 g, 0.17 mmol, 43% yield) as colourless oil and a mixture of **91** and **92** (0.02530 g, 0.10 mmol, 26% yield) as colourless oil.

Analytical data for **90:**

^1H *NMR* (400 MHz, $CDCl_3$, ol = oleyl)

δ 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.47 (m, 1H, H-C(4)) 4.20 (dd, ^3J =4.1, ^3J = 3.1, 1H, H-C(3)) 4.07 (m, 1H, H-C(2)) 3.68 (dd, ^2J = 10.7, ^3J = 6.5, 1H, H*H*C(5)) 3.58 (dd, ^2J = 9.6, ^3J = 5.5, 1H, H*H*C(6)) 3.45-3.36 (m, 4H, $H_2C(1)$ ol, *H*HC(5) and *H*HC(6)) 2.04 (s, 3H, $CH_3C(O)N$) 2.01 (m, 4H, $H_2C(8)$ and $H_2C(11)$ ol) 1.52 (m, 2H, $H_2C(2)$ ol) 1.27 (m, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.88 (t, ^3J = 6.5, 3H, $H_3C(18)$ ol)

HR-ESI-TOF-MS: calculated for $C_{25}H_{42}NO_4$: 426.3583, found 426.3578 ($[M+H]^+$)

Analytical data for mixture of **91-92:**

HR-ESI-TOF-MS: calculated for $C_{27}H_{49}NO_5$: 468.3689, found 468.3643.

Example 16: (2R,3R,4S)-3,4-dihydroxy-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}tetrahydro-1H-pyrrole-1-carboxamide **93** (Figure 16)

47 (=**9**, Examples 2) (0.03176 g, 0.083 mmol) was dissolved in ethanol (0.8 ml), HCl (0.01 ml of a 25% aqueous solution, 1.1 eq) then KOCN (0.00820 g, 0.1 mmol, 1.2 eq) were added and the solution was stirred at 50°C overnight. After cooling at room temperature, the reaction mixture was putted in an ice bath. The solid (KCl) was filtered off and the filtrated was washed with CH_2Cl_2/MeOH 9:1. The solvent was evaporated *in vacuo* and the pure product **93** (0.02667 g, 0.058 mmol, 70% yield) was obtained as a white foam after purification by column chromatography on silica gel (CH_2Cl_2/MeOH 93:7 with 1% NH_4OH aq).

^1H *NMR* (400 MHz, MeOH-d_4)

δ 5.46 (bs, H_2N-C(O)N) 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.22 (m, 1H, H-C(4)) 3.90 (m, 1H, H-C(3)) 3.83 (m, 1H, H-C(2)) 3.69 (m, 2H, *H*HC(5) and *H*HC(6)) 3.48-3.37 (m, 4H, $H_2C(1)$ ol, H*H*C(5) and H*H*C(6)) 2.01 (m, 4H, $H_2C(8)$ and $H_2C(11)$ ol) 1.55 (m, 2H, $H_2C(2)$ ol) 1.28 (m, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.88 (t, ^3J = 6.9, 3H, $H_3C(18)$ ol).

HR-ESI-TOF-MS: calculated for $C_{24}H_{46}N_2O_4$: 427.3536, found 427.3532 ($[M+H]^+$)

Example 17: (2R,3R,4S)-3,4-dimethoxy-2-{[(9Z)-octadec-9-en-1-yloxy)methyl]tetrahydro-1H-pyrrol-1-yl}-1-ethanone **94** (Figure 16)

90 (Example 15) (0.01988 g, 0.047 mmol) was dissolved in dry THF (0.5 ml), NaH (60% in oil, 0.00552 g, 0.14 mmol, 1.5 eq) was added and the mixture was stirred at 25°C for 30 minutes. CH_3I (0.0086 ml, 0.01916 g, 3 eq) was added dropwise and the mixture was stirred at 25°C until consuption of the starting material (reaction monitored by TLC : CH_2Cl_2/MeOH 95:5).The remaining hydride was quenched with methanol, the solvent was evaporated *in vacuo* and the pure product **94** (0.01443 g, 0.031 mmol, 66% yield) was obtained as a colourless oil after flash column chromatography on silica gel (CH_2Cl_2/MeOH 97:3).

^1H NMR (400 MHz, $CDCl_3$, ol = oleyl)

δ 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.25 (m, 1H, H-C(2)) 4.17 (ddd, ^3J = 7.8, ^3J = 7.8, ^3J = 4.4, 1H, H-C(4)) 3.88 (m, 1H, H-C(3)) 3.71 (dd, ^2J = 9.4, ^3J = 7.8, 1H, *H*HC(5)) 3.60 (dd, ^2J = 10.0, ^3J = 5.3, 1H, *H*HC(6)) 3.52 (dd, ^2J = 10.0, ^3J = 3.0, 1H, H*H*C(6)) 3.43-3.37 (m, 9H, H_2C(1) ol, H*H*C(5), 2 x H_3C-O) 2.05 (s, 3H, H_3C-C(O)N) 2.01 (m, 4H, H_2C(8) and H_2C(11) ol) 1.53 (m, 2H, H_2C(2) ol) 1.28 (m, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.88 (t, ^3J = 6.8, 3H, H_3C(18) ol).

HR-ESI-TOF-MS: calculated for $C_{27}H_{51}NO_4$: 454.3896, found 454.3898 ($[M+H]^+$)

Example 18: (2*R*,3*R*,4*S*)-4-[(2-chloroacetyl)oxy]-1-methyl-2-[(*Z*)-9-octadecenyloxy]methyl-tetrahydro-1*H*-pyrrol-3-yl 2-chloroacetate **95** (Figure 16)

85 (Example 13) (0.04905 g, 0.12 mmol) was dissolved in dichloromethane (0.72 ml) at 0°C, pyridine (0.06 ml, 0.06134 g, 0.77 mmol, 6.4 eq) then chloroacetic anhydride (0.04701 g, 0.27 mmol, 2.2 eq) were added and the solution was stirred at 0°C for 3h (reaction monitored by TLC: CH_2Cl_2/MeOH 9:1 with 1% of NH_3 aq). The reaction was quenched with HCl 0.5 N and extracted with dichloromethane (3 x 3 ml). The combined organic layers were washed with $NaHCO_3$ sat (1 x 5 ml) and brine (1 x 5 ml), dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Pure product **95** (0.02762 g, 0.05 mmol, 42% yield) was obtained as light yellow oil after flash column chromatography on silica gel (diethyl ether/petroleum ether from 3:1 to 100:0).

^1H NMR (400 MHz, $CDCl_3$, ol = oleyl)

δ 5.39-5.25 (m, 4H, H-C(9) and H-C(10) ol) 4.08 (s, 2H, Cl-CH_2-CO) 4.05 (s, 2H, Cl-CH_2-CO) 3.54-3.38 (m, 5H, H_2C(1) ol, H_2C(6) and H*H*C(5)) 2.71 (m, 1H, H-C(2)) 2.58 (dd, ^2J = 9.7, ^3J = 6.6, *H*HC(5)) 2.45 (s, 3H, H_3C-N) 2.00 (m, 4H, H_2C(8) and H_2C(11) ol) 1.27 (m, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol) 0.88 (t, ^3J = 6.7, H_3C(18) ol)

HR-MALDI-TOF-MS: calculated for $C_{28}H_{49}Cl_2NO_5$: 550.3056, found 550.3073.

(3aS,4S,6aR)-5-benzyl-4-[(7R)-10,1-dimethyl-9,11-dioxolan-7-yl]-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole **99** (Figure 17) was synthesized via the same pathway used for the synthesis of the starting material (compound **6**, Example 1), starting from L-gulonolactone instead of D-gulonolactone.

(2S,3S,4R)-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol **104** (Figure 18) is obtained by the same synthesis as compound **9** (= compound **47**), see Example 2, but using isomer **101** as starting material (Figures 3 and 18).

$[\alpha]_D^{25} = -13$ $[\alpha]_{577}^{25} = -57$ $[\alpha]_{435}^{25} = -42$ $[\alpha]_{405}^{25} = -50$ (c=0.0525, MeOH)

Example 19: (*5R*)-4-benzyl-5-benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **152** (Fig. 20)

The synthesis of the O-benzylserinol **130** has been described in Example 9 above (see Figure 9). Compound **151** is obtained as described below for enantiomer **173** (Example 24), using **130** instead of **170**.

A solution containing **151** (2.73 g, 7.1 mmol, 1 eq.) and cesium carbonate (4.63 g, 14.2 mmol, 2 eq.) in DMF (22 ml) was heated overnight at 80 °C. Water was added and the solution was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by flash column chromatography on silica gel (EP/AcOEt 3:1), the pure product **152** (2.17 g, 6.2 mmol, 88% yield) was obtained as colourless oil.

^1H NMR (400 MHz, $CDCl_3$)

δ 7.27-7.33 (m, 10H, H Ph), 4.69 (m, 2H, H*H*C(2), N-CH*H*-Ph), 4.56 (d, 1H, ^3J = 11.3, *H*HC(2)), 4.45 (dd, 2H, ^2J = 15.2 ^3J = 11.8, O-CH_2-Ph), 4.21 (d, 1H, ^3J = 14.7, N-C*H*H-Ph), 4.02 (m, 2H, H*H*C-C(5),*H*HC(6)), 3.79 (dd, 1H, ^2J = 9.7 ^3J = 4.5, *H*HC-C(5)), 3.60 (dd, 1H, ^2J = 12.1 ^3J = 2.5, H*H*C (6)), 3.46 (m, 1H, HC-N)

HR-ESI-TOF-MS: calculated for $C_{18}H_{21}NSO_4$: 348.1270, found 348.1259 ($[M+H]^+$)

Example 20: (*5R*)-4-benzyl-5-hydroxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **153** (Fig. 21)

A solution of **152** (see above) (300 mg, 0.84 mmol, 1 eq.) was prepared in ethanol (8.4 ml). The solution was pumped through the H-Cube hydrogenation reactor two times under the following conditions:

T= 45 °C, p= 40 bar, flow= 0.5 ml/min. The pure product **153** (160 mg, 0.62 mmol, 74% yield) was obtained after flash column chromatography on silica gel (AcOEt/EP 1:1)

^1H NMR (400 MHz, $CDCl_3$)

δ 7.38-7.33 (m, 4H, H arom) 4.68 (m, 2H, *H*HC(2), N-CH*H*-Ph) 4.55 (d, ^2J = 11.3, 1H, H*H*C(2)) 4.31 (d, ^2J = 14.8, 1H, N-C*H*H-Ph) 4.04 (m, 1H, CH_2-C(5)), 3.97 (m, 1H, $H_2C(7)$)

3.91 (dd, ^{2}J = 12.4, ^{3}J = 1.9, 1H, *H*HC(6)) 3.58 (dd, ^{2}J= 12.4, ^{3}J= 3.0 , 1H, H*H*C(6)) 3.41 (m, 1H, CH-N) 2.42 (s, 1H, OH)

HR-ESI-TOF-MS: calculated for $C_{11}H_{14}NSO_4Na$: 280.0620, found 280.0625 ($[M+Na]^+$)

Example 21: (*5R*)-4-benzyl-5-oleyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **154** (Fig. 21)

Tetrabuthylammonium iodide (86.13 mg, 0.23 mmol, 1 eq) was suspended in oleylmethane sulfonate (0.3 ml, in excess) and the mixture was stirred for 15 min at rt. Then **153** (see above) (60 mg, 0.23 mmol, 1 eq.) and 50 % aqueous sodium hydroxide (0.09 ml, 5 eq.) were added. The mixture was stirred overnight at rt. Water and dichloromethane were added and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were treated with NH_4Cl and finally washed with NaCl saturated. The solvent was removed under reduced pressure. The product **154** was purified by flash column chromatography on silica gel (EP/Et_2O/CH_2Cl_2 6.5:1:1, obtained: 40 mg, 0.08 mmol, 34% yield (also recovered a mixture of the product and oleylmethanesulfonate)).

^{1}H NMR (400 MHz, $CDCl_3$, ol = oleyl)

δ 7.37 (m, 4H, H arom) 5.35 (m, 2H, H-C(9) and H-C(10) ol) 4.71 (m, 2H, H*H*C(2), N-C*H*-Ph) 4.58 (d, ^{2}J = 11.2, 1H, *H*HC(2)) 4.25 (d, ^{2}J = 14.8, 1H, N-CH*H*-Ph) 4.00 (dd, ^{2}J = 12.1, ^{3}J = 2.3, 1H, *H*HC(6)) 3.92 (m, 1H, H*H*C(1) ol) 3.71 (m, 1H, *H*HC(7)) 3.61 (dd, ^{2}J = 12.1, ^{3}J = 2.5, 1H, H*H*C(6)) 3.39 (m, 3H, H-C(5), *H*HC(1) ol, H*H*C(7)) 2.02 (d, ^{3}J = 5.80, 4H, H_2C(8) and H_2C(11) ol) 1.51 (m, 2H, C(2) ol), 1.27 (s, 22H, C(2)-$(CH_2)_5$-C(8) and C(11)-$(CH_2)_6$-C(18) ol), 0.89 (t, 3H, ^{3}J = 6.7, H_3C(18) ol)

HR-ESI-TOF-MS: calculated for $C_{29}H_{49}NSO_4Na$: 530.3280, found 530.3278 ($[M+Na]^+$)

The same pathway was used for the synthesis of:

(*5R*)-4-benzyl-5-(4-fluoro)benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **155** (Fig. 22) using fluorobenzylbromide as alkylating agent,

(*5R*)-4-benzyl-5-(3-methoxy)benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **156** (Fig. 22) using methoxybenzylbromide as alkylating agent, and

(*5R*)-4-benzyl-5-benzylazamethyl-[1,3,4]-oxathiazinane-3,3-dioxide **159** (Fig. 24), prepared via the Sn2 reaction between the triflate of **153** (Example 20) and benzylamine.

