

DIMERS OF ARTEMISININ DERIVATIVES, PREPARATION THEREOF
AND THERAPEUTIC USE THEREOF

5 The present invention relates to dimers of artemisinin derivatives, their preparation and their therapeutic application.

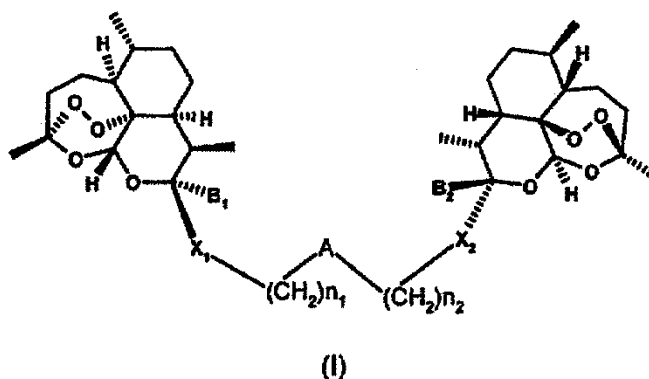
10 More particularly, the invention relates to dimers of artemisinin derivatives having an anticancer activity, and in particular a cell proliferation inhibiting activity.

15 Currently, most commercial compounds used in chemotherapy have major problems of side effects, of tolerance by patients or of resistance. Thus, there is a great need for novel classes of compounds capable of acting as anticancer agents.

20 Among natural products, artemisinin is a sesquiterpene endoperoxide which was isolated in 1971 from the plant *Artemisia annua* and has antimalarial properties. Some simple derivatives, such as dihydroartemisinin or artemether, have been prepared and also have antimalarial properties. In addition to this activity,
25 it has been shown that some artemisin derivatives and dimers have anticancer properties (J. Med. Chem. 2003, 46, 987-994; patent US 6,790,863).

30 The problem which the present invention proposes to solve is to obtain novel products in the form of artemisinin dimers having an anticancer activity.

The subject of the present invention is products corresponding to the general formula (I)



in which:

- 5 a) A is a divalent group chosen from -S-, -SO-,
 -SO₂-, -NR_a-, -N⁺(O⁻)R_a-, -CONR_a-, -NR_aSO₂-, -CO-,
 -COO-, -NR_aCONR_b-, -NR_aSO₂NR_b-, -OP(O)(OR_a)O-,
 -OCONR_a-, -OCOO-, -O-, -C(=N-OR_a)-, or an
 10 epoxide, (C₁-C₆)alkylene, (C₁-C₆)alkenylene,
 (C₁-C₆)alkynylene, (C₃-C₈)cycloalkylene, (C₄-C₈)-
 cycloalkenylene, arylene, heteroarylene or
 heterocyclyl group, it being possible for these
 last nine groups to be optionally substituted
 with one or more substituents R_a or R_b;
 15
- b) X₁ and X₂ are identical or different, and are
 chosen from N, O, S;
- c) B₁ and B₂ are identical or different and
 20 represent a -(CF₂)_p-R_c in which R_c is
 independently F, (C₁-C₆)alkyl, (C₁-C₆)alkenyl,
 (C₁-C₆)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₈)cyclo-
 alkenyl, aryl, heteroaryl, heterocyclyl, -COR₁,
 -COOR₁, -CONR₁R₂, -OR₁ or -SR₁, it being possible
 25 for these groups to be optionally substituted
 with one or more substituents R_a or R_b, which
 are identical or different, and p has the value
 1, 2 or 3;
- 30 d) n₁ and n₂ are identical or different and have
 the value 0, 1, 2, 3 or 4;

- 5 e) R_a and R_b are identical or different and are independently chosen from: H, halogen, $-(C_1-C_6)$ -alkyl, $-(C_1-C_6)$ alkyl-COO- R_1 , $-(C_1-C_6)$ alkyl-N R_1R_2 , $-(C_1-C_6)$ alkylaryl, $-(C_1-C_6)$ alkenyl, $-(C_1-C_6)$ alkynyl, aryl, heteroaryl, (C_3-C_8) cycloalkyl, (C_4-C_8) cycloalkenyl, heterocyclyl, -OR₁, -OCOR₁, -COR₁, -COOR₁, -CONR₁R₂, -NR₁R₂, -NR₁COR₂, -SR₁, -SO₂R₁, -CN;
- 10 f) R_1 and R_2 are identical or different and are independently chosen from H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_3-C_8) cycloalkyl, (C_4-C_8) cycloalkenyl, aryl, heteroaryl, heterocyclyl;
- 15 in the form of a base or of an addition salt with an acid, and in the form of a hydrate or a solvate.

None of these dimers of the prior art (J. Med. Chem. 2003, 46, 987-994; patent US 6,790,863) is substituted
20 with a B_1 or B_2 group as described above according to the present invention.

Among the products of general formula (I) which are the subject of the invention, there may be mentioned in
25 particular the products for which B_1 and B_2 are identical and are CF_3 .

Among the products of general formula (I) which are the subject of the invention, there may also be mentioned
30 the products of general formula (I) for which X_1 and X_2 are identical and are O.

Among these products, preferred products are those for which A is -S-, -SO- or -SO₂-.

35 Other products of general formula (I) are those for which A is -N(CH₃)-.

According to the present invention, n_1 and n_2 are

preferably identical and have the value 2, 3 or 4.

Other products of general formula (I) are those for which A is chosen from -NH-, -N(CH₂-C(O)O-CH₂-CH₃)- or
5 -N(CH₂-COOH)-, and optionally characterized in that n₁ and n₂ are identical and have the value 2.

Other products of general formula (I) are those for which A is chosen from (C₁-C₆)alkenylene or epoxide, and
10 optionally characterized in that n₁ and n₂ are identical and have the value 1.

Other products of general formula (I) are those for which A is chosen from -NHCO- or -1,2,3-triazole, and
15 optionally characterized in that n₁ and n₂ are different and independently have the value 1 or 2.

The products of formula (I) may contain one or more asymmetric carbon atoms. They can therefore exist in
20 the form of enantiomers or diastereoisomers. These enantiomers, diastereoisomers and mixtures thereof, including the racemic mixtures, form part of the invention.

25 The products of formula (I) can exist in the form of bases or of addition salts with acids. Such addition salts form part of the invention.

These salts may be prepared with pharmaceutically
30 acceptable acids, but the salts of other useful acids, for example, for the purification or isolation of the products of formula (I) also form part of the invention.

35 The products of formula (I) can also exist in the form of hydrates or solvates, namely in the form of associations or combinations with one or more molecules of water or with a solvent. Such hydrates and solvates also form part of the invention.

In the context of the present invention:

- a halogen atom is understood to mean: a
5 fluorine, a chlorine, a bromine or an iodine;

- an alkyl group is understood to mean a
saturated linear or branched aliphatic group. By way of
examples, there may be mentioned the methyl, ethyl,
10 propyl, isopropyl, butyl, isobutyl, tert-butyl and
pentyl groups, and the like;

- a cycloalkyl group is understood to mean: a
cyclic alkyl group. By way of examples, there may be
15 mentioned the cyclopropyl, methylcyclopropyl,
cyclobutyl, cyclopentyl and cyclohexyl groups, and the
like;

- a fluoroalkyl group is understood to mean: an
20 alkyl group in which one or more hydrogen atoms have
been substituted with a fluorine atom;

- an alkenyl group is understood to mean: a mono-
or polyunsaturated, linear or branched, aliphatic group
25 comprising, for example, one or two ethylenic
unsaturations;

- an alkynyl group is understood to mean: a mono-
or polyunsaturated, linear or branched, aliphatic group
30 comprising, for example, one or two acetylenic
unsaturations;

- an alkoxy group is understood to mean: an
-O-alkyl radical where the alkyl group is as defined
35 above;

- an aryl group is understood to mean: a cyclic
aromatic group comprising from 5 to 14 carbon atoms.
The phenyl, naphth-1-yl, naphth-2-yl, anthracen-9-yl,

1,2,3,4-tetrahydronaphth-5-yl and 1,2,3,4-tetrahydronaphth-6-yl substituents are examples of aryl substituents;

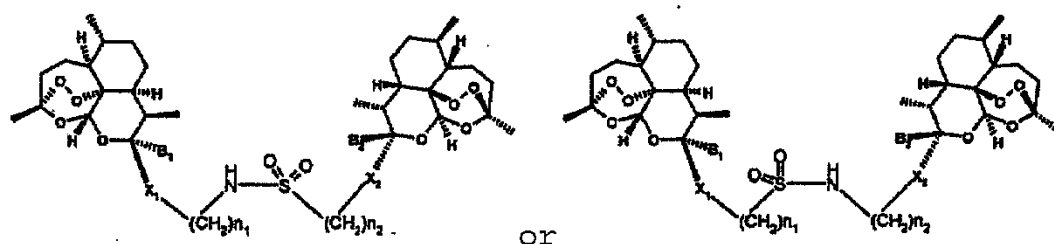
5 - a heteroaryl group is understood to mean: a cyclic aromatic group comprising from 1 to 13 carbon atoms and from 1 to 4 heteroatoms. The pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, 1,2,4-
10 triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, 1,3,5-triazinyl, indolyl, benzo[b]furyl, benzo[b]thienyl, indazolyl, benzimidazolyl, azaindolyl, quinolyl, isoquinolyl, carbazolyl and acridyl substituents are examples of
15 heteroaryl substituent. The term "heteroatom" refers here to an at least divalent atom different from carbon. N, O, S and Se are examples of heteroatom.

 - a cycloalkyl group is understood to mean: a
20 saturated or partially unsaturated cyclic hydrocarbon substituent having from 3 to 12 carbon atoms. The cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclooctyl,
25 bicyclo[2.2.2]octyl, adamantyl and perhydronaphthyl substituents are examples of cycloalkyl substituent.

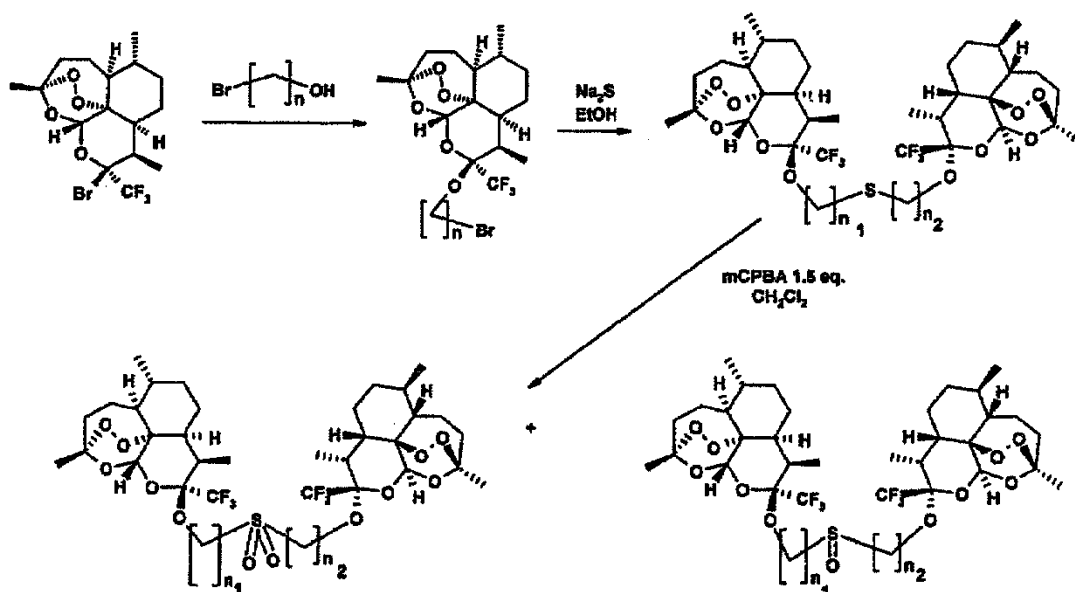
 - a heterocyclyl group is understood to mean: a
30 saturated or partially unsaturated cyclic hydrocarbon substituent having from 1 to 13 carbon atoms and from 1 to 4 heteroatoms. Preferably, the saturated or partially unsaturated cyclic hydrocarbon substituent will be monocyclic and will contain 4 or 5 carbon atoms and 1 to 3 heteroatoms.