Example 22: (*5R*)-4-benzyl-5-benzoyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **157** (Fig. 23)

DMAP (33.2 mg, 17 mmol, 2 eq.) and benzoylchloride (63 µl, 0.54 mmol, 4 eq.) were added to a solution of **153** (Example 20) (35 mg, 0.14 mmol, 1 eq.) in dichloromethane (6 ml). The reaction mixture was heated to reflux and monitored by TLC (AcOEt/EP 1:1) until

total conversion of the starting material. $NaHCO_3$ saturated was added to quench the reaction and the two phases were separated. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O and NaCl saturated. The organic phase was finally dried over $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash column chromatography on silica gel (EP/AcOEt 2:1) leading to pure **157** (36 mg, 0.099 mmol, 73% yield) as colourless oil. See scheme in Fig. 23.

^1H NMR (400 MHz, $CDCl_3$)

δ 7.99-7.29 (m, 10H, H arom) 4.83 (m, 4H, $H_2C(2)$, N-CH*H*-Ph, *H*HC(7)) 4.62 (d, ^3J = 11.3, 1H, H*H*C(7)) 4.27 (d, ^2J = 14.7, 1H, N-C*H*H-Ph) 4.04 (dd, ^2J = 12.3, ^3J = 1.6, 1H, *H*HC(6)) 3.68 (dd, ^2J = 12.3, ^3J = 2.4, 1H, H*H*C(6)) 3.62 (m, 1H, H-C(5))

HR-ESI-TOF-MS: calculated for $C_{18}H_{19}NSO_4$: 362.1062, found 362.1066 ($[M+H]^+$)

Example 23: (*5R*)-5-hydroxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **160** (Figure 25)

A solution of **153** (Example 20) (400 mg, 1.15 mmol, 1 eq.) was prepared in ethanol (23 ml). The solution was pumped through the H-Cube hydrogenation reactor five times under the following conditions:

T = 50 °C, p = 30 bar, flow = 1 ml/min. The product **160** (18 mg, 0.11 mmol, 10% yield) was purified by flash column chromatography on silica gel (AcOEt/EP 3:1).

^1H NMR (400 MHz, MeOH-d_4) δ 4.72 (d, ^2J= 11.6, 1H, *H*HC(2)) 4.52 (d, ^2J= 11.6, 1H, H*H*C(2)) 3.97 (m, 1H, *H*HC(7)) 3.75 (m, 1H, H-C(5)) 3.59 (m, 3H, $H_2C(6)$ and H*H*C(7))

HR-ESI-TOF-MS: calculated for $C_{11}H_{14}NSO_4Na$: 190.0150, found 190.0153 ($[M+Na]^+$)

(*5R*)-4-methyl-5-benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **162** (Figure 26) was prepared through the same synthetic pathway as **152** (Example 19, scheme of Fig. 20) using methyliodide instead that benzylbromide (see scheme of Fig. 27).

(*5R*)-4-methyl-5-hydroxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **163** (Figure 26) was produced using the same procedure as **153** (Example 20) starting from **162**.

(*5R*)-4-methyl-5-oleyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **164** (Figure 27) was produced with same procedure as used for **154** (Example 21) but starting from **163**.

With the same synthetic pathway as **164** were prepared:

(*5R*)-4-methyl-5-biphenylmethyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **165** (Figure 27), using *p*-phenylbenzylbromide as the alkylating agent, and

(5R)-4-methyl-5-naphtalenylmethyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **166** (Figure 27), using naphtalenemethylenebromide as the alkylating agent.

Example 24: (*1S*)-N-benzyl-N-[2-(benzyloxy)-1-(hydroxymethyl)ethyl]-1-chloromethane sulfonamide **173** (Figures 28 and 29)

The O-benzylserinol **170** (Figure 28) is obtained as **130** according to the procedure described in Example 9 (Figure 9), using (*S*)-O-benzyl serine **168** as starting product. Triethylamine (5.03 ml, 36.2 mmol, 2 eq.) was added to a solution of (*2S*)-2-amino-3-benzyloxypropan-1-ol **170** (3.28 g, 18.1 mmol, 1 eq.) in CH_2Cl_2 (103 ml) at 0°C. A second solution of chloromethane sulfonylchloride (1.97 ml, 21.7 mmol, 1.2 eq) in CH_2Cl_2 (103 ml) was added dropwise over 1 hour to the solution of alcohol at 0°C. The mixture was stirred overnight at room temperature. Ammonium chloride was added and the aqueous phase was extracted three times with dichloromethane. Finally the combined organic layers were washed with NaCl sat., dried over $MgSO_4$ and concentrated under reduced pressure. The pure (*1S*)-N-[(2-benzyloxy)-1-(hydroxymethyl)ethyl]-chloromethane sulphonamide **171** (2.79 g, 9.5 mmol, 51% yield) was obtained after flash column chromatography on silica gel (AcOEt/EP 1:1).

171 (2.45 g, 8.34 mmol, 1 eq.) was dissolved in DMF (41.7 ml) at room temperature. A second solution containing benzyl bromide (1.44 ml, 9.17 mmol, 1.1 eq) and potassium carbonate (3.45 g, 25.02 mmol, 3 eq.) in DMF (41.7 ml) was added dropwise to the solution of sulfonamide. The mixture was stirred for 30 minutes at rt. HCl 1M and ethyl acetate were then added. The aqueous phase was extracted three times with AcOEt. The combined organic layers were washed with water, NaCl sat. and dried over $MgSO_4$. The solvent was removed under reduced pressure. The pure product **173** (2.56 g, 6.7 mmol, 80% yield) was obtained as colourless oil after flash column chromatography on silica gel (EP/AcOEt 3:1).

$[\alpha]_D^{25} = -20$ $[\alpha]_{577}^{25} = -29$ $[\alpha]_{435}^{25} = -31$ $[\alpha]_{405}^{25} = -37$ (c = 0.084, $CHCl_3$)

IR (solid, cm^{-1}):

3531, 3062, 3027, 2948, 2866, 1341, 1160, 878, 698.

^1H NMR (400 MHz, $CDCl_3$, Ph = phenyl)

δ 7.36-7.29 (m, 10H, H Ph) 4.73 (d, ^3J = 15.7, 1H, Cl-CH*H*-SO_2) 4.56-4. 43 (m, 4H, O-CH_2-Ph, N-CH_2-Ph) 4.41 (d, ^3J = 15.7, 1H, Cl-C*H*H-SO_2) 4.14 (m, 1H, N-CH) 3.61 (m, 1H, BnO-CH*H*) 3.49 (m, 3H, BnO-C*H*H and CH_2-OH)

HR-ESI-TOF-MS: calculated for $C_{18}H_{22}NSO_4ClNa$: 406.0856, found 406.0864 ($[M+Na]^+$)

Example 25: (*5S*)-5-[(benzyloxy)methyl]-[1,3,4]-oxathiazinane-3,3-dioxide **172** (Figure 28)

A solution of **170** (Example 24) (3.28 g, 18.1 mmol) was prepared in CH_2Cl_2 (103 ml) at 0°C. Then triethylamine (5.03 ml, 36.2 mmol, 2 eq.) was added. A second solution of chloromethane sulfonylchloride (1.97 ml, 21.7 mmol, 1.2 eq) in CH_2Cl_2 (103 ml) was added over 1 hour to the solution of alcohol at 0°C. The mixture was stirred overnight at room temperature. Ammonium chloride was added and the aqueous phase was extracted three times

with dichloromethane. Finally the combined organic layers were washed with NaCl sat., dried over $MgSO_4$ and concentrated under reduced pressure. A flash column chromatography on silica gel (AcOEt/EP 1:1) allowed to separate the (1S)-N-benzyl-N-[2-(benzyloxy)-1-(hydroxymethyl)ethyl]-1-chloromethane sulphonamide **171**. The desired product **172** (0.126 g, 0.5 mmol, 3% yield) was obtained after purification by a second flash column chromatography on silica gel (EP/AcOEt 4:1).

^1H NMR (400 MHz, $CDCl_3$, Ph = phenyl) δ 7.38-7. 32 (m, 4H, H Ph) 5.09 (d, ^3J = 8.9, 1H, H-N) 4.57-4.49 (m, 4H, O-CH_2-Ph, $H_2C(2)$) 3.91 (m, 1H, H-C(5)) 3.75 (m, 3H, *H*HC(7), $H_2C(6)$) 3.63 (m, 1H, H*H*C(7))

HR-ESI-TOF-MS: calculated for $C_{11}H_{15}NSO_4$: 258.0800, found 258.0805 ($[M+H]^+$)

(*5S*)-4-benzyl-5-benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **174** (Figure 29) is obtained by the same pathway as **152** (Example 19), using enantiomer **173** instead of **151**.

(*5S*)-4-benzyl-5-hydroxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **175** (Figure 29) is obtained by the same synthesis as **153** (Example 20), but starting from **174**.

(*5S*)-4-benzyl-5-oleyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide **176** (Figure 29) is obtained by the same synthetic pathway as **154** (Example 21).

Example 26: Determination of Cell Growth Inhibition by a Dihydroxypyrrolidine Derivative

Materials and methods

Cell lines and reagents: The tumor cell lines used for the in vitro evaluation of cell growth inhibition by dihydroxypyrrolidine derivatives were U87 (glioblastoma), PC3 (prostate cancer), A549 (lung carcinoma), MDA-MB231, MCF7, BT474, and SKBR3 (breast cancer). Cells were grown in 10-cm culture dishes with McCoy medium containing 10% fetal calf serum (FCS) and antibiotics at 37°C and 5% CO_2. The dihydroxypyrrolidine derivative CB264 (9) was weighted and dissolved in DMSO to prepare a stock solution concentrated 100 mM.

Viability assays. For the viability assays, 5 x 10^4 cells/well were plated in 200 µl medium in 96 well plates. 48 hours later, the dihydroxypyrrolidine derivatives were added to the wells at concentrations ranging between 10^{-2} and 400 µM, such that the vehicle DMSO never exceeded 0.4%. Each drug concentration was tested in duplicate. Viability was determined 72 hours later using CellTiter 96 Aqueous1 (Promega) according to the manufacturer's instructions. Incubation times with CellTiter96 Aqueous1 ranged between 2 and 4 hours. Plates were read with a spectrophotometer (Labsystems iEMS Reader MF) at 490 nm wave length. IC50s were estimated using GraphPad Prism4.

Microscopy. Cells were imaged using the 40X magnification of a Zeiss AXIOVERT200 microscope, camera Qlympus C-4040ZOOM. The image files were downloaded using the software Olympus CAMEDIA Master 2.5.

Cell cycle analysis. For cell cycle analysis, 10^5 cells/well were seeded in 0.5 ml medium in 24-well plates and treated 48 hours later with the indicated concentrations of dihydroxypyrrolidine derivatives. After 24 hours, cells were harvested, washed with PBS and resuspended in a buffer containing 0.1% sodium citrate, 0.1% Triton-X, and 50 µg/ml propidium iodide. Cell cycle analysis with the isolated cell nuclei was performed by flow cytometry using a FACS Calibur (Becton Dickinson).

Results

The dihydroxypyrrolidine derivative CB264 was evaluated for their capacity to inhibit cell growth on seven established human tumor cell lines of different histology (glioblastoma, prostate cancer, lung cancer, and breast cancer). CB264 showed potent cytotoxic activity in all the cell lines tested for concentrations <200 µM, as is shown in Table 1 and Figures 30 and 31.

Table 1

Cell lines	**IC50 (µM)**
	CB264
A549	20.9
PC3	1.90
U87	7.3
MCF7	9.2
MDA-MB-231	4.7
BT474	7.1
SKBR3	2

As shown for SKBR3 cells, treatment with **9** (CB264) resulted in cell cycle arrest in G1-phase upon exposure to low compound concentrations (2 µM for this cell line) (Figure 32). Higher concentrations of **9** led to cell demise with DNA fragmentation and appearance of hypodyploid cell nuclei (Figure 34).

Example 27: Determination of Cell Growth Inhibition by other Dihydroxypyrrolidine Derivatives

Most compounds were tested in the same assay as reported in Example 25 above, but with the SKBR3 tumor cell line. Measurements made after 72 hours of exposure of the compounds of the invention are summarized for increasing concentrations in **Table 2** below.

Table 2: measurements of viability of SKBR3 cell line after 72h exposure to compounds of the invention

	%Viability				
Product	**6.25 µM**	**12.5**	**25 µM**	**50 µM**	**100 µM**
43	95	89	73	46	17
47(9)	12	10	9	8	8
48	9	9	8	9	9
49	10	9	9	8	8
51	-	20	14	8	9
18	100	11	8	8	8
20	95	89	88	88	83
24	86	87	9	7	8
24-is	86	87	9	7	8
14 +15	-	93	30	8	8
70	90	94	92	96	96
72	94	92	91	94	96
73	99	100	100	100	100
74	100	100	77	11	9
75	99	100	77	11	9
76	-	9	8	9	10
78	100	100	100	100	100
80	100	100	100	93	9
82	87	89	88	84	83
84	86	84	85	84	83
85	69	20	12	10	9
86	53	15	10	10	9
87	-	9	9	9	9
88	-	100	9	8	9
89	-	59	30	8	8
90	100	100	100	10	9
91+92	100	100	100	74	9
93	100	96	84	78	9
94	100	100	100	12	9
95	100	100	24	13	9
104	13	9	9	10	9
152	85	90	81	83	97
153	100	100	86	86	100
154	100	100	100	100	100
155	93	86	83	100	96
156	100	100	100	96	80
157	81	98	88	89	100
159	77	76	73	78	79
160	-	79	93	84	92
162	72	70	68	67	74
163	72	70	67	65	70
164	72	70	65	65	65
165	89	66	60	61	52

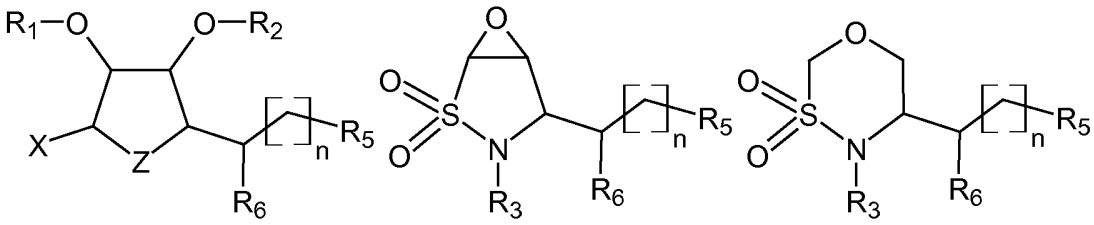
166	70	76	72	78	79
172	95	89	73	46	17
174	81	80	82	86	98
175	85	86	85	85	98
176	71	81	81	82	96

The different product numbers **47** (**9**) in the same line designate the same single compound. In some cases, mixtures of two compounds were tested (**14+15**) and (**91+92**). Compound **24** is the isomer **24** shown on the left side of the products in Figure 6, whereas compound **24-is** is the isomer on the right side of the two products in Figure 6. Compound **20** is the corresponding compound shown in Figure 6, but with the Boc and acetonide groups being removed (thus having an –NH- and two –OH groups).

From Table 2 it can be seen that the present invention provides many compounds that show a high toxicity towards the cancer cell line tested.

Claims

1. A compound of a formula selected from formulae (I), (II) and (III):



(I) (II) (III)

wherein:
in formula (I), Z is selected from –O-, -N(-R_3)-, -N(-O-R_3)-, -N(-C(=O)-R_3)-, -N(SO_2R_3)-, -S-, -S(=O)-, and -S(O_2)-;

R_1, R_2 and R_3 are selected, independently of each other, from H, C1-C26 alkyl, C1-C26 acyl, C2-C26 alkenyl, C2-C26 alkynyl, C6-C26 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms;

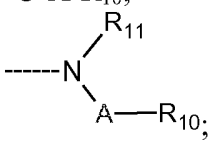
R_5 is a C0-C30 hydrocarbon substituent comprising one or more heteroatoms selected from O, N, S, B, P and halogen;

n is 0, 1 or 2;

R_6 is H if n = 0; and if n = 1 or 2, R_6 is selected, independently from any other substituent, from H and from substituents as R_5;

X is selected from H, C5-C30 aryl,5-membered and six membered heterocycle, wherein said aryl and said heterocycle may be further substituted;
wherein the compound of formula (I), (II) or (III)may be may be charged or neutral and/or may be present in the form of a salt and/or an optically resolved enantiomer.

2. The compound of claim 1, wherein –R_5 is selected from:
-O-A-R_{10};

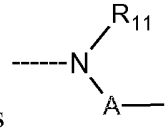


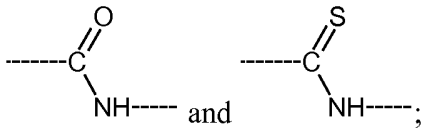
-S-R_{10},
-S(=O)-R_{10},

-$S(O_2)$- R_{10} and,

-O-(α or β) glycopyranosyl;

wherein:

A is optional and, if present, is selected from –C(=O)- , -S(-O)-, -S(=O)-, and, if –R_5 is  , and R_{11} = H, A may also be selected from:



R_{11} is selected from: H, -OH, C1-C10 alkyl, C1-C10 alkoxyl, C1-C10 acyl, said alkyl, alkoxyl and acyl optionally being substituted and optionally comprising 1 or more heteroatoms;

R_{10} is selected from H, C1-C30 alkyl, C1-C30 acyl, C2-C30 alkenyl, C2-C30 alkynyl, C6-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl, may be further substituted and may comprise one or more heteroatoms.

3. The compound of claim 2, wherein R_{10} is selected from a C8-C30 alkyl, C8-C30 acyl, C8-C30 alkenyl, C8-C30 alkynyl, C8-C30 aryl, wherein said alkyl, acyl, alkenyl, alkynyl, and aryl may be further substituted and may comprise one or more heteroatoms.

4. The compound of claim 2 or 3, wherein R_{10} is selected from:

a C2- C30 alk-m-enyl, wherein m indicates the position of a single double bond and is an integer from 2-16;

a C5-C30 alk-m,o-dienyl, with m being as defined above, o indicates the position of a second double bond and o = m+i, with i being an integer of 2-16;

a C3-C30 alk-m-ynyl, with m being as defined above;

a C5-C30 alk-m-en-o-ynyl, with m and o being as defined above, but with o indicating the position of a triple bond;

a C5-C30 alk-o-en-m-ynyl, with m and o being as defined above, but with o indicating the position of the double bond and m indicating the position of a triple bond;

wherein:

if R_{10} comprises a single double bond, R_{10} may have a (Z) or and (E) configuration,

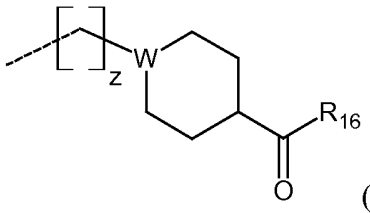
if R_{10} is a dienyl, it may have (E,E), (E,Z), (Z,E), or (Z,Z) configuration,

if R_{10} is alkenynyl, it may have a (Z) or and (E) configuration.

5. The compound of claim 2, wherein R_{10} is selected from (1) and (2) as defined below:

(1) $-CH_2CH_2O-(CH_2CH_2O)_i-R_{15}$, wherein i is 0 or an integer of 1-6;

(2) a substituent of formula (IV):



(IV), wherein Z is an integer of 1-5 and W is selected, independently, from CH and N;

wherein R_{15} is selected, independently from other substituents, from H, C1-C10 alkyl, C2-C10 alkenyl and from a substituent of formula (IV);

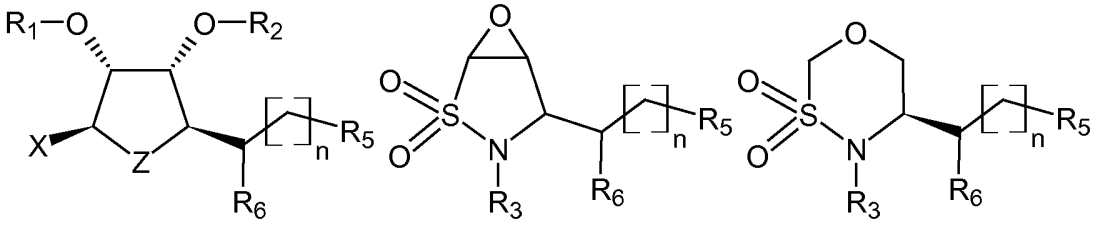
wherein R_{16} is selected from H, C1-C10 alkyl, C2-C10 alkenyl, C6-C12 aryl, -OH, $-O-R_{17}$, $-NH-R_{17}$, $-NMe-R_{17}$;

wherein $-R_{17}$ is selected from H, C1-C10 alkyl, C2-C10 alkenyl, C6-C12 aryl.

6. The compounds of any one of claims 2-4, wherein R_{10} is a C8-C26, preferably C9-C26, more preferably a C10-C26 alkenyl, which may optionally be further substituted.

7. The compounds of any one of claims 2-6, wherein R_{10} is $(CH_2)_8CH=CH(CH_2)_7-CH_3$.

8. The compound of any one of the preceding claims, being selected from a compound of formula (V), (VI) and (VII):



(V) (VI) (VII)

9. The compound of any one of the preceding claims, wherein R_5 is selected from $-O-R_{10}$ and $-NH-R_{10}$, with R_{10} being defined as in Claims 2-7.

10. The compound of any one of the preceding claims, wherein R_6 is selected from H, from $-O-R_{10}$ and $-NH-R_{10}$, with R_{10} being defined as in Claims 2-7.

11. The compounds of any one of the preceding claims, wherein:
n=0,
R_5 and R_6 is selected from H, -O-R_{10} and –NH-R_{10}, with R_{10} being as defined in Claims 3-6;
with the proviso that one of R_5 or R_6 is H and the other, R_6 or R_5, respectively, is selected from -O-R_{10} and –NH-R_{10}.

12. The compound of any one of the preceding claims, which is selected from:
(2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}pyrrolidine-3,4-diol,
(2R,3R,4S)-2-{[(9Z)-octadec-9-en-1-ylamino]methyl}pyrrolidine-3,4-diol, and,
(2R,3R,4S)-2-{(1S)-1-hydroxy-2-[(9Z)-octadec-9-en-1-yloxy]ethyl} pyrrolidine-3,4-diol.

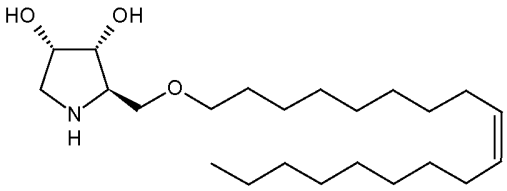
13. The compound of any one of the preceding claims, which is selected from any one of compounds 9 (=47), 48, 49, 51, 18, 20, 24, 24-is, 67, 68, 74, 75, 76, 80, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 104, 164, 165, 172 as more specifically defined in the examples and the figures, wherein said compounds may be charged or neutral, and which may be present in the form of a salt and/or an optically resolved enantiomer.

14. The compounds of any one of the preceding claims for use as a medicament.

15. The compounds of any one of the preceding claims for the treatment of cancer.

16. The compound of any one of the preceding claims in the treatment of a non-solid neoplasm.

17. A method of treating cancer, the method comprising the step of administering to an individual in need thereof an effective amount of a compound according to any one of claims 1-16.



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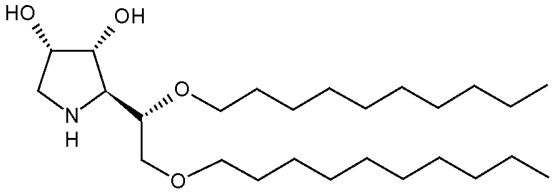

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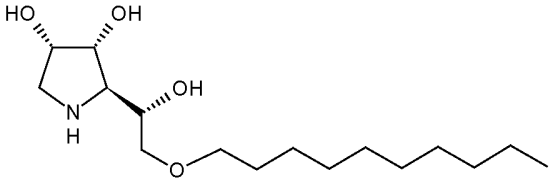

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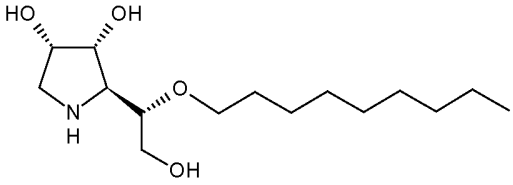

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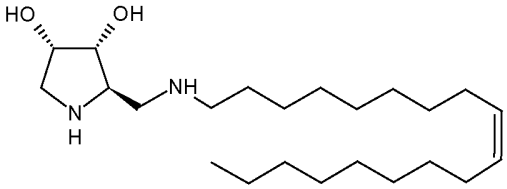

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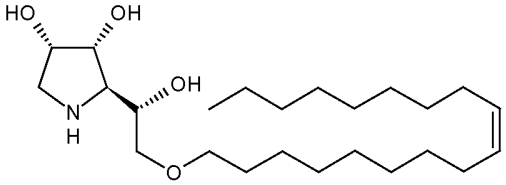

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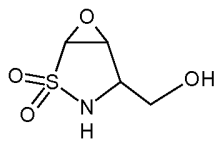

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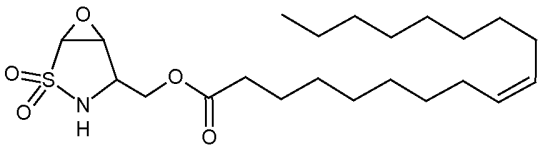

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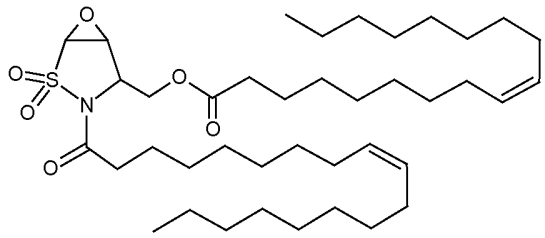

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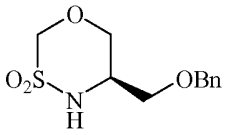