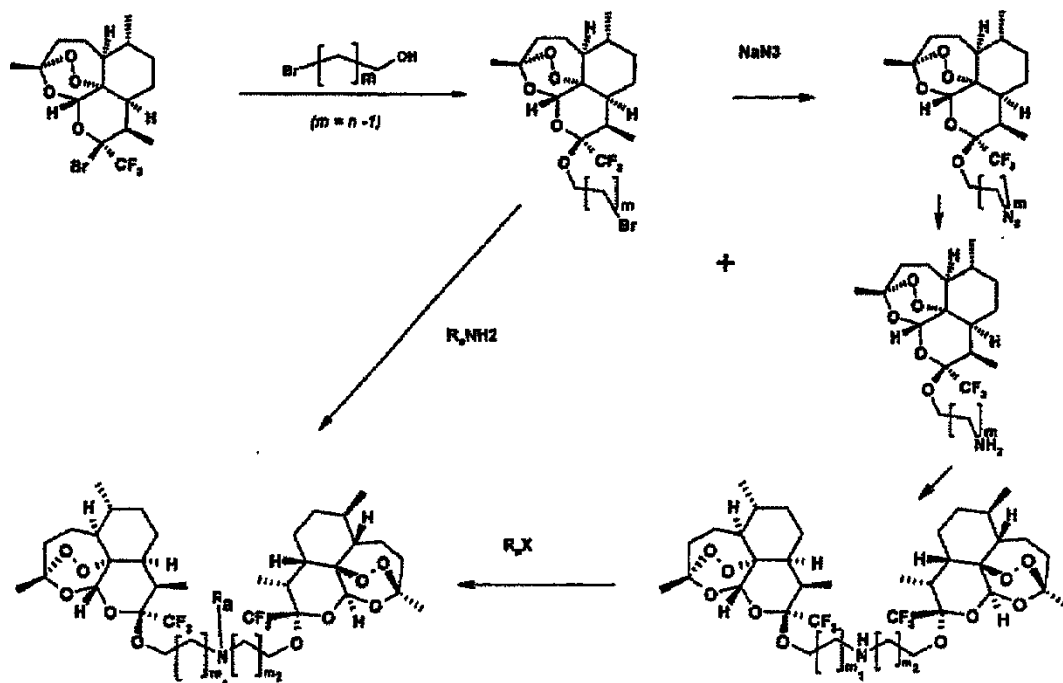
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It is understood that the divalent group A is capable of being bonded in the two possible directions. For example, when the divalent group A is $\text{-NHSO}_2\text{-}$, the product of general formula (I) may be:

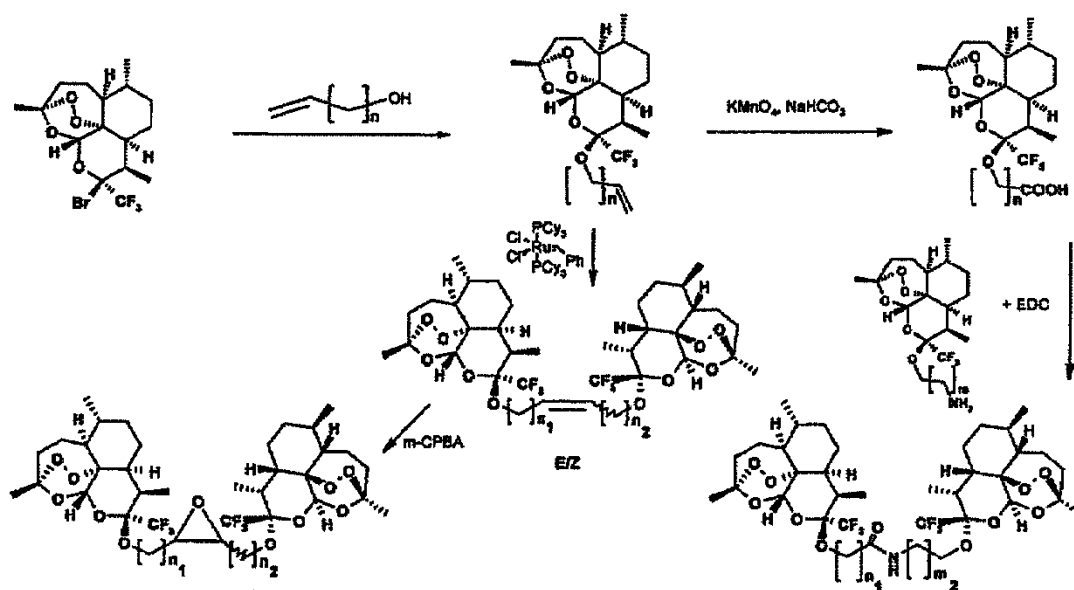


In accordance with the present invention, the products of general formula (I) may be prepared according to conventional methods of organic chemistry. Examples of sythesis are illustrated in schemes 1 to 4 below, in which the starting materials and reagents, when their mode of preparation is not described, are commercially available or are described in the literature or may be prepared according to methods which are described therein or which are known to persons skilled in the art.

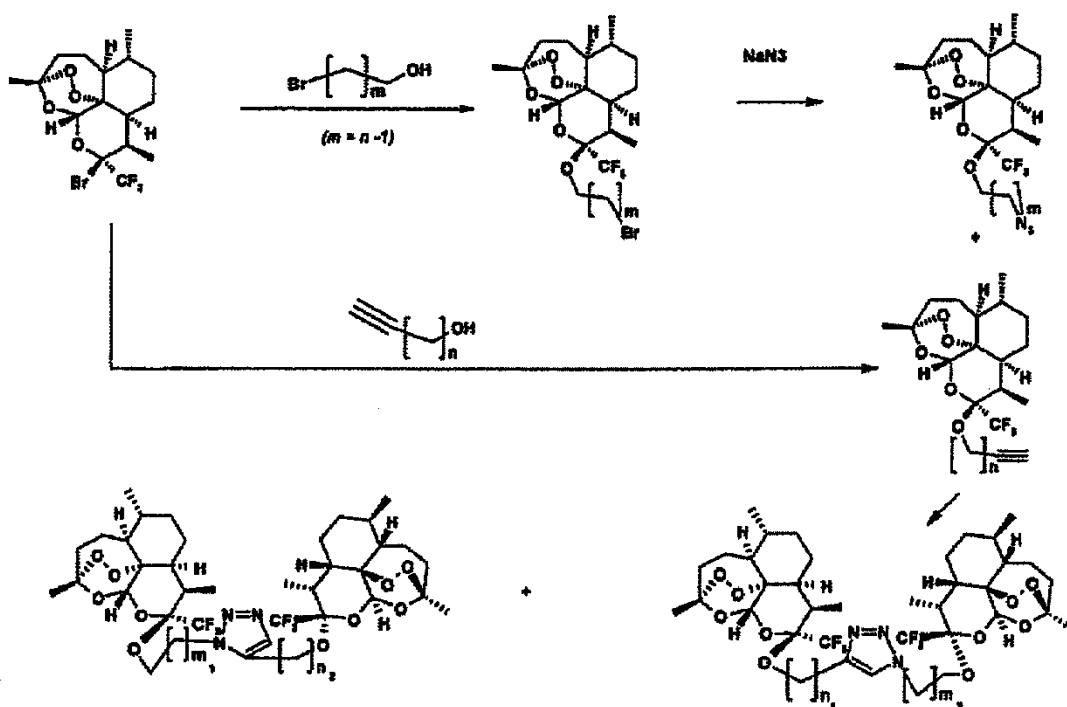




Scheme 2



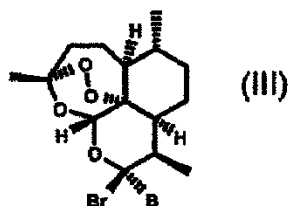
Scheme 3



Scheme 4

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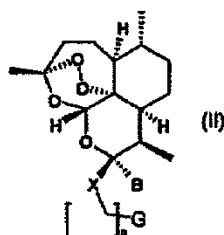
The subject of the present invention relates to a process for preparing a product of general formula (I), characterized in that the product of the following general formula (III):



10

in which B represents a substituent B₁ or B₂ as defined above, undergoes a substitution of the bromine atom with the aid of a nucleophile such as a bromoalcohol, to give a product of the following general formula

15 (II):



in which X represents a substituent X_1 or X_2 , as defined above, n represents n_1 or n_2 , as defined above, and in which either G represents a leaving group such as a bromine atom, and then this product of general formula
5 (II) undergoes a nucleophilic substitution in order to form a dimer of general formula (I) or a precursor of a product of general formula (I), or G represents a chemical functional group F1, which may be optionally activated by a reduction or oxidation reaction, and
10 then this product of general formula (II) reacts with another product of formula (II) where G represents a leaving group such as a bromine atom or a chemical functional group F2 capable of reacting with F1, in order to form a dimer of general formula (I) or a
15 precursor of a product of general formula (I).

The subject of the present invention relates more particularly to the products of general formula (II) in which X is an oxygen atom, n has the value 0, 1, 2, 3
20 or 4, B is a trifluoromethyl group and G represents a bromine atom or an $-N_3$, $-NH_2$, alkenyl, alkynyl or $-COOH$ group. These compounds are useful as intermediate products for the synthesis of the products of general formula (I).

25 The expression leaving group is understood to mean a group which can be easily cleaved from the molecule by breaking a heterolytic bond, with departure of an electron pair. This group may thus be easily replaced
30 by another group during a substitution reaction for example. Such leaving groups are, for example, halogens or an activated hydroxyl group such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, triflate, acetate and the like. Examples of leaving
35 groups and references for their preparation are given in "Advances in Organic Chemistry", J. March, 3rd Edition, Wiley Interscience, p. 310-316.