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Figure 1

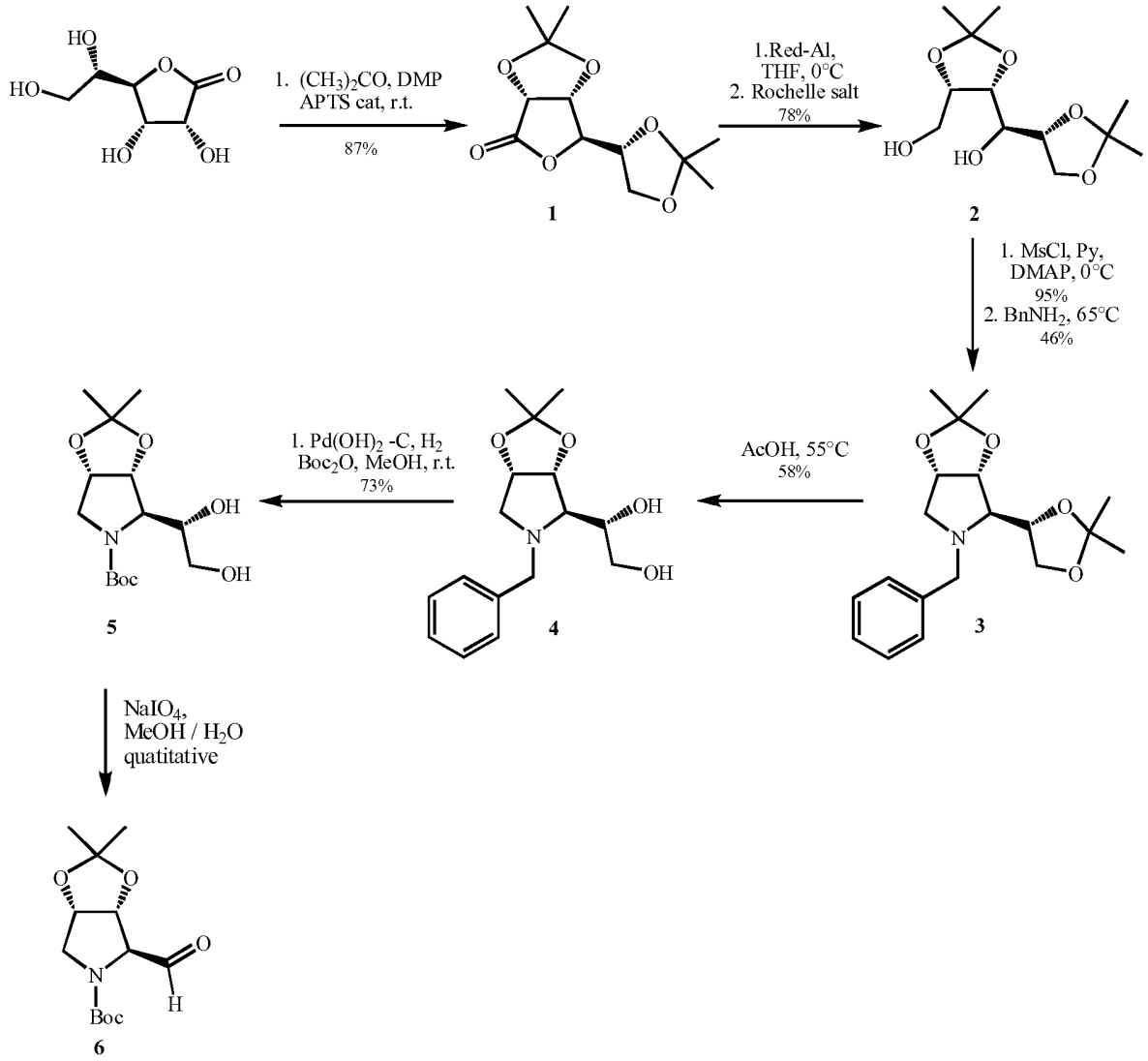
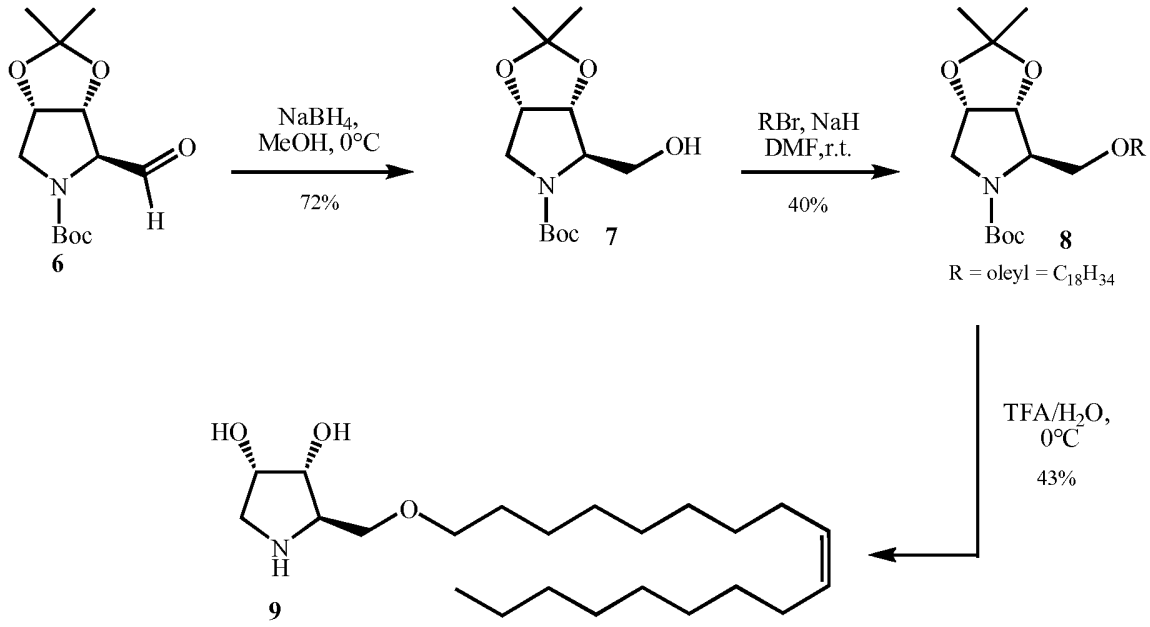

1. $(CH_3)_2CO$, DMP
APTS cat, r.t.
87%
1.Red-Al,
THF, 0°C
2. Rochelle salt
78%
1. MsCl, Py,
DMAP, 0°C
95%
2. $BnNH_2$, 65°C
46%
AcOH, 55°C
58%
1. $Pd(OH)_2$ -C, H_2
Boc_2O, MeOH, r.t.
73%
$NaIO_4$,
$MeOH / H_2O$
quatitative
1
2
3
4
5
6

Figure 2



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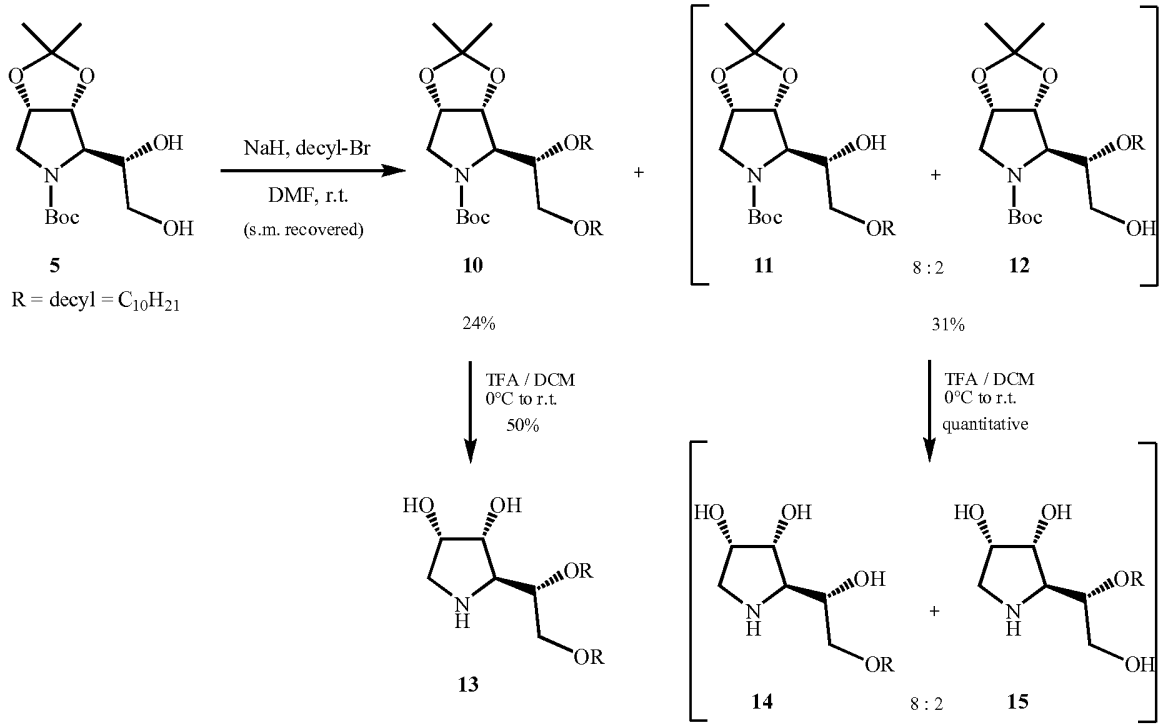

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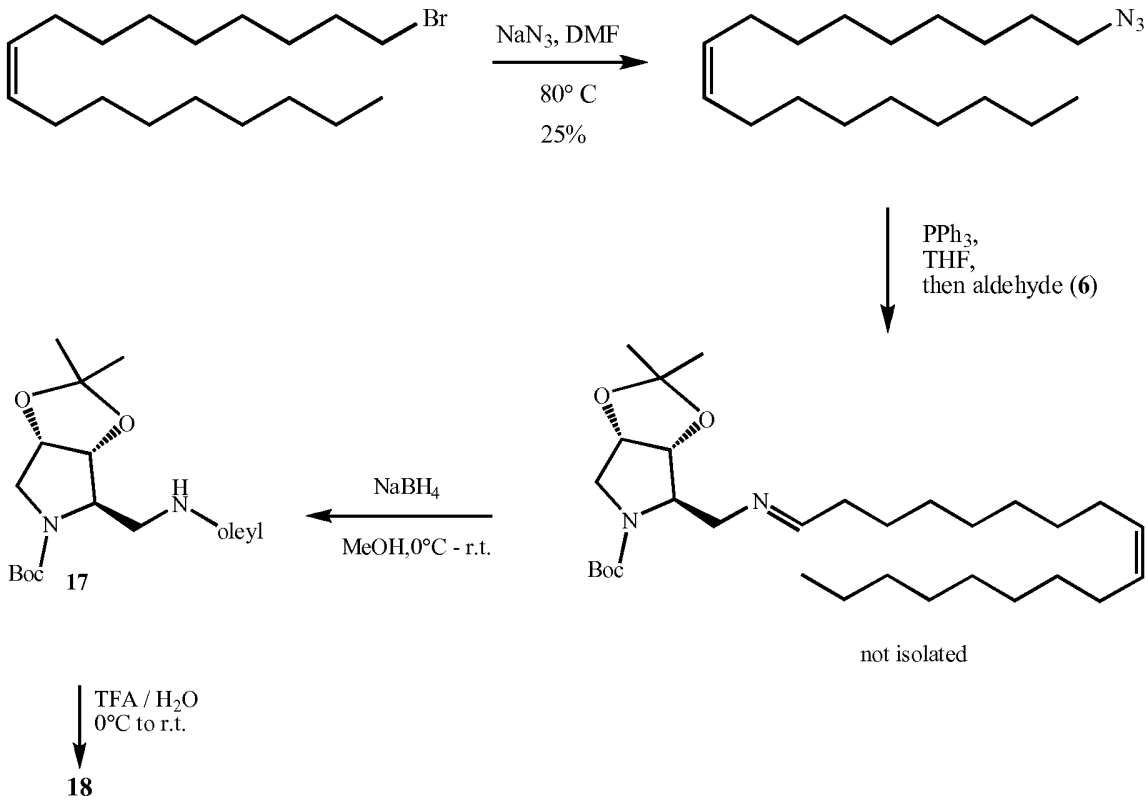
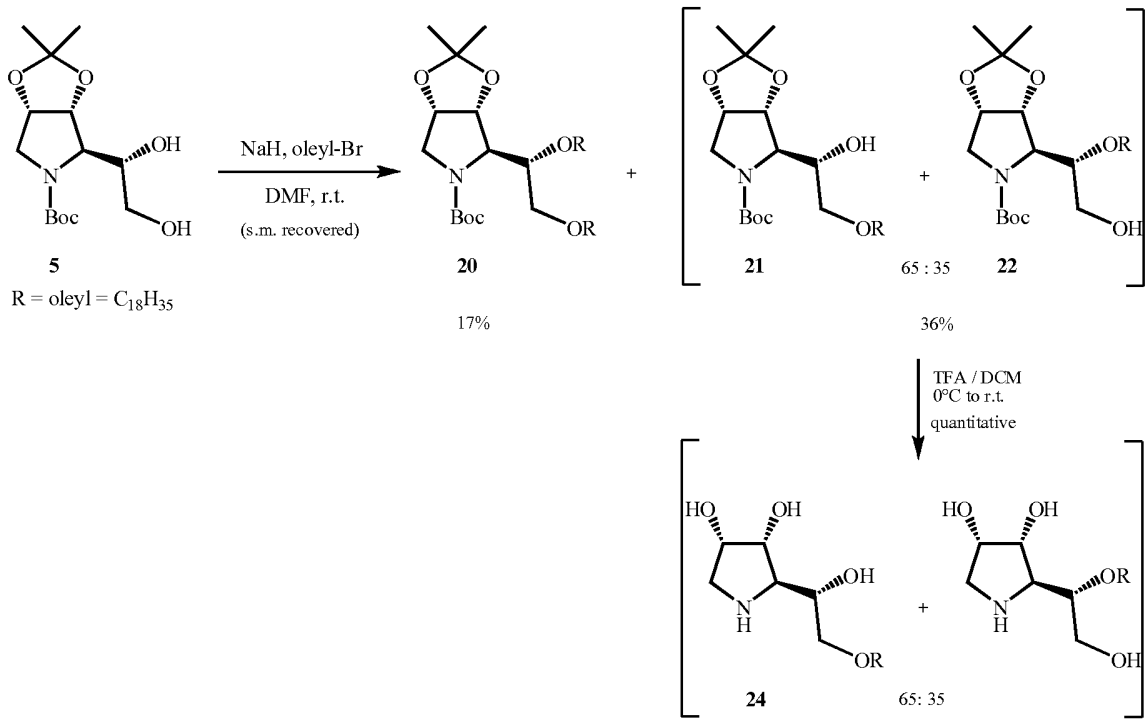


Figure 5



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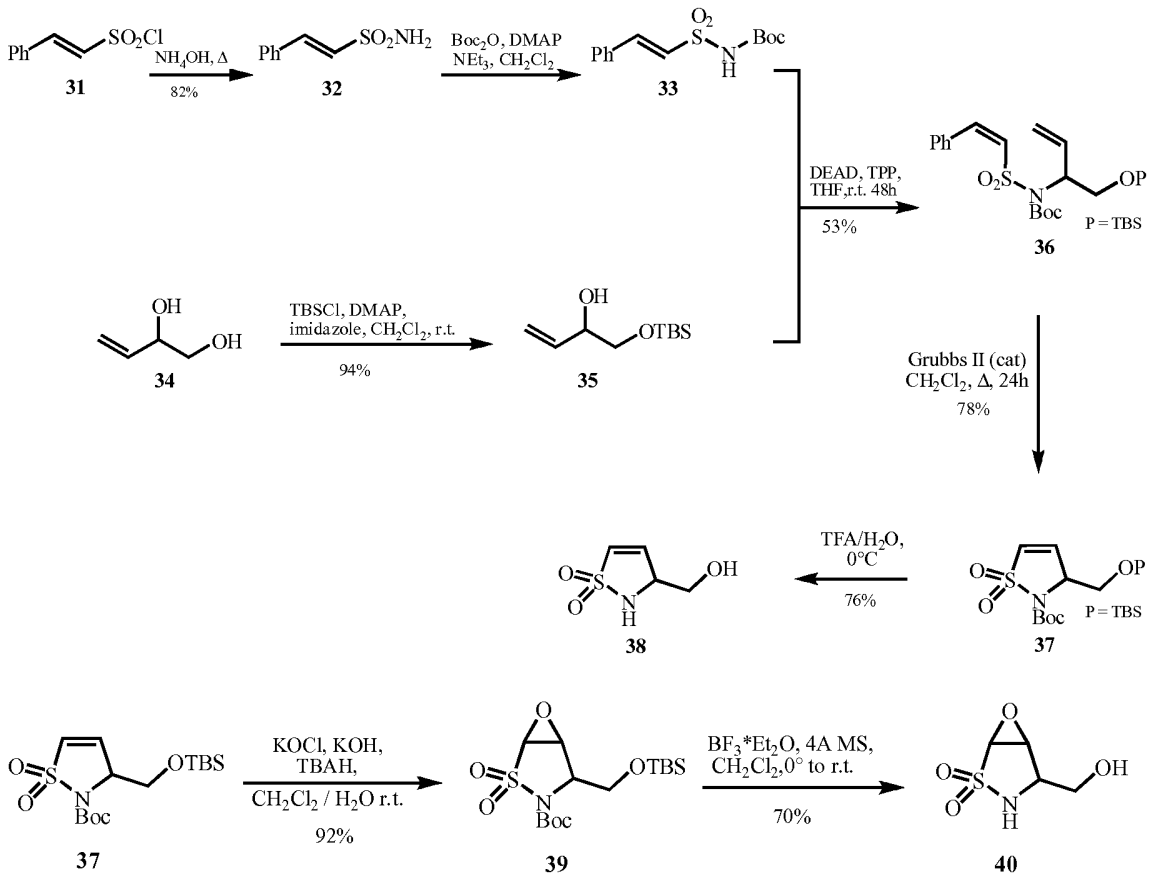

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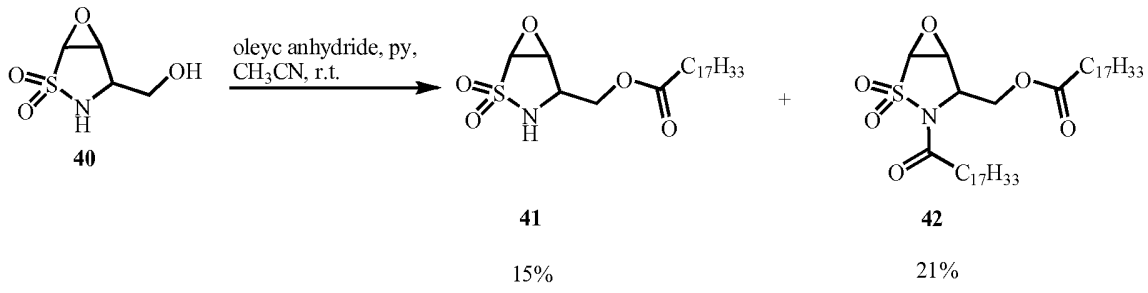
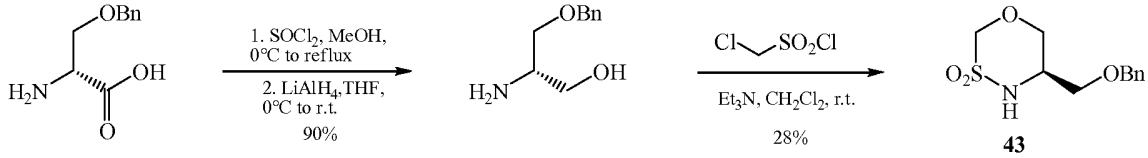


Figure 8



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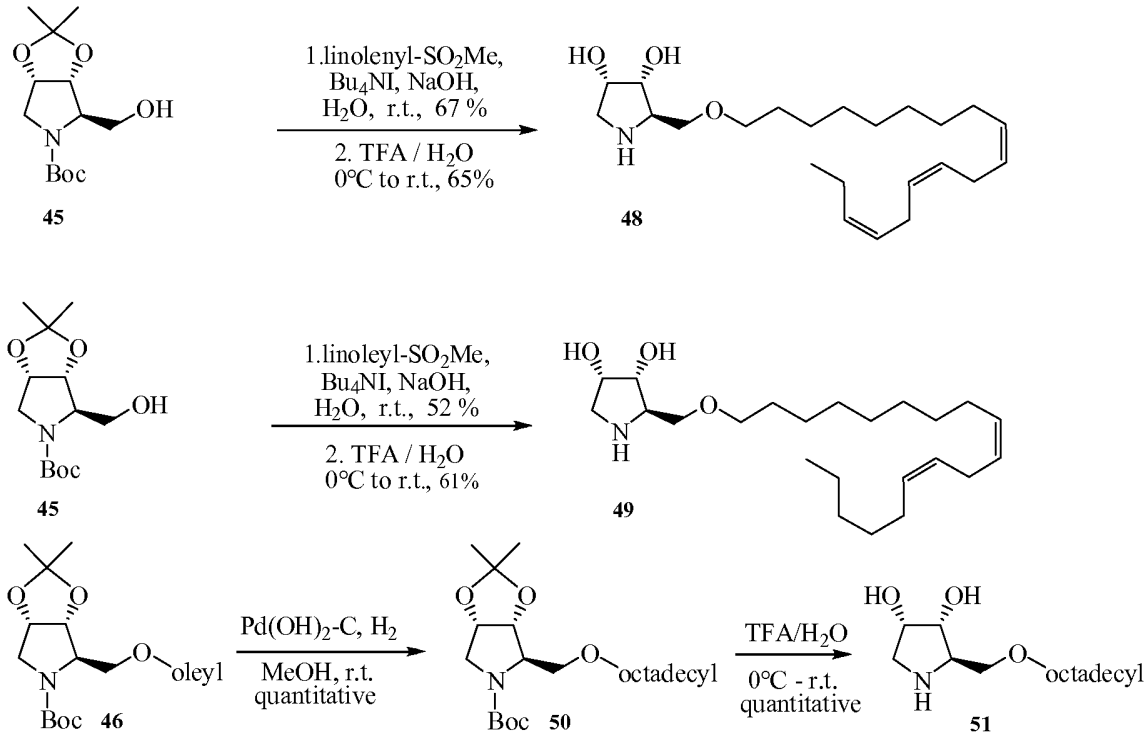

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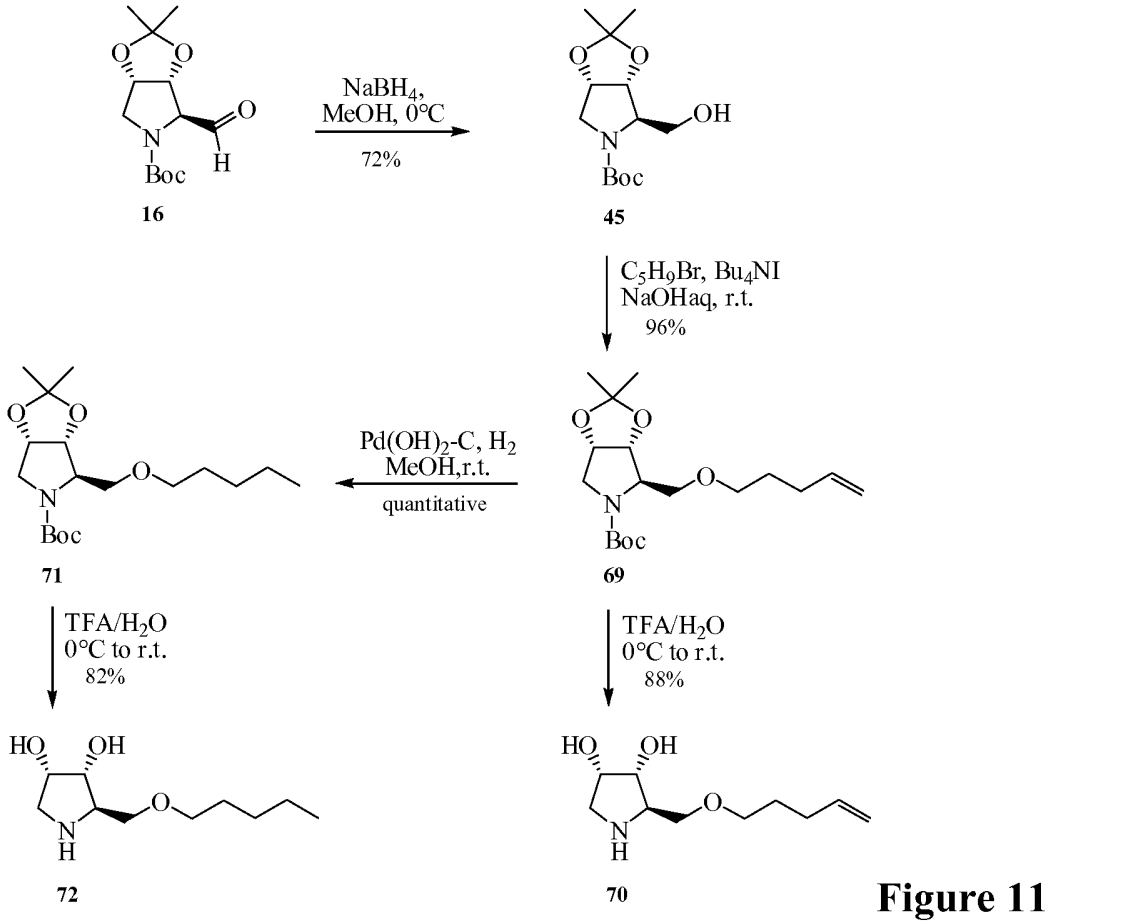