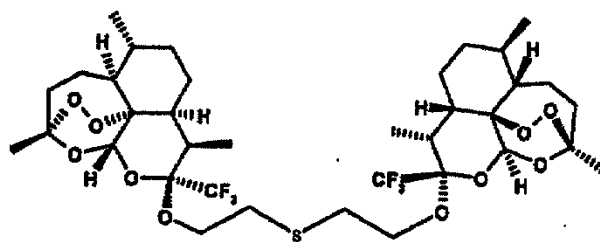
The following examples describe the preparation of some

products in accordance with the invention. These examples are not limiting and only illustrate the present invention.

5 Abbreviations:

°C degrees Celsius; TLC thin layer chromatography; δ chemical shift; d doublet; dd doublet of doublets; DMSO-d⁶ deuterated dimethyl sulfoxide; dt doublet of
 10 triplets; eq. equivalent; ES+/- electrospray (positive/negative modes); g gram; h hour; Hz hertz; IC₅₀ inhibition constant at 50% of activity; J coupling constant; m multiplet; mg milligram; MHz megahertz; ml milliliter; μ l microliter; mm millimeter; μ m
 15 micrometer; mmol millimole; ppm parts per million; q quadruplet; Rf retardation factor; ¹H NMR proton nuclear magnetic resonance; s singlet; bs broad singlet; t triplet; U.V. ultraviolet

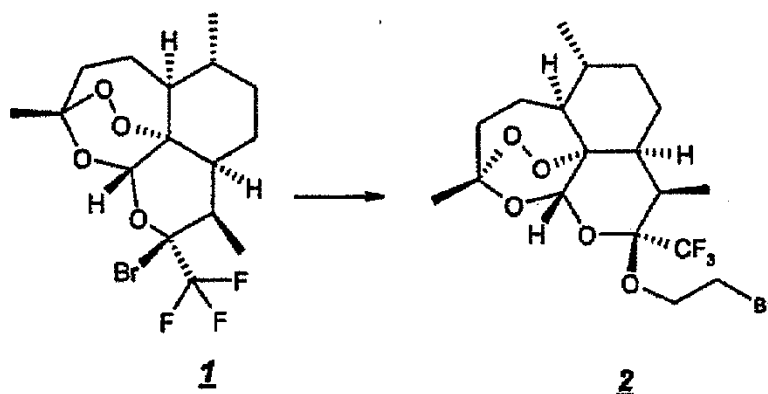
20 **EX1:** (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS,-9'R,10'R,12'R,12'aR)-10,10'-[thiobis(2,1-ethanediyloxy)]bis[decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine



EX1

25

a) Step 1: Preparation of (3S,5aS,6R,8aS,9R,10R,12R,-12aR,3'S,5'aS,6'R,8'aS,9'R,10'R,12'R,12'aR)-10-(2-bromoethoxy)decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine 2
 30



1.2 ml of hexafluoropropanol (5 eq.) and then 1.6 ml of 2-bromoethanol (10 eq.) are successively added at room temperature to a solution of 942 mg (2.27 mmol) of (3S,5aS,6R,8aS,9R,10S,12R,12aR)-10-(bromo)decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine 1 (prepared according to Org. Lett. 2002, 4, 757-759), in 20 ml of dichloromethane. The reaction mixture is then stirred at room temperature for 2 hours 15 minutes, and then 10 ml of a saturated sodium bicarbonate solution are added. The organic phase is dried over magnesium sulfate and evaporated to dryness under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand in heptane and then eluted with a linear gradient from 0 to 100% of the mixture B [(Heptane/Ethyl acetate), (90/10), (V/V)] in A (Heptane). 217 mg (21%) of the expected product 2 are obtained in the form of an oil.

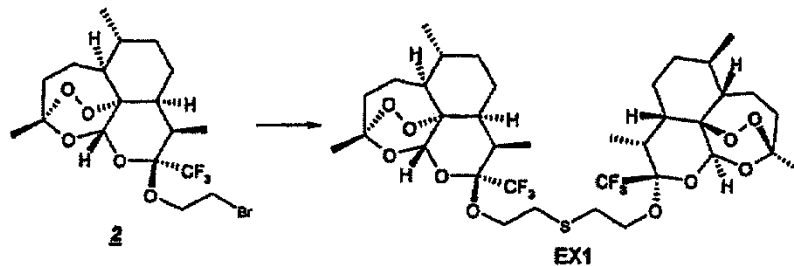
R_f = 0.45 in the system (Heptane/Ethyl acetate), (90/10), (V/V)

ES: m/z=481 (MNa⁺)

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: 0.92 (partially masked m, 1H); 0.96 (d, J = 6.5 Hz, 3H); 1.01 (broad d, J = 7.5 Hz, 3H); from 1.21 to 1.58 (m, 4H); 1.42 (s, 3H); from 1.65 to 2.08 (m, 5H); 2.38 (m, 1H); 2.88 (m, 1H); from

3.45 to 3.57 (m, 2H); 4.02 (m, 1H); 4.17 (m, 1H); 5.57 (s, 1H).

b) Step 2: Preparation of **EX1**



18 mg (0.234 mmol) of sodium sulfate are added, after 10 minutes, to a solution of 215 mg (0.47 mmol) of **2** in 16 ml of anhydrous ethanol, under an inert atmosphere of argon at a temperature in the region of 20°C. The stirring is maintained at this temperature for about 190 hours. 20 ml of saturated sodium chloride solution are then added. The mixture is extracted with 3 x 20 ml of ethyl acetate. The organic phases are combined, washed with 20 ml of a saturated NaCl solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand in heptane, and then eluted with a linear gradient from 0 to 100% of the mixture B [(Heptane/Ethyl acetate), (85/15), (V/V)] in A (Heptane). 60 mg (33%) of the expected product **EX1** are obtained in the form of a foam.

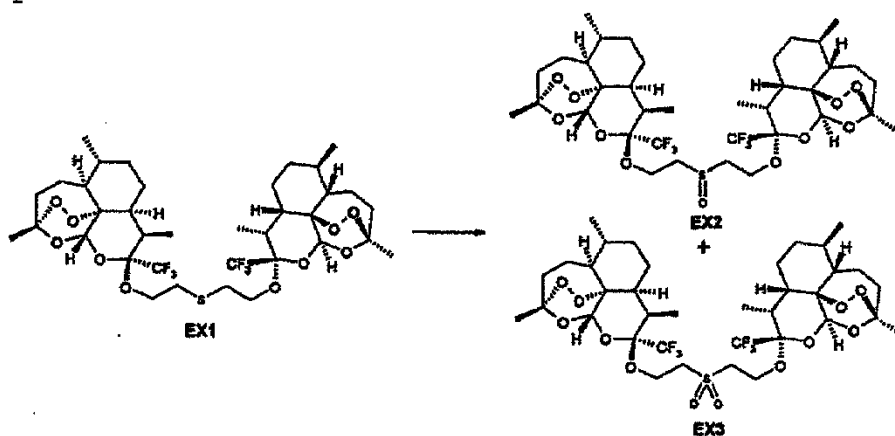
R_f = 0.20 in the system (Heptane/Ethyl acetate), (90/10), (V/V)

ES: m/z=835 (M + HCOOH-H)⁻

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent dimethyl sulfoxide-d₆ (DMSO-d₆) referenced at 2.50 ppm at the temperature of 303K: 0.86 (partially masked m, 2H); 0.90 (d, J = 6.5 Hz, 6H); 0.93 (broad d, J = 7.5 Hz, 6H); 1.22 (m, 2H); from 1.27 to 1.60 (m, 8H); 1.31 (s, 6H); 1.66 (m, 2H); from 1.75 to 1.89 (m, 4H); 2.04 (m, 2H); 2.21 (m, 2H); 2.67 (m, 2H); from 2.71 to 2.87 (m, 4H); 3.64 (m, 2H); 3.94 (m, 2H); 5.58

(s, 2H)

EX2: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS,-
9'R,10'R,12'R,12'aR)-10,10'-[sulfinylbis(2,1-ethane-
5 diyloxy)]bis[decahydro-3,6,9-trimethyl-10-(trifluoro-
methyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine
and **EX3:** (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,-
8'aS,9'R,10'R,12'R,12'aR)-10,10'-[sulfonylbis(2,1-
ethanediylloxy)]bis[decahydro-3,6,9-trimethyl-10-tri-
10 fluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzo-
dioxepine



16.4 mg (0.066 mmol) of meta-chloroperbenzoic acid are
15 slowly added to a solution of 35 mg (0.044 mmol) of **EX1**
in 3 ml of dichloromethane at a temperature in the
region of 20°C. The stirring is maintained at this
temperature for about 3 hours and then 3 ml of a
saturated sodium bicarbonate solution are added. The
20 mixture is extracted with 3 × 10 ml of ethyl acetate.
The organic phases are combined, washed with 2 × 10 ml
of a saturated aqueous sodium chloride solution, dried
over magnesium sulfate, filtered and evaporated to
dryness under reduced pressure. The oily residue
25 obtained is chromatographed on silica gel conditioned
beforehand in heptane, and then eluted with a linear
gradient from 0 to 100% of ethyl acetate in heptane.
14.5 mg (40%) of the product **EX3** are obtained in the
form of a white solid:

30 R_f = 0.60 in the system (Heptane/Ethyl acetate),
(50/50) (v/v)

ES: $m/z=867$ ($M + \text{HCOOH-H}$)⁻

¹H NMR at 500 MHz on a BRUKER AVANCE DRX-500 spectrometer with the chemical shifts (δ in ppm) - in the solvent dimethyl sulfoxide-d₆ (DMSO-d₆) referenced at 2.50 ppm at a temperature of 298K: 0.85 (partially masked m, 2H); 0.89 (d, $J = 6.5$ Hz, 6H); 0.92 (broad d, $J = 7.5$ Hz, 6H); 1.18 (m, 2H); 1.32 (s, 6H); 1.36 (m, 2H); from 1.47 to 1.58 (m, 6H); 1.62 (m, 2H); 1.71 (m, 2H); 1.84 (m, 2H); 2.04 (m, 2H); 2.21 (m, 2H); 2.68 (m, 2H); 3.48 (m, 2H); 3.59 (m, 2H); 3.83 (m, 2H); 4.19 (m, 2H); 5.63 (s, 2H).