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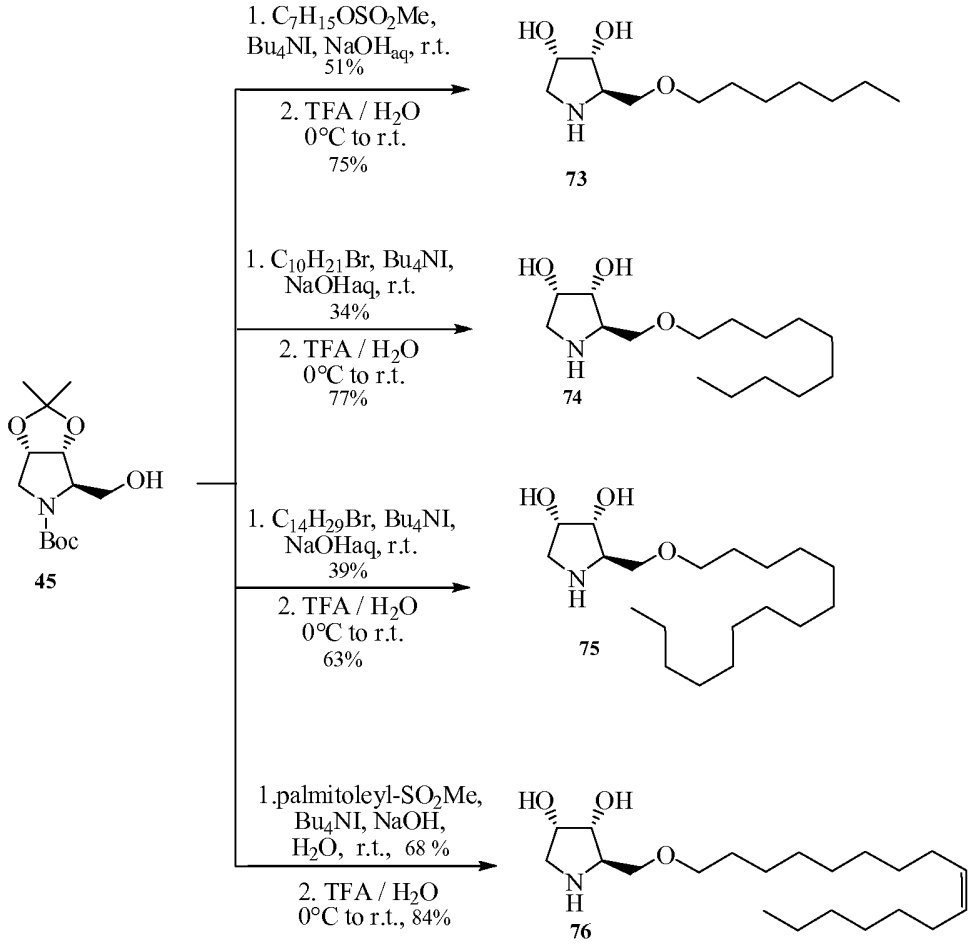

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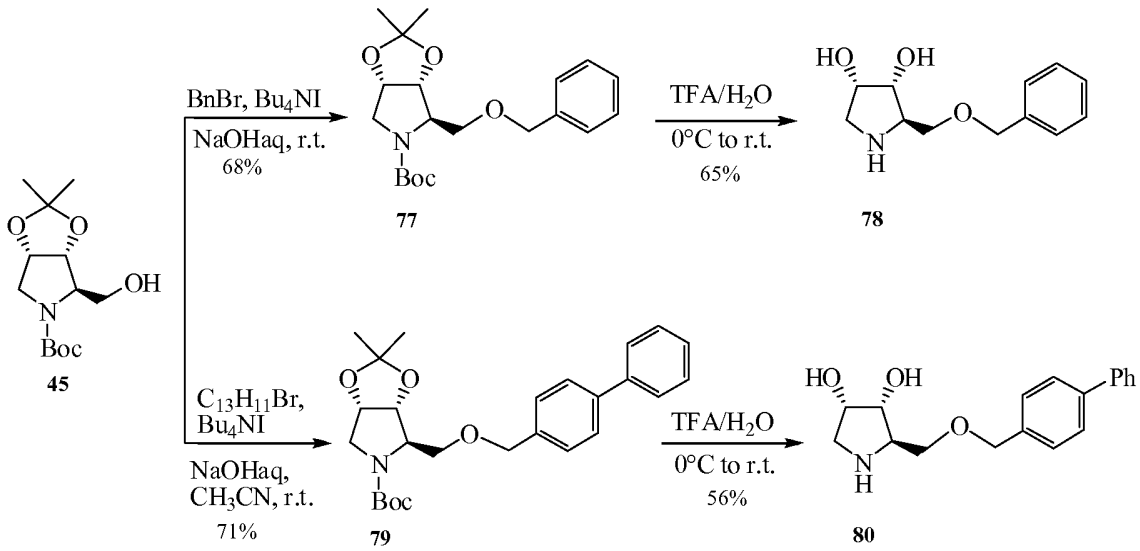

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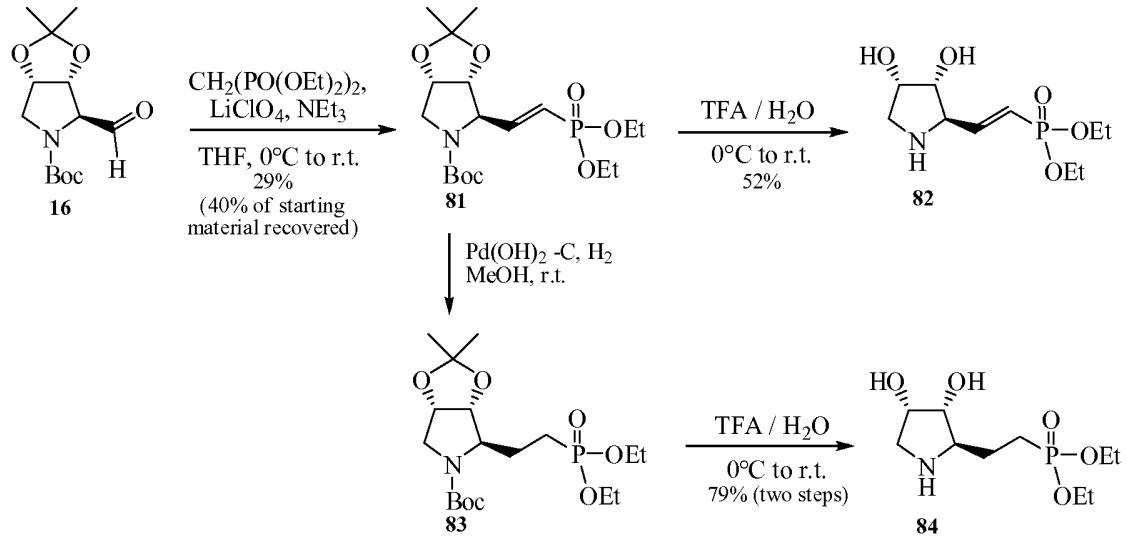

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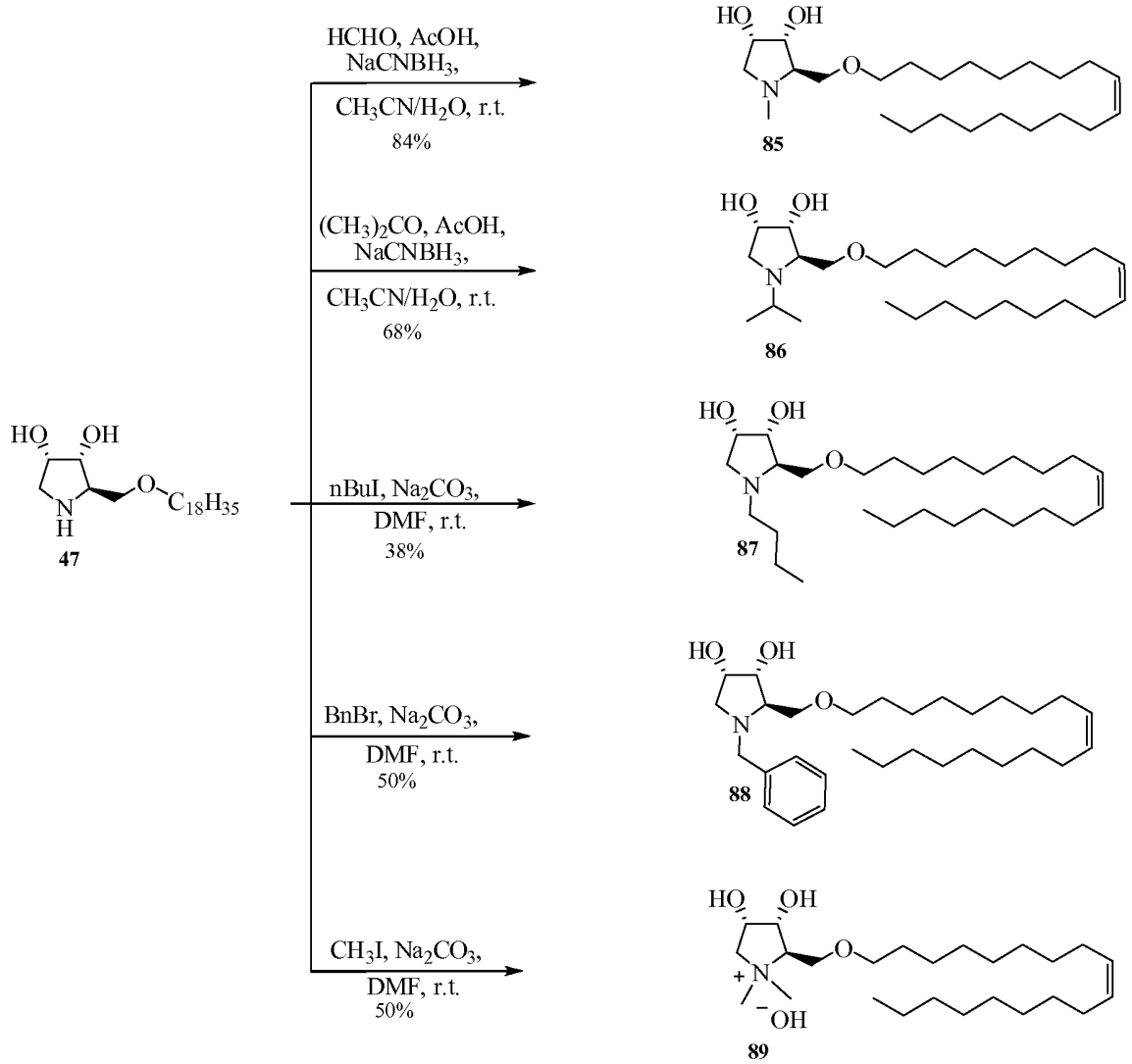

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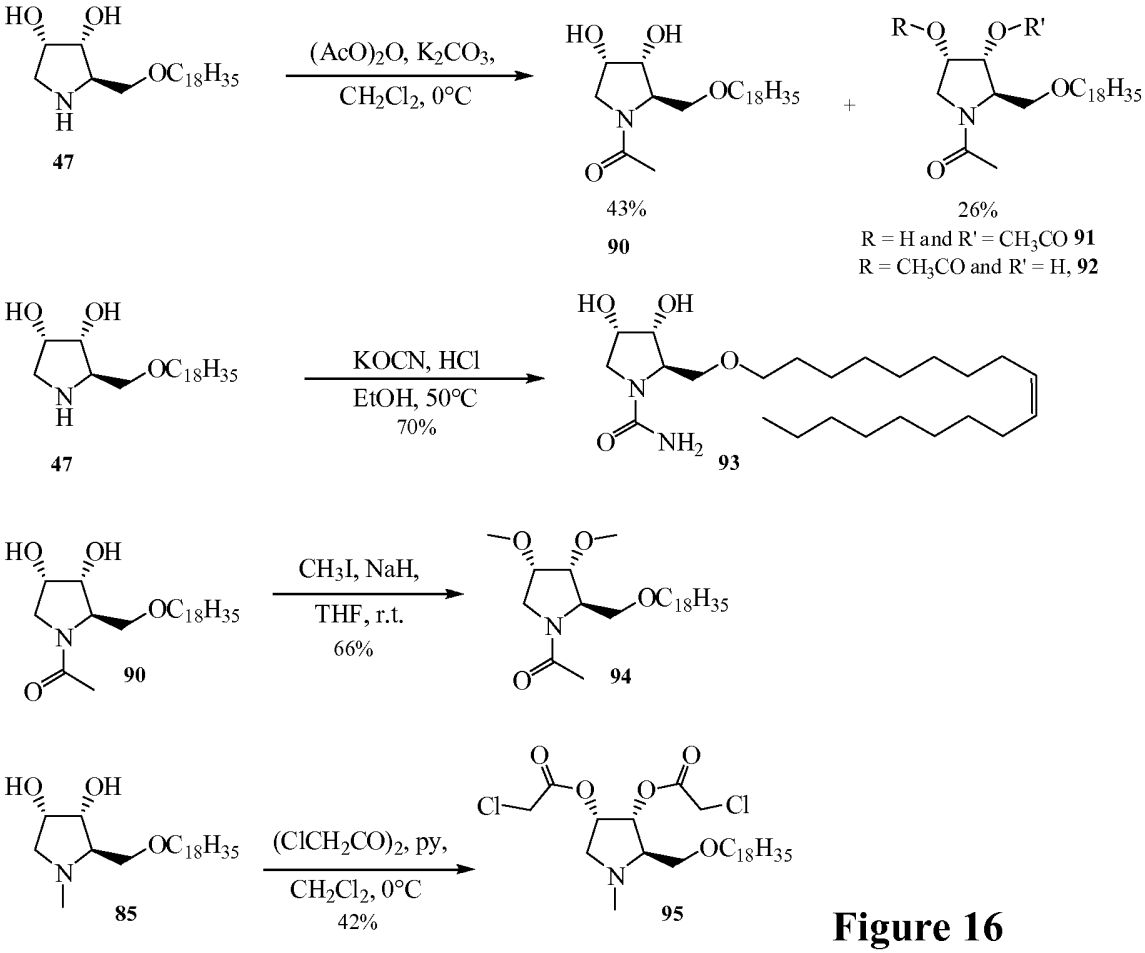