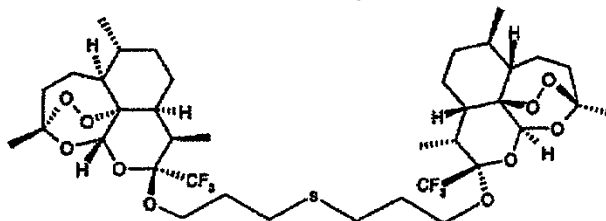
and 12.4 mg (35%) of the product **EX2** in the form of a white foam:

R_f = 0.22 in the system (Heptane/Ethyl acetate), (50/50), (V/V)

ES: $m/z=851$ ($M + \text{HCOOH-H}$)⁻

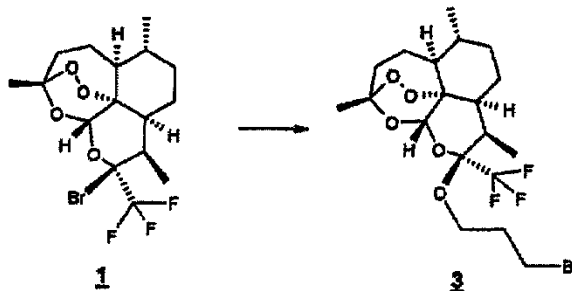
¹H NMR at 500 MHz on a BRUKER AVANCE DRX-500 spectrometer with the chemical shifts (δ in ppm) - in the solvent dimethyl sulfoxide-d₆ (DMSO-d₆) referenced at 2.50 ppm at a temperature of 298K (a 50%-50% mixture of isomers): 0.85 (partially masked m, 2H); 0.88 (d, $J = 6.5$ Hz, 3H); 0.90 (d, $J = 6.5$ Hz, 3H); 0.93 (broad d, $J = 7.5$ Hz, 6H); from 1.14 to 1.89 (m, 16H); 1.31 (s, 3H); 1.32 (s, 3H); 2.03 (m, 2H); 2.20 (m, 2H); 2.67 (m, 2H); 2.98 (m, 2H); 3.12 (m, 2H); 3.79 (m, 1H); 3.87 (m, 1H); from 4.11 to 4.20 (m, 2H); 5.58 (s, 1H); 5.61 (s, 1H).

EX4: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS,-9'R,10'R,12'R,12'aR)-10,10'-[thiobis(3,1-propanediyl-oxy)]bis[decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine



EX4

a) Step 1: Preparation of (3*S*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*, -
12*aR*,3'*S*,5'*aS*,6'*R*,8'*aS*,9'*R*,10'*R*,12'*R*,12'*aR*)-10(3-bromo-
propoxy)decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-
3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepine 3



0.607 ml of hexafluoropropanol (5 eq.) and then 1.03 ml
of 3-bromopropanol (10 eq.) are successively added at
room temperature to a solution of 471 mg (1.14 mmol) of
1 in 7 ml of dichloromethane. The reaction mixture is
then stirred at room temperature for 2 hours
30 minutes, and then 5 ml of a saturated sodium
bicarbonate solution are added, the organic phase is
dried over magnesium sulfate, filtered and evaporated
to dryness under reduced pressure. The oily residue
obtained is chromatographed on silica gel conditioned
beforehand in heptane and then eluted with a linear
gradient from 0 to 100% of the mixture B
[(Heptane/Ethyl acetate), (90/10), (V/V)] in A
(Heptane). 229 mg (43%) of the expected product 3 are
obtained in the form of an oil.

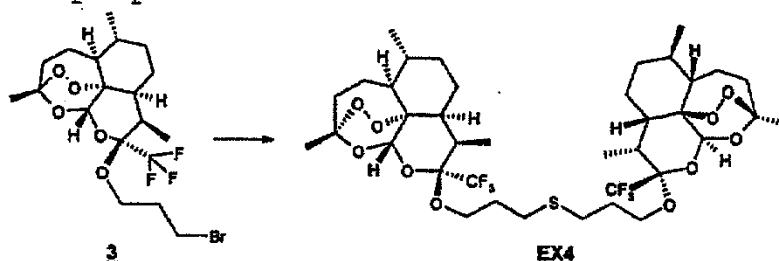
$R_f = 0.38$ in the system (Heptane/Ethyl acetate),
(90/10), (V/V)

CI: $m/z=490$ (MNH_4)⁺; $m/z=354$ ($m/z=490 - BrCH_2CH_2CH_2OH + 2H$)⁺

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400
spectrometer with the chemical shifts (δ in ppm) - in
the solvent chloroform-*d*₁ (CDCl₃-*d*₁) referenced at 7.27
ppm at the temperature of 303K: 0.90 (partially masked
m, 1H); 0.97 (d, $J = 6.5$ Hz, 3H); 1.00 (broad d, $J =$
7.5 Hz, 3H); from 1.22 to 1.54 (m, 4H); 1.44 (s, 3H);
from 1.60 to 1.73 (m, 2H); 1.82 (m, 1H); 1.91 (m, 1H);

from 2.00 to 2.20 (m, 3H); 2.39 (m, 1H); 2.87 (m, 1H);
from 3.45 to 3.55 (m, 2H); 3.80 (m, 1H); 3.94 (m, 1H);
5.41 (s, 1H).

5 b) Step 2: preparation of **EX4**



18.2 mg (0.23 mmol) of sodium sulfide are added, after
10 minutes, to a solution of 220 mg (0.46 mmol) of the
product **3** in 16 ml of anhydrous ethanol, under an inert
10 atmosphere of argon at a temperature in the region of
20°C, the stirring is maintained at this temperature
for about 80 hours and then 20 ml of a saturated sodium
chloride solution are added. The mixture is extracted
with 3 × 20 ml of ethyl acetate. The organic phases are
15 combined, washed with 20 ml of a saturated aqueous
sodium chloride solution, dried over magnesium sulfate,
filtered and evaporated to dryness under reduced
pressure. The oily residue obtained is chromatographed
on silica gel conditioned beforehand in heptane and
20 then eluted with a linear gradient from 0 to 100% of
the mixture B [(Heptane/Ethyl acetate), (85/15), (V/V)]
in A (Heptane). 103 mg (54%) of the expected product
EX4 are obtained in the form of a white solid.

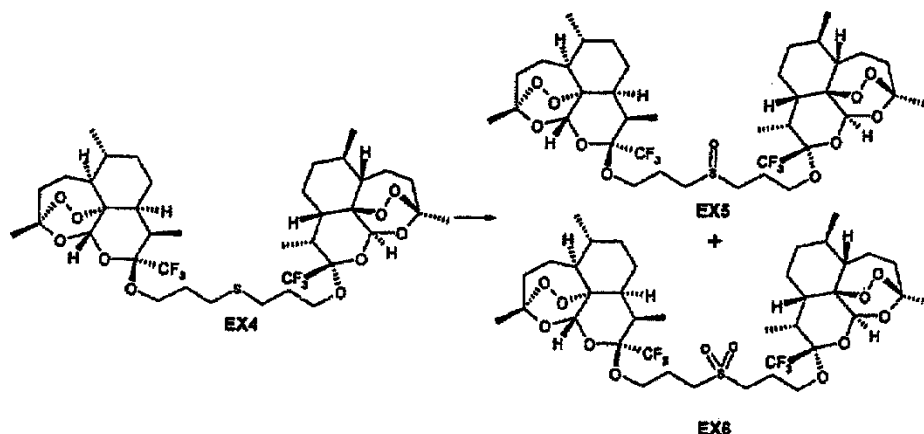
R_f = 0.20 in the system (Heptane/Ethyl acetate),
25 (90/10), (V/V)

ES: m/z=841 MNa⁺

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400
spectrometer with the chemical shifts (δ in ppm) - in
the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27
30 at the temperature of 303K: 0.93 (partially masked m,
2H); 0.97 (d, J = 6.5 Hz, 6H); 1.00 (broad d, J =
7.5 Hz, 6H); from 1.22 to 1.38 (m, 4H); 1.43 (s, 6H);
from 1.44 to 1.55 (m, 4H); from 1.63 to 1.74 (m, 12H);
2.04 (m, 2H); 2.38 (m, 2H); from 2.51 to 2.66 (m, 4H);

2.85 (m, 2H); 3.71 (m, 2H); 3.91 (m, 2H); 5.37 (s, 2H).

EX5: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS,-
9'R,10'R,12'R,12'aR)-10,10'-[sulfinylbis(3,1-propane-
5 diyloxy)]bis[decahydro-3,6,9-trimethyl-10-(trifluoro-
methyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine
and **EX6:** (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,-
8'aS,9'R,10'R,12'R,12'aR)-10,10'-[sulfonylbis(3,1-
10 propanediylloxy)]bis[decahydro-3,6,9-trimethyl-10-
(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-
benzodioxepine



9.1 mg (0.036 mmol) of meta-chloroperbenzoic acid are
slowly added to a solution of 21.4 mg (0.026 mmol) of
15 **EX4** in 2 ml of dichloromethane at a temperature in the
region of 20°C. The stirring is maintained at this
temperature for about 3 hours and then 3 ml of a
saturated sodium bicarbonate solution are added. The
mixture is extracted with 3 x 10 ml of ethyl acetate.
20 The organic phases are combined, washed with 2 x 10 ml
of a saturated aqueous sodium chloride solution, dried
over magnesium sulfate, filtered and evaporated to
dryness under reduced pressure. The oily residue
obtained is chromatographed on silica gel conditioned
25 beforehand in heptane and then eluted with a linear
gradient from 0 to 100% of ethyl acetate in heptane.
7.7 mg (34%) of the product **EX6** are obtained in the
form of a white solid.

R_f = 0.68 in the system (Heptane/Ethyl acetate),
30 (50/50), (V/V)

ES. m/z-873 MNa⁺

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d1 (CDCl3-d1) referenced at 7.27 at the temperature of 303K: 0.92 (partially masked m, 2H); 0.97 (d, J = 6.5 Hz, 6H); 1.00 (broad d, J = 7.5 Hz, 6H); from 1.23 to 1.38 (m, 4H); 1.43 (s, 6H); from 1.44 to 1.72 (m, 8H); 1.83 (m, 2H); 1.92 (m, 2H); 2.05 (m, 2H); 2.12 (m, 4H); 2.38 (m, 2H); 2.87 (m, 2H); 3.00 (m, 2H); 3.13 (m, 2H); 3.75 (m, 2H); 3.97 (m, 2H); 5.34 (s, 2H).

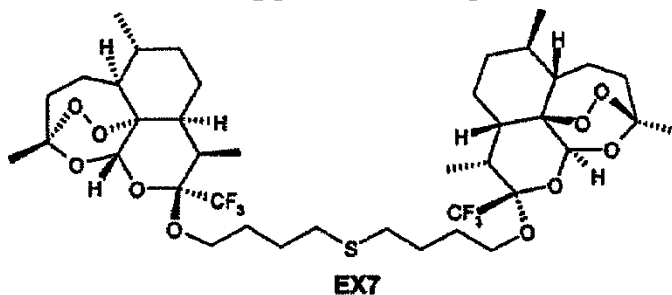
and 8.5 mg (39%) of the product **EX5** in the form of a white foam.

Rf = 0.20 in the system (Heptane/Ethyl acetate), (50/50), (V/V)

ES: m/z=857 MNa⁺

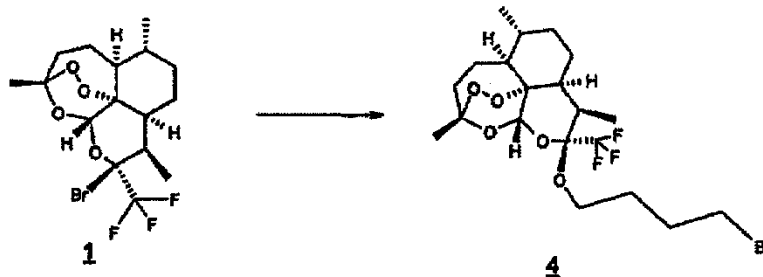
¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d1 (CDCl3-d1) referenced at 7.27 at the temperature of 303K (50%-50% mixture of isomers): 0.90 (partially masked m, 2H); 0.97 (d, J = 6.5 Hz, 6H); 1.00 (broad d, J = 7.5 Hz, 6H); from 1.24 to 1.36 (m, 4H); 1.43 (s, 6H); from 1.45 to 1.72 (m, 8H); 1.82 (m, 2H); 1.92 (m, 2H); from 2.00 to 2.11 (m, 6H), 2.38 (m, 2H); from 2.68 to 2.82 (m, 4H); 2.86 (m, 2H); 3.77 (m, 2H); 3.96 (m, 2H); 5.33 (s, 1H); 5.35 (s, 1H).

EX7: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS, - 9'R,10'R,12'R,12'aR) -10,10' - [thiobis(4,1-butanediyl-oxy)]bis[decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine



a) Step 1: Preparation of 3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,8'aS, - 9'R,10'R,12'R,12'aR

12R,12aR,3'S,5'aS,6'R,8'aS,9'R,10'R,12'R,12'aR)-10-(4-bromobutoxy)decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine, 4



5

1.36 ml of hexafluoropropanol (5 eq.) and then 2.5 g of 4-bromobutanol (6.3 eq.) are successively added at room temperature to a solution of 1.07 g (2.58 mmol) of 1 in 15 ml of dichloromethane. The reaction mixture is then stirred at room temperature for 3 hours and then 6 ml of a saturated sodium bicarbonate solution. The organic phase is dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand in heptane and then eluted with a linear gradient from 0 to 100% of the mixture B [(Heptane/Ethyl acetate), (90/10), (V/V)] in A (Heptane). 90 mg (7%) of the expected product 4 are obtained in the form of an oil.

R_f = 0.40 in the system (Heptane/Ethyl acetate), (9/1), (V/V)

CI: m/z=504 MNH₄⁺

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent dimethyl sulfoxide-d₆ (DMSO-d₆) referenced at 2.50 ppm at the temperature of 298K: 0.92 (partially masked m, 1H); 0.97 (d, J = 6.0 Hz, 3H); 1.00 (broad d, J = 7.5 Hz, 3H); from 1.05 to 1.62 (partially masked m, 6H); 1.43 (s, 3H); from 1.65 to 2.10 (m, 7H); from 2.33 to 2.45 (m, 1H); 2.84 (m, 1H); from 3.40 to 3.51 (m, 2H), 3.63 (m, 1H); 3.88 (m, 1H); 5.32 (s, 1H).

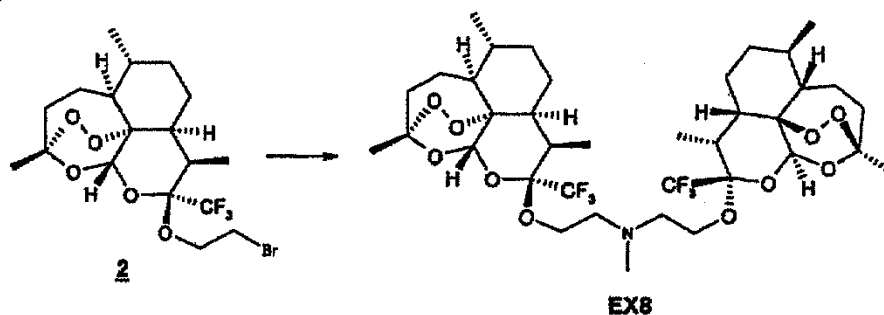
b) Step 2: preparation of **EX7**

Rf = 0.20 in the system (Heptane/Ethyl acetate), (9/1),
(V/V)

¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent dimethyl sulfoxide-d6 (DMSO-d6) referenced at 2.50 ppm at the temperature of 298K: 0.93 (partially masked m, 2H); 0.97 (d, J = 6.0 Hz, 6H); 1.00 (broad d, J = 7.5 Hz, 6H); from 1.22 to 1.37 (m, 4H); 1.43 (s, 6H); 1.50 (m, 4H); from 1.62 to 1.86 (m, 14H); 1.91 (m, 2H); 2.04 (m, 2H); 2.38 (m, 2H); 2.54 (m, 4H); 2.84 (m, 2H); 3.62 (m, 2H); 3.85 (m, 2H); 5.33 (s, 2H).

EX8: 2-[[[(3R,5aS,6R,8aS,9R,10R,12R,12aR)-decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl]oxy]-N-[2-[[[(3R,5aS,6R,8aS,9R,10R,12R,12aR)-decahydro-3,6,9-

trimethyl-10-(trifluoromethyl)-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl]oxy]ethyl]-N-methylethanamine



5 33 mg (0.218 mmol) of sodium iodide and 0.545 ml (1.09 mmol) of a 2M methylamine solution in tetrahydrofuran are successively added to a solution of 100 mg (0.218 mmol) of compound **2** in 0.6 ml of tetrahydrofuran under an inert argon atmosphere at a temperature in the region of 20°C. The stirring is maintained at 40°C for about 20 hours. The reaction mixture is taken up in 3 ml of a saturated aqueous sodium bicarbonate solution and then extracted with 3 × 3 ml of dichloromethane. The organic phases are combined and then dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand in heptane and then eluted with a gradient from 0 to 30% of ethyl acetate in heptane.

10 15 mg (18%) of the expected product **EX8** are obtained in the form of a white solid.

R_f = 0.25 in the system (Heptane/Ethyl acetate), (7/3), (V/V)

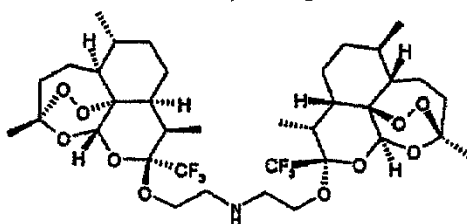
ES: m/z=788 MH⁺

25 ¹H NMR at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K after addition of a drop of acetic acid-d₄ (CD₃OD-d₄): 0.91 (partially masked m, 2H); 0.95 (d, J = 6.5 Hz, 6H); 0.98 (broad d, J = 7.0 Hz, 6H); 1.28 (m, 2H); from 1.33 to 1.63 (m, 8H); 1.39 (s, 6H); 1.69 (m, 2H); 1.78 (m, 2H); 1.89 (m, 2H); 2.02 (partially masked m, 2H); 2.36 (m, 2H); 2.86

30

(partially masked m, 2H); 2.89 (s, 3H); 3.38 (m, 4H); 4.19 (m, 4H); 5.38 (s, 2H).

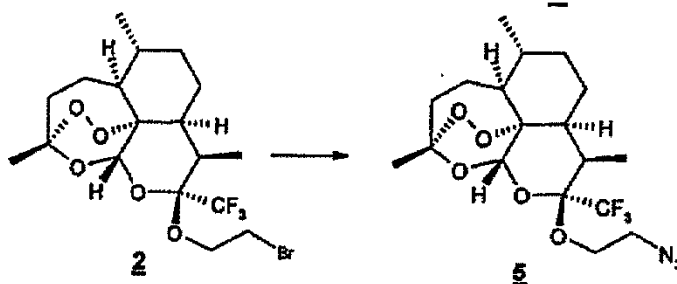
EX 9: 2-{ [(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}-N-(2-{ [(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)ethanamine



EX9

10

a) step 1: preparation of (3R,5aS,6R,8aS,9R,10R,12R,12aR)-10-(2-azidoethoxy)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromene 5



162.5 mg (2.5 mmol) of sodium azide are added to a solution of 574 mg (1.25 mmol) of compound 2 in 20 ml of dimethylformamide under an inert atmosphere of argon at a temperature in the region of 20°C. The stirring is maintained at a temperature in the region of 20°C for 3 hours. The reaction mixture is taken up in 60 ml of distilled water and then extracted with 2 x 100 ml of ethyl acetate. The organic phase is washed with 2 x 80 ml of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. 527 mg (quantitative yield) of the expected product 5 are obtained in the

form of a yellow oil.

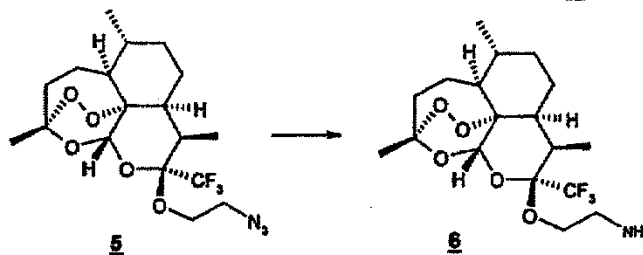
R_f = 0.43 in the system (Heptane/Ethyl acetate), (8/2), (V/V)

¹H NMR (CDCl₃, 400 MHz) δ_{ppm}: 5.48 (s, 1H); 3.97 (m, 1H);
5 3.78 (m, 1H); 3.48 (m, 2H); 2.88 (qu, 1H); 2.39 (td, 1H); 2.05 (dt, 1H); 1.97-1.88 (m, 1H); 1.87-1.77 (m, 2H); 1.76-1.68 (m, 1H); 1.53 (m, 1H); 1.50 (m, 1H); 1.43 (s, 3H); 1.39-1.25 (m, 2H); 1.03 (d, 3H); 1.01-0.89 (m, 1H); 0.98 (d, 3H).

10

b) step 2: preparation of

2-{[(3R,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino-[4,3-i]isochromen-10-yl]oxy}ethanamine, 6



15

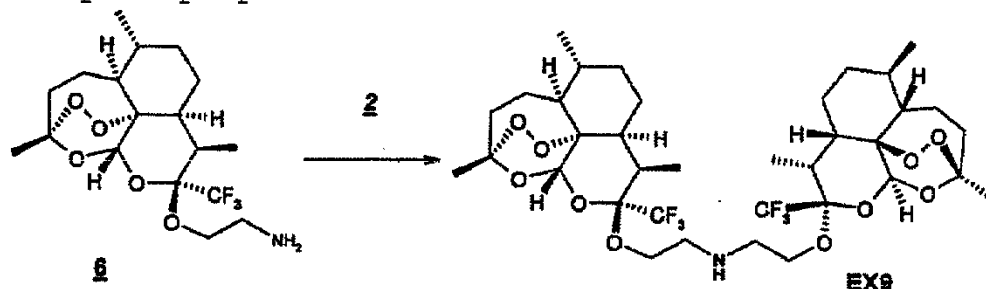
328 mg (1.25 mmol) of triphenylphosphine are added to a solution of 527 mg (1.25 mmol) of compound 5 in 7 ml of tetrahydrofuran under an inert atmosphere of argon at a
20 temperature in the region of 20°C. The stirring is maintained at a temperature in the region of 20°C for about 24 hours. The reaction mixture is taken up in 1 ml of distilled water and then the stirring is continued for about 24 hours at the same temperature.
25 The reaction mixture is concentrated under vacuum and the residue thus obtained is taken up in 5 ml of dichloromethane, washed with 2 ml of a saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered and evaporated to dryness
30 under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand in dichloromethane and then eluted with a linear gradient from 0 to 100% of the mixture B [(Dichloromethane/Methanol), (90/10), (V/V)] in A

(Dichloromethane). 344 mg (70%) of the expected product 6 are obtained in the form of a white powder.