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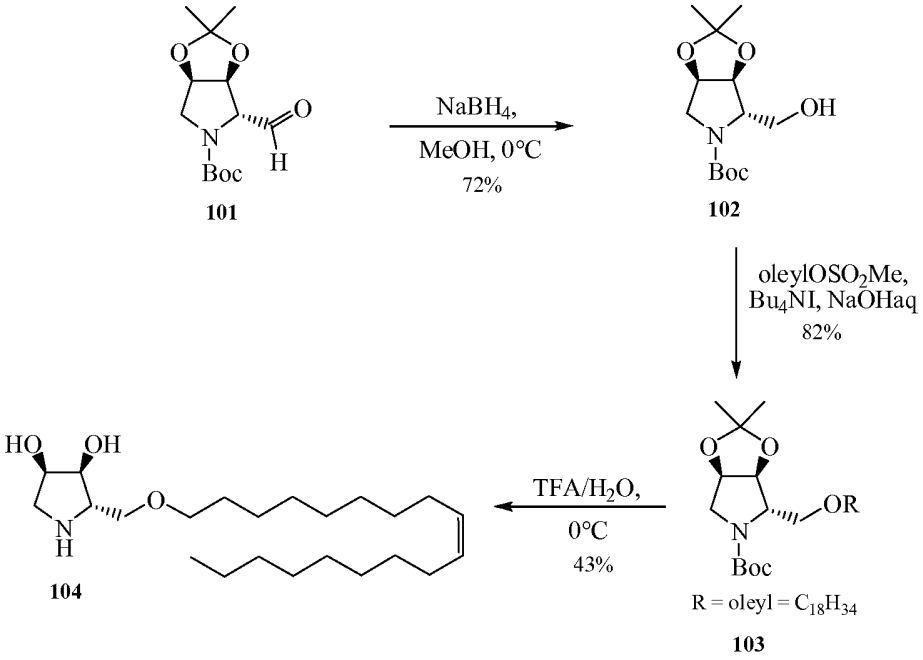

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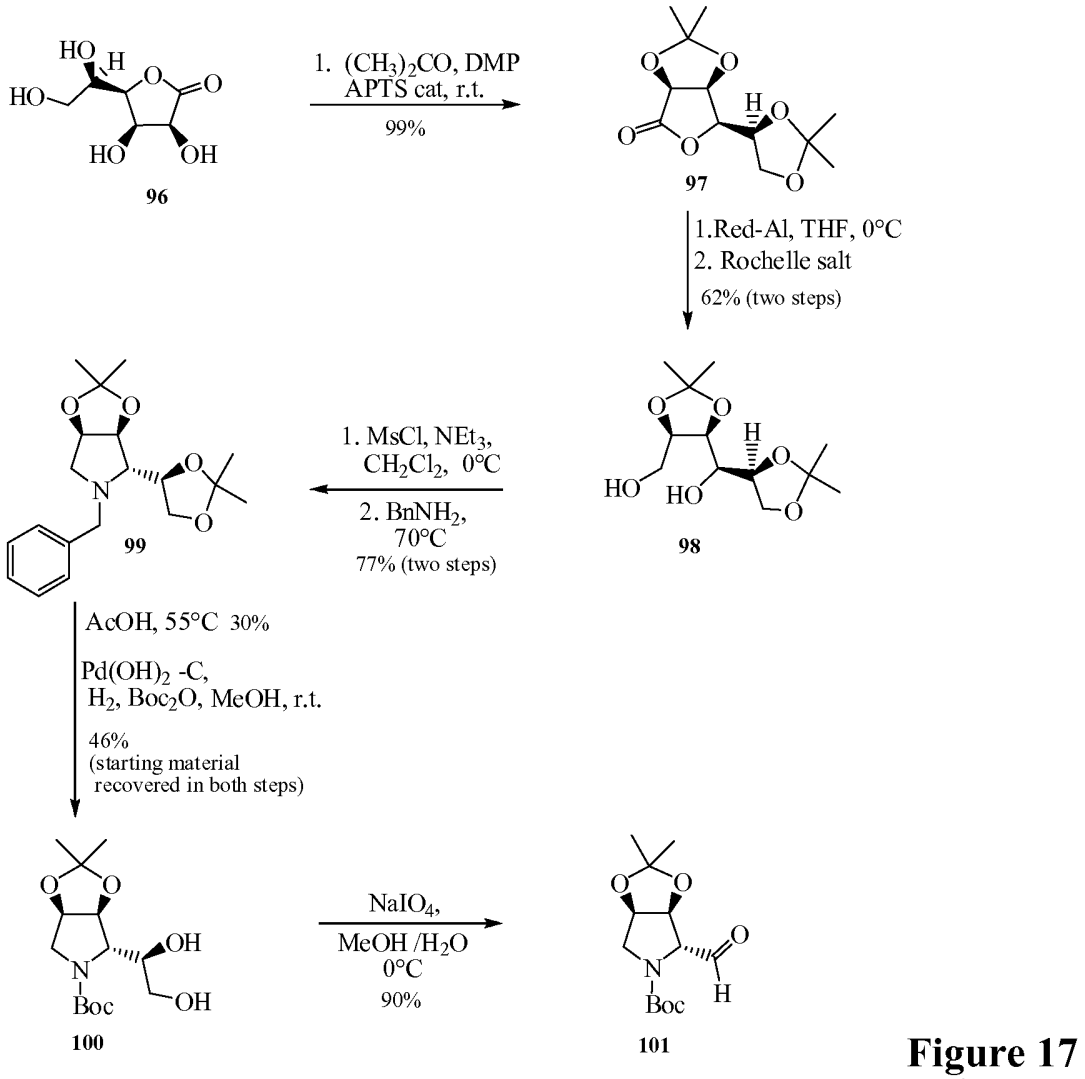

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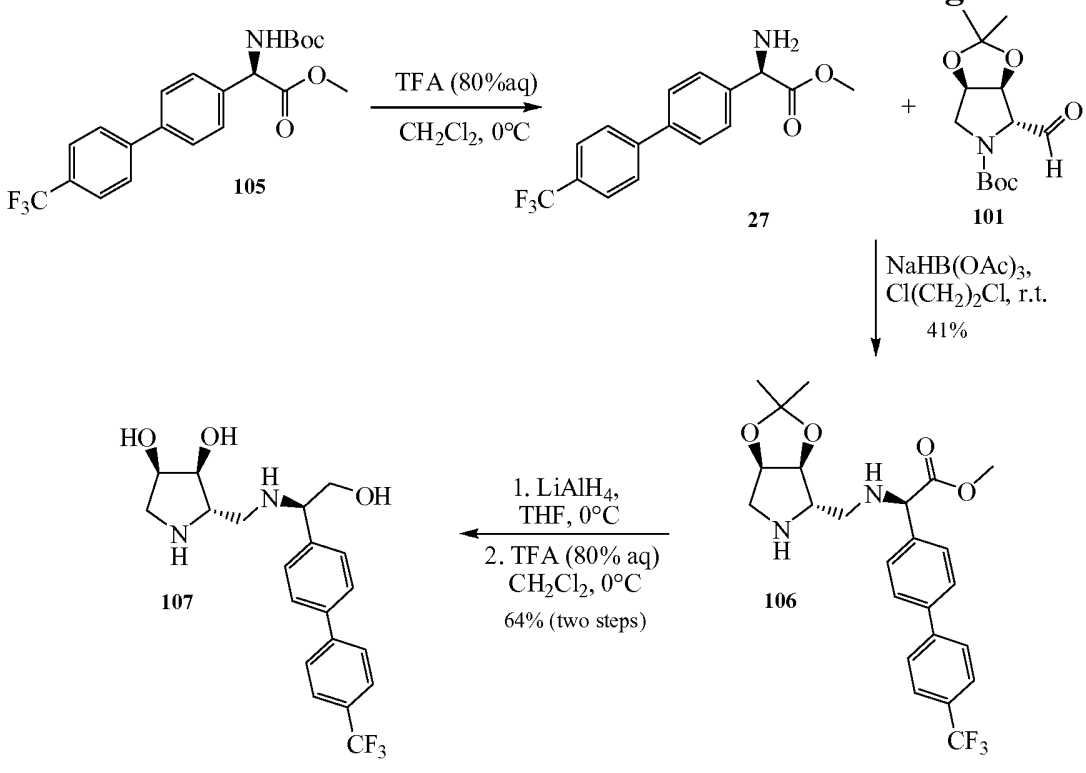
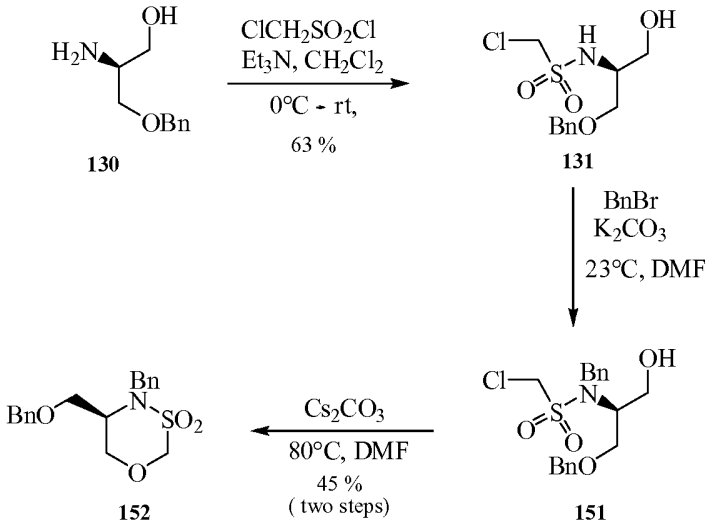


Fig. 19



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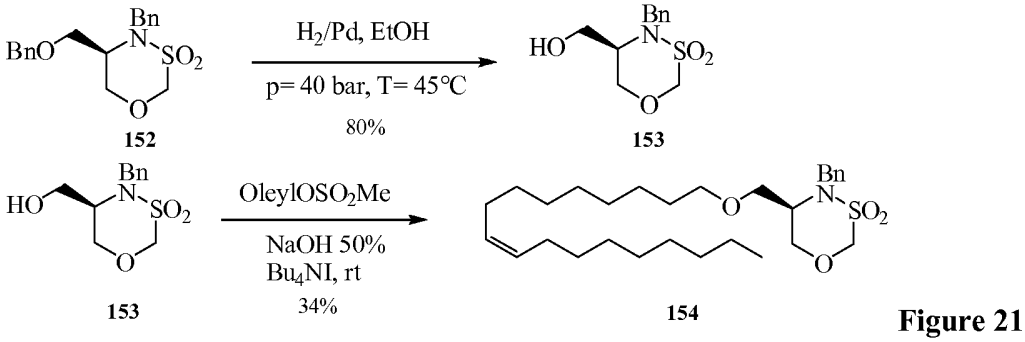

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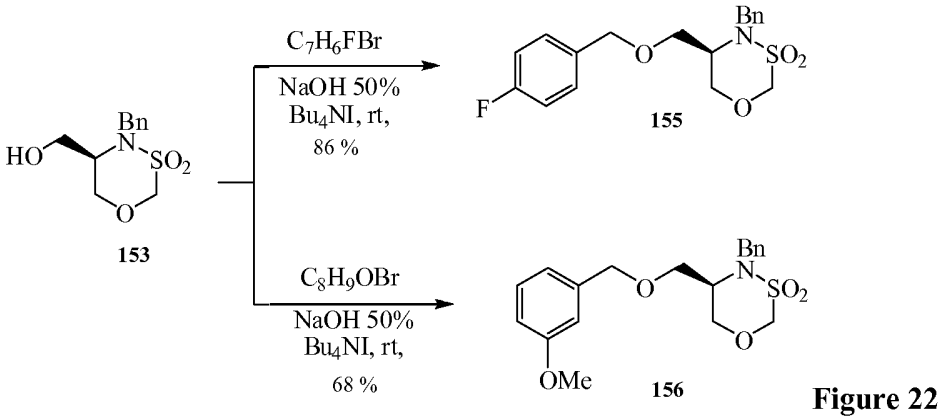

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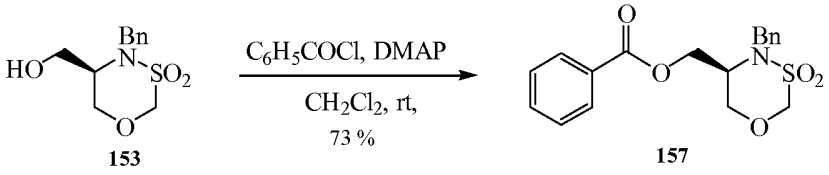

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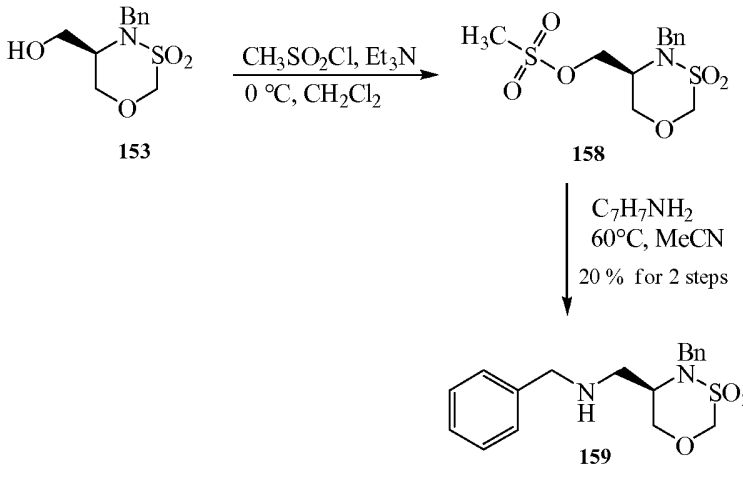

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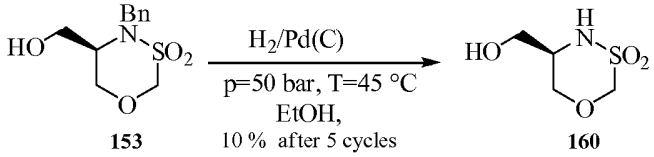