MS: ES⁺: [M+H]⁺ = 396.

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: 0.94 (partially masked m, 1H); 0.97 (d, J = 6.5 Hz, 3H); 1.03 (broad d, J = 7.0 Hz, 3H); 1.30 (m, 2H); from 1.40 to 1.56 (m, 2H); 1.42 (s, 3H); from 1.63 to 1.95 (m, 4H); 2.04 (m, 1H); 2.38 (m, 1H); 2.45 (m spread, 2H); 2.87 (m, 1H); 2.94 (m, 2H); 3.75 (m, 1H); 3.85 (m, 1H); 5.42 (s, 1H).

c) step 3: preparation of EX9



98 mg (0.593 mmol) of potassium iodide, 164 mg (1.19 mmol) of potassium carbonate and 232 mg (0.587 mmol) of compound 6 are successively added to a solution of 282 mg (0.534 mmol) of compound 2 in 7 ml of dimethylformamide under an inert atmosphere of argon at a temperature in the region of 20°C. The stirring is maintained at 70°C for about 7 hours. The reaction mixture is concentrated to dryness under reduced pressure. The residue obtained is taken up in 10 ml of dichloromethane and then washed with 6 ml of distilled water, the aqueous phase is again extracted with 10 ml of dichloromethane. The combined organic phases are washed with 6 ml of a saturated aqueous sodium bicarbonate solution and then dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue obtained is chromatographed on silica gel conditioned beforehand in the mixture (Hexane/Ethyl acetate) (9/1) (V/V) and

then eluted with a gradient from 10 to 60% of ethyl acetate in heptane. 116 mg (28%) of the expected product **EX9** are obtained in the form of a pale yellow solid.

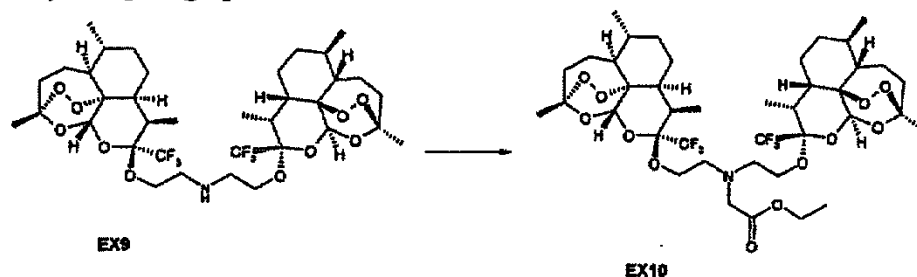
- 5 Rf = 0.16 in the system (Heptane/Ethyl acetate), (8/2), (V/V)

MS: ES⁺: [M+H]⁺ = 774.

ES⁻: [M+HCOOH+H]⁺ = 818.

- 10 ¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d1 (CDCl3-d1) referenced at 7.27 at the temperature of 303K: 0.92 (partially masked m, 2H); 0.98 (d, J = 6.5 Hz, 6H); 1.00 (broad d, J =
15 7.0 Hz, 6H); from 1.20 to 1.39 (m, 4H); 1.42 (s, 6H); from 1.40 to 1.83 (m, 11H); 1.90 (m, 2H); 2.03 (m, 2H); 2.38 (m, 2H); from 2.73 to 2.91 (m, 6H); 3.75 (m, 2H); 3.91 (m, 2H); 5.47 (s, 2H).

- 20 **EX 10:** ethyl N,N-bis(2-{[(3S,5aS,6R,8aS,9R,10R,-12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)glycinate



25

15 μl (0.133 mmol) of the ethyl ester of bromoacetic acid, 8 mg (0.047 mmol) of potassium iodide and 10 mg (0.071 mmol) of potassium carbonate are successively added to a solution of 37 mg (0.047 mmol) of the
30 compound **EX9** in 1 ml of dimethylformamide under an inert atmosphere of argon at a temperature in the region of 20°C. The stirring is maintained at 50°C for 1 hour. The reaction mixture is concentrated to dryness under reduced pressure. The residue obtained is taken

up in 5 ml of ethyl acetate and then washed with 3 ml of distilled water and the aqueous phase is again extracted with 2 × 5 ml of ethyl acetate. The combined organic phases are washed with 2 × 5 ml of a saturated aqueous sodium chloride solution and then dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue obtained is chromatographed on silica gel conditioned beforehand and then eluted in the mixture (Heptane/Ethyl acetate), (80/20), (V/V). 30 mg (74%) of the expected product **EX10** are obtained in the form of a colorless paste.

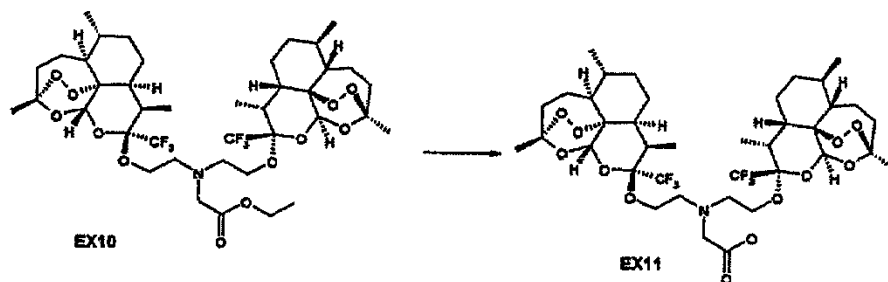
TLC R_f = 0.49 in the system (Heptane/Ethyl acetate), (7/3), (V/V)

MS: ES⁺: [M+H]⁺ = 860.

15 ES⁻: [M+HCOOH+H]⁺ = 904.

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: from 0.80 to 1.00 (m, 14H); from 1.19 to 1.38 (partially masked m, 4H); 1.28 (t, J = 7.0 Hz, 3H); 1.40 (s, 6H); from 1.44 to 1.58 (partially masked m, 4H); from 1.61 to 1.82 (m, 6H); 1.89 (m, 2H); 2.02 (m, 2H); 2.36 (m, 2H); from 2.70 to 2.90 (m, 4H); 3.02 (m, 2H); 3.40 (d, J = 17.5 Hz, 1H); 25 3.61 (m, 2H); 3.67 (d, J = 17.5 Hz, 1H); 3.98 (m, 2H); from 4.06 to 4.22 (m, 2H); 5.40 (s, 2H).

EX 11: N,N-bis(2-{[(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)-glycine



59 μl (0.059 mmol) of a 1N aqueous sodium hydroxide

solution are added to a solution of 10 mg (0.011 mmol) of the compound **EX10** in 0.5 ml of methanol at a temperature in the region of 20°C. The stirring is maintained at the same temperature for about 6.5 hours.

- 5 The reaction mixture is concentrated to dryness under reduced pressure. The residue obtained is taken up in 3 ml of ethyl acetate and then washed with 1 ml of a saturated aqueous sodium chloride solution. The aqueous phase is again extracted with 3 ml of ethyl acetate.
- 10 The combined organic phases are dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue obtained is chromatographed on silica gel conditioned beforehand and then eluted in the mixture
- 15 (Dichloromethane/Methanol), (95/05), (V/V). 8 mg (81%) of the expected product **EX11** are obtained in the form of a colorless solid.

MS: ES⁺: [M+H]⁺ = 832

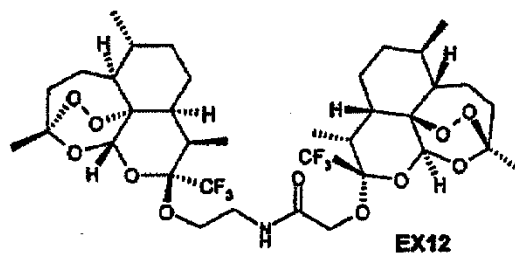
ES⁻: [M-H]⁻ = 830.

- 20 ¹H NMR spectrum at 300 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: 0.92 (partially masked m, 2H); 0.97 (d, J = 6.5 Hz, 6H); 1.01 (broad d, J =
- 25 7.0 Hz, 6H); from 1.20 to 1.38 (partially masked m, 4H); 1.42 (s, 6H); from 1.44 to 1.75 (m, 8H); from 1.80 to 2.10 (m, 6H); 2.39 (m, 2H); from 2.80 to 3.02 (m, 6H); 3.38 (d, J = 17.5 Hz, 1H); 3.55 (d, J = 17.5 Hz, 1H); from 3.77 to 3.98 (m, 4H); 5.32 (s, 2H).

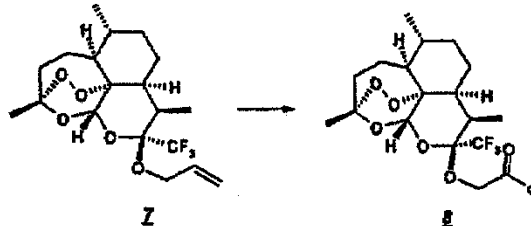
30

EX 12: 2-{ [(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}-N-(2-{ [(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino-

35 [4,3-i]isochromen-10-yl]oxy}ethyl)acetamide



a) step 1: preparation of {[(3R,5aS,6R,8aS,9R,10R,-
12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)deca-
5 hydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-
yl]oxy}ethyl)acetic acid, 8

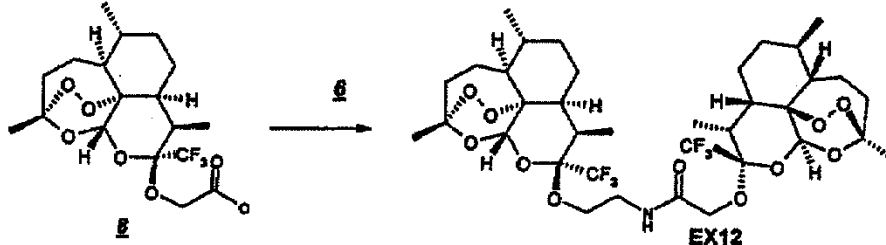


117 mg (0.742 mmol) of potassium permanganate and then
10 11 mg (0.127 mmol) of sodium bicarbonate are
successively added at room temperature to a solution of
100 mg (0.255 mmol) of 7 (prepared according to
WO2003035651), in 2 ml of acetone. The reaction mixture
is then stirred at room temperature for 3 hours and
15 then 1 eq. of a 1N aqueous hydrochloric acid solution
are added. The stirring is continued at room
temperature for about 18 hours. The reaction medium is
filtered and then evaporated to dryness under reduced
pressure. The residue obtained is taken up in 10 ml of
20 ethyl acetate. The organic phase is washed with 3 ml of
distilled water, the aqueous phase is acidified with
2 ml of a 1N aqueous hydrochloric acid solution and
then extracted with 10 ml of ethyl acetate. The organic
phase is dried over magnesium sulfate, filtered and
25 then evaporated to dryness under reduced pressure.
27 mg (26%) of the expected product 8 are obtained in
the form of a white solid.

¹H NMR (CDCl₃, 300 MHz) δ_{ppm} : 5.47 (s, 1H); 4.67 (d, 1H);
4.26 (d, 1H); 2.91 (qu, 1H); 2.38 (td, 1H); 2.19 (dq,
30 1H); 2.04 (dt, 1H); 1.90 (m, 1H); 1.77 (m, 2H); 1.70
(m, 1H); 1.50-1.48 (m, 1H); 1.42-1.45 (m, 1H); 1.42 (s

3H); 1.40-1.24 (m, 2H); 1.05 (d, 3H); 0.98-0.87 (m, 1H); 0.96 (d, 3H).

b) step 2: preparation of EX12



5

36 mg (0.27 mmol) of hydroxybenzotriazole and 52 mg (0.27 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are successively added to a solution of 37 mg (0.09 mmol) of the compound **8** in 3 ml of dichloromethane under an inert atmosphere of argon at a temperature in the region of 20°C. The stirring is maintained at a temperature in the region of 20°C for about 30 minutes and then 39 mg (0.099 mmol) of the compound **6** are added. The stirring is continued at this temperature for 1 hour. The reaction mixture is taken up in 5 ml of distilled water and then extracted with 3 × 20 ml of ethyl acetate. The organic phase is washed with 2 × 10 ml of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue obtained is chromatographed on silica gel conditioned beforehand in the mixture (Heptane/Ethyl acetate), (90/10), (V/V) and then eluted with a gradient from 10 to 20% of ethyl acetate in heptane. 40 mg (56%) of the expected product EX12 are obtained in the form of a viscous gum.

MS: ES⁺: [M+H]⁺ = 788; [M+Na]⁺ = 810

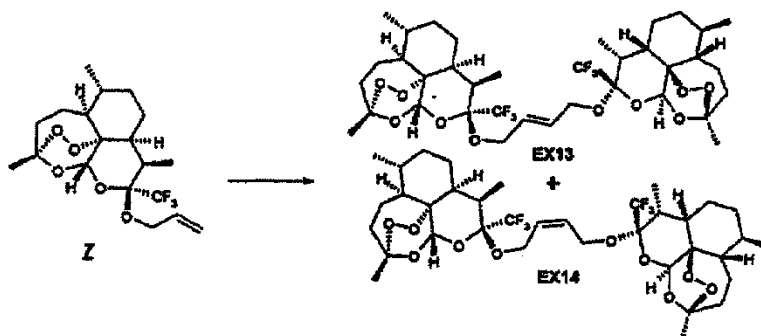
ES⁻: [M-H]⁻ = 786; [M+HCOOH+H]⁺ = 832.

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: from 0.87 to 1.03 (m, 11H); 1.08 (broad d, 3H); from 1.21 to 1.40 (m, 4H); 1.43 (s,

30

6H); from 1.45 to 1.65 (partially masked m, 6H); 1.69 (m, 2H); from 1.78 to 1.97 (m, 4H); 2.05 (m, 2H); from 2.32 to 2.43 (partially masked m, 2H); from 2.82 to 2.98 (m, 2H); 3.37 (m, 1H); from 3.65 to 3.81 (m, 2H);
 5 3.95 (m, 1H); 4.14 (d, J = 16.0 Hz, 1H); 4.43 (d, J = 16.0 Hz, 1H); 5.33 (s, 1H); 5.36 (s, 1H); 6.52 (m, 1H).

EX 13: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,-
 8'aS,9'R,10'R,12'R,12'aR)-10,10'-[(2E)-but-2-ene-1,4-
 10 diylbis(oxy)]bis[3,6,9-trimethyl-10-(trifluoromethyl)-
 decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromene]
 and **EX14:** (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,-
 8'aS,9'R,10'R,12'R,12'aR)-10,10'-[(2Z)-but-2-ene-1,4-
 15 diylbis(oxy)]bis[3,6,9-trimethyl-10-(trifluoromethyl)-
 decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromene]



A suspension of 200 mg (0.51 mmol) of the compound **7**
 and 43 mg (0.051 mmol) of benzylidenebis(tricyclohexyl-
 20 phosphine)dichlororuthenium in 1.3 ml of dichloro-
 methane is stirred for about 7 hours at a temperature
 in the region of 20°C. A solution containing 633 mg
 (5.10 mmol) of trishydroxymethylphosphine and 1.43 ml
 (10.2 mmol) of triethylamine in 3 ml of dichloromethane
 25 is added. Vigorous stirring is maintained at a
 temperature in the region of 20°C for about 10 minutes
 and then 6 ml of water are added, the stirring is
 continued for 1 hour. The organic phase is washed with
 3 ml of distilled water, dried over magnesium sulfate,
 30 filtered and evaporated to dryness under reduced
 pressure. The oily residue obtained is chromatographed
 on silica gel conditioned beforehand and then eluted in
 the mixture (Hexane/Ethyl acetate) (95/5) (V/V)

57.5 mg (38%) of the E isomer **EX13** are obtained in the form of white crystals. 20 mg (10%) of the Z isomer **EX14** are obtained in the form of white crystals.

5 **EX13:**

R_f = 0.41 in the system (Heptane/Ethyl acetate), (8/2), (V/V)

IR: 983 cm⁻¹ (characteristic trans CH=CH band).

MS: ES⁺: [M+Na]⁺ = 779.

10 ES⁻: [M+HCOOH+H]⁺ = 801.

¹H NMR (CDCl₃, 300 MHz) δ_{ppm}: 5.79 (t, 2H); 5.32 (s, 2H); 4.37 (dd, 2H); 4.19 (dd, 2H); 2.87 (qu, 2H); 2.39 (td, 2H); 2.04 (dt, 2H); 1.97-1.87 (m, 2H); 1.85-1.75 (m, 2H); 1.75-1.62 (m, 4H); 1.57-1.49 (m, 2H); 1.47 (m, 2H); 1.43 (s, 6H); 1.37-1.20 (m, 4H); 1.02 (d, 6H); 1.00-0.84 (m, 2H); 0.97 (d, 6H).

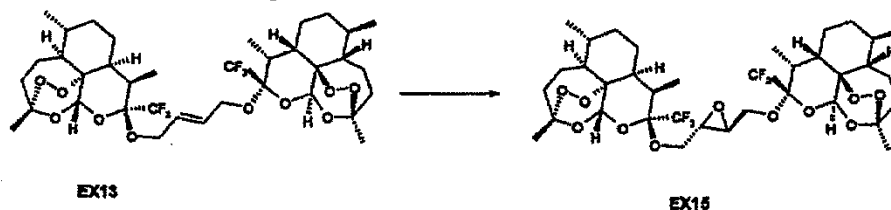
EX14:

20 R_f = 0.47 in the system (Heptane/Ethyl acetate), (8/2), (V/V)

MS: ES⁺: [M+NH₄]⁺ = 774.

25 ¹H NMR (CDCl₃, 300 MHz) δ_{ppm}: 5.67 (t, 2H); 5.31 (s, 2H); 4.42 (dd, 2H); 4.25 (dd, 2H); 2.85 (qu, 2H); 2.38 (td, 2H); 2.04 (dt, 2H); 1.96-1.84 (m, 2H); 1.84-1.74 (m, 2H); 1.74-1.61 (m, 4H); 1.57-1.49 (m, 2H); 1.47 (m, 2H); 1.43 (s, 6H); 1.37-1.20 (m, 4H); 1.01 (d, 6H); 1.00-0.87 (m, 2H); 0.97 (d, 6H).

EX15: (3S,5aS,6R,8aS,9R,10R,12R,12aR,3'S,5'aS,6'R,-
30 8'aS,9'R,10'R,12'R,12'aR)-10,10'-[(2R,3R)-oxirane-2,3-diylbis(methyleneoxy)]bis[3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino-[4,3-i]isochromene]

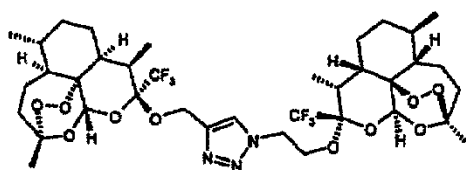


103 mg (0.417 mmol) of meta-chloroperbenzoic acid are added to a solution of 158 mg (0.209 mmol) of the compound **EX13** in 2.75 ml of dichloromethane at a temperature in the region of 20°C. The stirring is maintained at this temperature for about 8 hours. The reaction mixture is successively washed with 3 x 5 ml of a saturated aqueous sodium bicarbonate solution and 13 ml of a saturated aqueous sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The oily residue obtained is chromatographed on silica gel conditioned beforehand and then eluted in the mixture (Heptane/Ethyl acetate), (95/5), (V/V). 70 mg (43%) of one of the two trans isomers **EX15** are obtained in the form of white crystals.

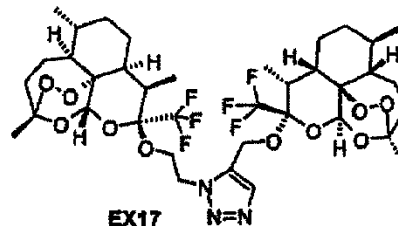
MS: ES⁺: [M+Na]⁺ = 795.

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d₁ (CDCl₃-d₁) referenced at 7.27 at the temperature of 303K: from 0.86 to 0.98 (m, 14H); from 1.20 to 1.39 (m, 4H); 1.42 (s, 6H); from 1.44 to 1.55 (m, 4H); from 1.62 to 1.77 (m, 6H); 1.89 (m, 2H); 2.04 (m, 2H); 2.37 (m, 2H); 2.85 (m, 2H); 3.11 (broad s, 2H); 3.69 (broad d, J = 12.5 Hz, 2H); 4.31 (d, J = 12.5 Hz, 2H); 5.39 (s, 2H).

EX 16: (1-(2-{[(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)-4-({[(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}methyl)-1H-1,2,3-triazole and **EX17:** (1-(2-{[(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)-5-({[(3S,5aS,6R,8aS,9R,10R,12R,12aR)-3,6,9-trimethyl-10-(trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl]oxy}ethyl)-1H-1,2,3-triazole

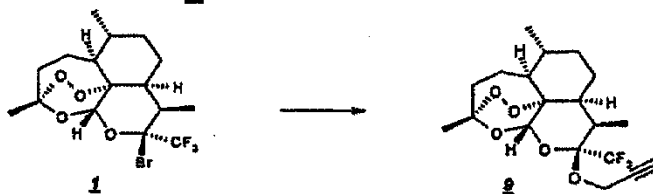


EX16



EX17

a) **step 1:** preparation of (3R,5aS,6R,8aS,9R,10R,12R, -
12aR)-3,6,9-trimethyl-10-(prop-2-yn-1-yloxy)-10-
5 (trifluoromethyl)decahydro-3,12-epoxy[1,2]dioxepino-
[4,3-i]isochromene, 9



0.266 ml of hexafluoropropanol (5 eq.) and then
10 0.289 ml of propargyl alcohol (10 eq.) are successively
added at room temperature to a solution of 0.206 g
(0.5 mmol) of (3S,5aS,6R,8aS,9R,10S,12R,12aR)-10-
(bromo)decahydro-3,6,9-trimethyl-10-(trifluoromethyl)-
3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepine 1
15 (prepared according to Org. Lett. 2002, 4, 757-759) in
5 ml of dichloromethane. The reaction mixture is then
stirred at room temperature for 1 hour 15 minutes and
then 5 ml of a saturated sodium bicarbonate solution
are added. The organic phase is dried over magnesium
20 sulfate and evaporated to dryness under reduced
pressure. The oily residue obtained is chromatographed
on silica gel conditioned beforehand in heptane and
then eluted with a linear gradient from 0 to 50% of
ethyl acetate in heptane. 0.064 g (34%) of the expected
25 product 9 are obtained in the form of an oil.