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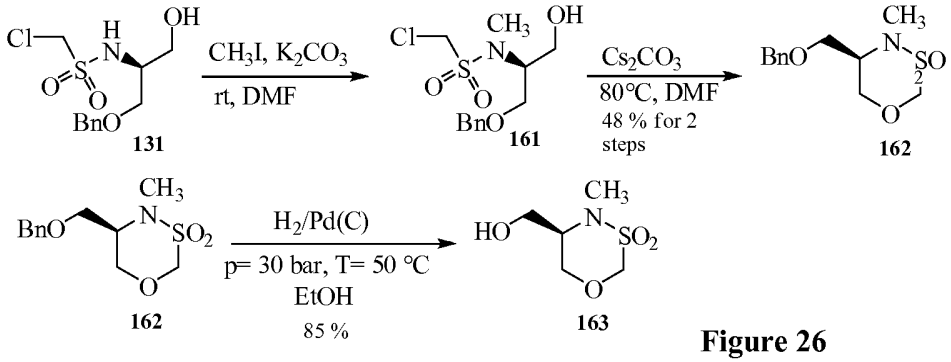

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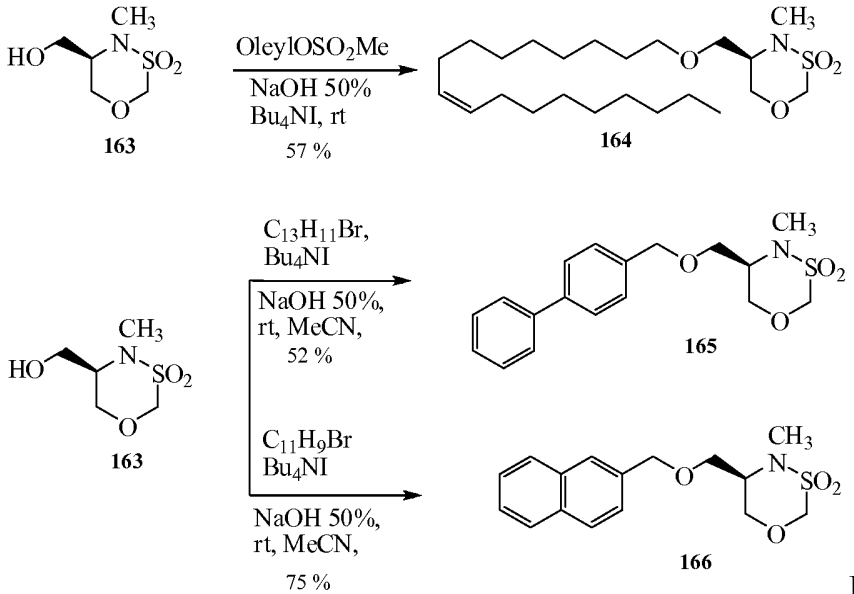

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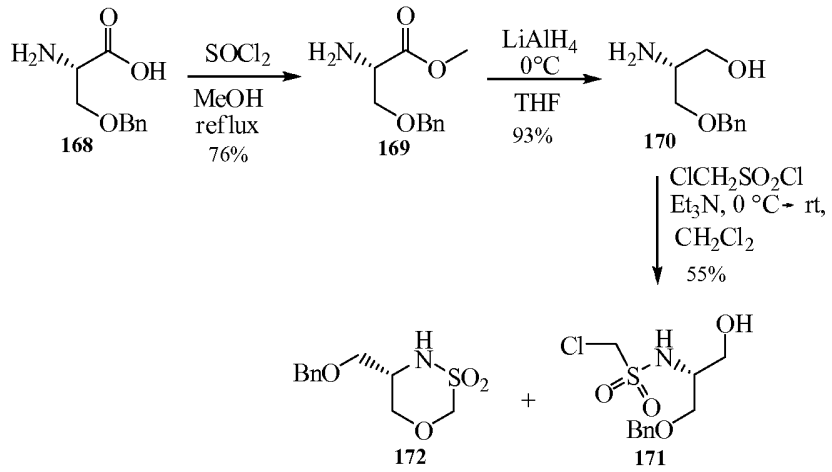

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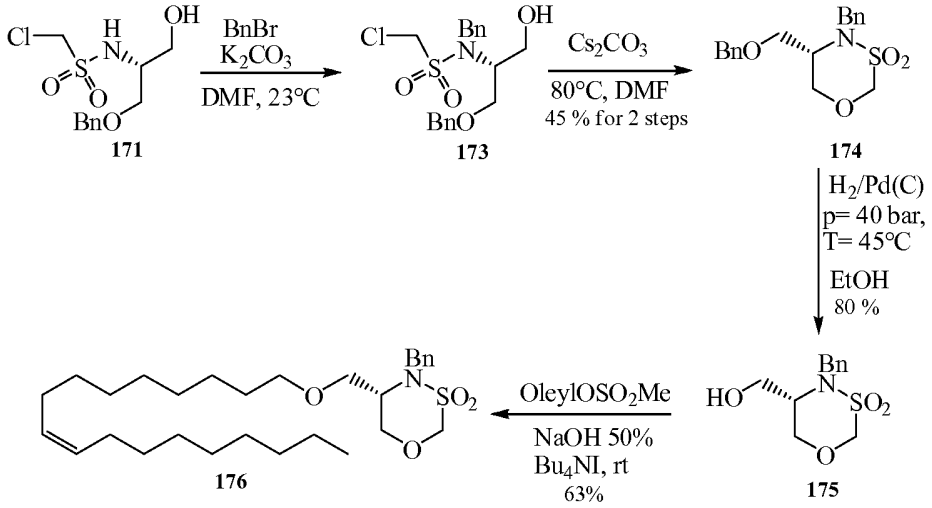

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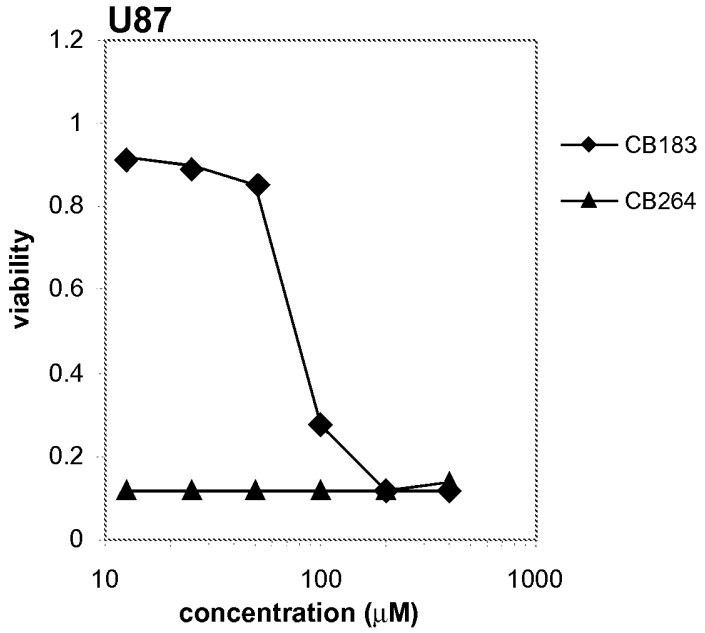


Figure 30

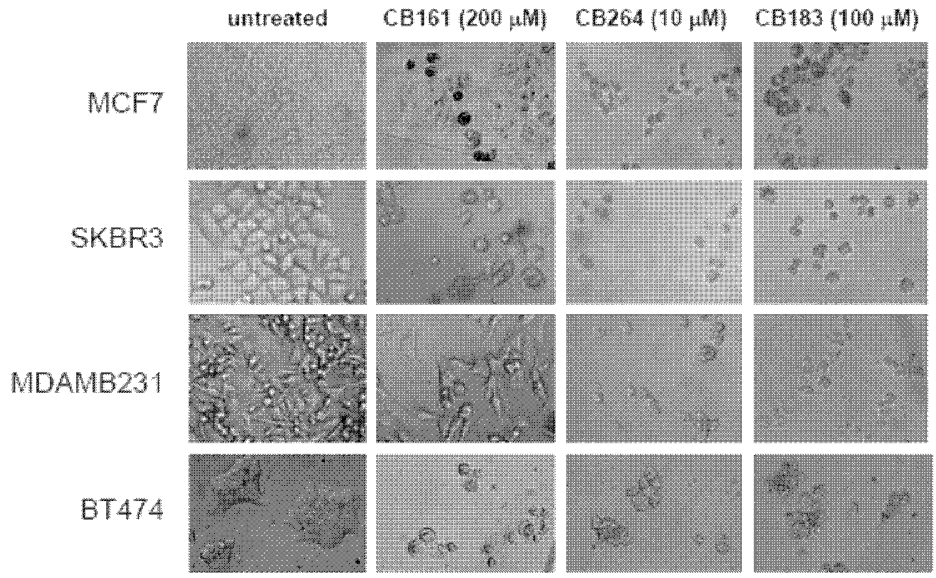
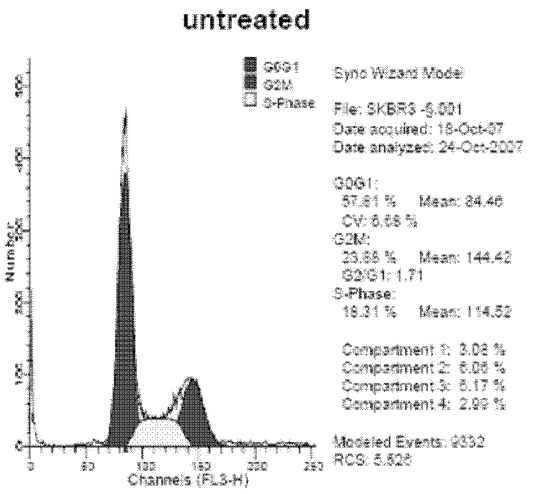

untreated
CB161 (200 μM)
CB264 (10 μM)
CB183 (100 μM)
MCF7
SKBR3
MDAMB231
BT474

Figure 31



Figures 32 A

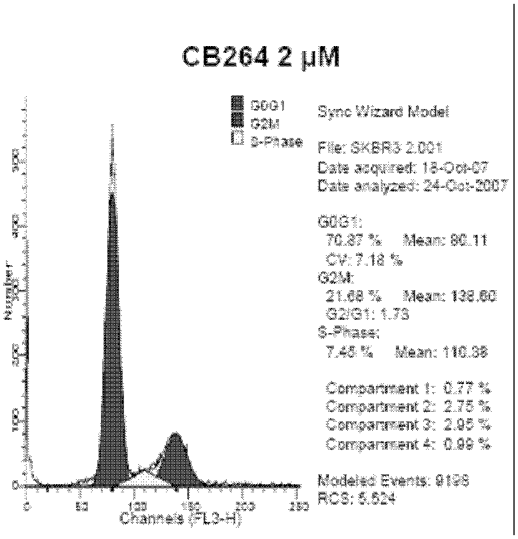
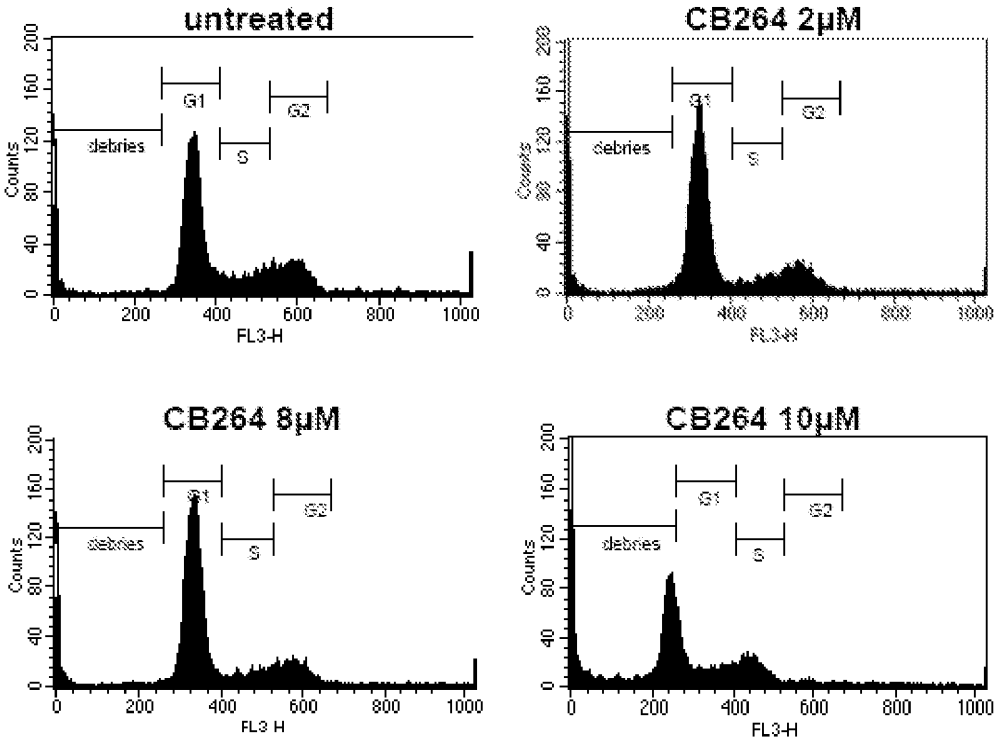


Figure 32 B



Figures 33 A - D