R_f = 0.40 in the system (Heptane/Ethyl acetate),
(85/15), (V/V)

ES m/z=391 MH⁺
m/z=335 MH⁺-C₃H₄O

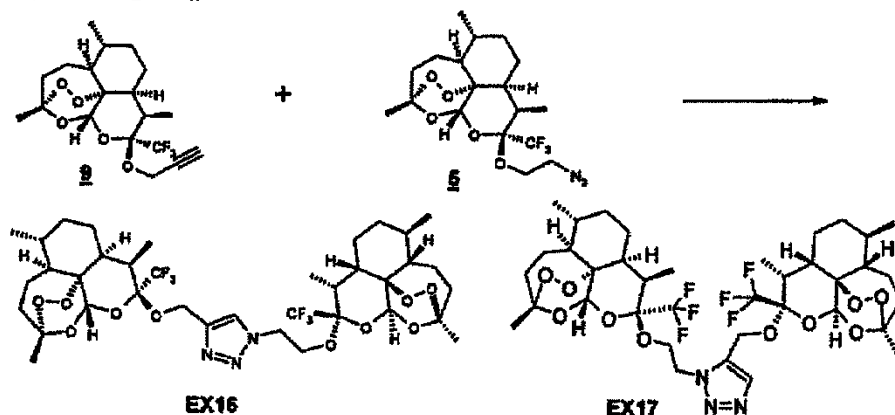
30

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400
spectrometer with the chemical shifts (δ in ppm) - in

the solvent dimethyl sulfoxide-d6 (DMSO-d6) referenced at 2.50 ppm at the temperature of 303K: 0.88 (partially masked m, 1H); 0.91 (d, J = 6.5 Hz, 3H); 0.95 (broad d, J = 7.5 Hz, 3H); 1.23 (m, 1H); from 1.28 to 1.43 (m, 2H); 1.32 (s, 3H); from 1.50 to 1.63 (m, 2H); from 1.73 to 1.90 (m, 3H); 2.03 (m, 1H); 2.21 (m, 1H); 2.68 (m, 1H); 3.52 (t, J = 2.5 Hz, 1H); 4.30 (dd, J = 2.5 and 16.0 Hz, 1H); 4.51 (dd, J = 2.5 and 16.0 Hz, 1H); 5.57 (s, 1H).

10

b) step 2: preparation of **EX16** and **EX17**



257 mg (0.610 mmol) of compound **5** are added to a solution of 119 mg (0.305 mmol) of the compound **9** in 2.5 ml of ethanol at a temperature in the region of 20°C. The stirring is maintained under reflux for about 48 hours. The reaction mixture is evaporated to dryness in a rotavapor and the oily residue obtained is chromatographed on silica gel conditioned beforehand in dichloromethane and then eluted with a linear gradient from 0 to 100% of the mixture B [(Dichloromethane/Ethyl acetate), (96/4), (V/V)] in A (Dichloromethane). 43 mg (18%) of the expected product **EX16** are obtained in the form of a white solid and 17 mg (7%) of the expected product **EX17** are obtained in the form of a white solid.

EX16:

R_f = 0.26 in the system (Dichloromethane/Ethyl acetate), (96/4), (V/V).

ES m/z=834 MNa⁺
m/z=812 MH⁺

¹H NMR spectrum at 400 MHz on a BRUKER AVANCE DRX-400 spectrometer with the chemical shifts (δ in ppm) - in the solvent chloroform-d1 (CDCl3-d1) referenced at 7.27
5 at the temperature of 303K: from 0.75 to 1.70 (partially masked m, 16H); 0.92 (broad d, J = 7.0 Hz, 9H); 0.98 (broad d, J = 7.0 Hz, 3H); 1.41 (s, 3H); 1.43 (s, 3H); 1.89 (m, 2H); 2.03 (m, 2H); 2.37 (m, 2H); 2.84 (m, 2H); 4.11 (m, 1H); 4.32 (m, 1H); from 4.40 to 4.60
10 (m, 2H); 4.71 (d, J = 12.5 Hz, 1H); 5.04 (d, J = 12.5 Hz, 1H); 5.20 (s, 1H); 5.70 (s, 1H); 7.53 (s, 1H).

EX17:

TLC Rf = 0.32 in the system (dichloromethane/ethyl
15 acetate), (96/4), (V/V)

ES m/z=834 MNa⁺

m/z=812 MH⁺

¹H NMR spectrum at 500 MHz on a BRUKER AVANCE DRX-500 spectrometer with the chemical shifts (δ in ppm) - in
20 the solvent chloroform-d1 (CDCl3-d1) referenced at 7.27 at the temperature of 303K: from 0.55 to 1.70 (partially masked m, 16H); 0.90 (broad d, J = 7.0 Hz, 9H); 1.01 (broad d, J = 7.0 Hz, 3H); 1.39 (s, 3H); 1.44 (s, 3H); from 2.30 to 2.43 (m, 2H); from 1.97 to 2.09
25 (m, 2H); from 2.28 to 2.42 (m, 2H); 2.80 (m, 1H); 2.90 (m, 1H); 4.11 (m, 1H); from 4.42 to 4.63 (m, 3H); 4.40 (d, J = 13.0 Hz, 1H); 5.04 (d, J = 13.0 Hz, 1H); 5.11 (s, 1H); 5.24 (s, 1H); 7.61 (s, 1H).

30 **Antiproliferative activity of the products prepared:**

The products according to the invention have been the subject of pharmacological trials which make it possible to determine their antiproliferative activity.
35 It was determined by measuring the inhibition of cell proliferation of HCT116 cells. The cells are inoculated in a cell culture medium at a concentration of 10 000 cells per well, in 0.17 ml of medium, and 20 µl of test product. at various concentrations. and 10 µl

of Thymidine [methyl-14C] (100 μ Ci/ml - specific activity 47.90 mCi/mmol; NEN Technologies reference NEC568 batch 3550-001) are added, and then the cells are incubated at 37°C and 5% CO₂.

5

Medium used for the culture of HCT116 cells: DMEM medium 2 mM L-glutamine, 200 IU/ml penicillin, 200 μ g/ml streptomycin and 10% (V/V) fetal calf serum (Life Technologies).

10

After 96 hours, the incorporation of ¹⁴C-thymidine is counted in a liquid scintillation counter 1450 Microbeta Wallac Trilux. The results R are expressed in cpm (counts per minute) and converted to percentage of growth inhibition GI% by first subtracting the mean of the number of cpm of the wells without cells B and then by dividing by the number of cpm of the wells of the untreated cells C comprising 20 μ l of medium for dilution of the product containing 1% of ethanol (GI% = (R-B) $\times$ 100/C%).

20

The IC₅₀ values are calculated with the aid of the equation 205 of the XLFit software (IDBS company, UK) by nonlinear regression analysis using the Marquardt algorithm (Donald W. MARQUARDT, J. Soc. industry appl., vol. 11, No. 2, June, 1963).

25

The products have an IC₅₀ on the HCT116 cells generally of less than 10 μ M and preferably of less than 100 nM.

30

Examples	IC ₅₀ (nM) /HCT116
EX1	47
EX2	23
EX3	21
EX8	30

The products according to the invention may therefore be used for the preparation of medicaments.

Thus, according to another of its aspects, the subject of the invention is medicaments comprising a product of formula (I) or an addition salt of the latter with a pharmaceutically acceptable acid, or a hydrate or a
5 solvate.

These medicaments find use in therapy, especially in the treatment of cancer.

10 The present invention therefore relates to the use of a product of formula (I) for the manufacture of a medicament useful for treating a pathological condition and more particularly the use of a product of formula (I) for the manufacture of a medicament useful for
15 treating cancer.

The present invention also relates to the use of a product of formula (I) for the manufacture of a medicament useful for treating pathologies where new
20 vascularization or angiogenesis occurs inappropriately, that is to say in cancers in general but also in specific cancers such as Kaposi's sarcoma or infantile hemoangioma, and also in rheumatoid arthritis, osteoarthritis and/or its associated pains, and
25 inflammatory bowel diseases such as hemorrhagic rectocolitis or Crohn's disease, eye diseases such as age-related macular degeneration, diabetic retinopathies, chronic inflammation and psoriasis.

30 Angiogenesis is a process of generation of new capillary vessels from preexisting vessels. Tumor angiogenesis (formation of blood neovessels), essential for tumor growth, is also one of the main factors in metastatic dissemination (Oncogene. 2003 May 19;22(20):
35 3172-9; Nat Med. 1995 Jan; 1(1): 27-31).

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a product according

to the invention. These pharmaceutical compositions contain an effective dose of at least one product according to the invention or a pharmaceutically acceptable salt, a hydrate or a solvate of the said
5 product, and at least one pharmaceutically acceptable excipient.

The said excipients are chosen according to their pharmaceutical dosage form and the desired mode of
10 administration from the usual excipients which are known to persons skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous,
15 intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active ingredient of formula (I) above, or its salt, solvate or hydrate, may be administered in unit form, as a mixture with
20 conventional pharmaceutical excipients, to animals and to human beings for the prophylaxis or treatment of the above disorders or diseases.

The appropriate unit forms for administration comprise
25 the forms for administration by the oral route such as tablets, soft or hard gelatin capsules, powders, granules and oral solutions or suspensions, the forms for sublingual, buccal, intratracheal, intraocular or intranasal administration, the forms for administration
30 by inhalation, the forms for topical, transdermal, subcutaneous, intramuscular or intravenous administration, the forms for rectal administration or implants. For topical application, the products according to the invention may be used in creams, gels,
35 ointments or lotions.

By way of example, a unit form for administration of a product according to the invention in tablet form may comprise the following components:

Product according to the invention	50.0 mg
Mannitol	223.75 mg
Croscarmellose sodium	6.0 mg
Corn starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

There may be particular cases where higher or lower dosages are appropriate: such dosages do not depart
5 from the scope of the invention. According to the usual practice, the dosage appropriate to each patient is determined by the doctor according to the mode of administration, the weight and the response of the said patient.

10

The present invention, according to another of its aspects, also relates to a method of treating the pathologies indicated above which comprises the administration, to a patient, of an effective dose of a
15 product according to the invention or one of its pharmaceutically acceptable salts or its hydrates or solvates.

The products of the present invention may be
20 administered alone or as a mixture with other anticancer agents. Among the possible combinations, there may be mentioned:

- alkylating agents, and in particular
25 cyclophosphamide, melphalan, ifosfamide, chlorambucil, busulfan, thiotepa, prednimustine, carmustine, lomustine, semustine, streptozotocin, decarbazine, temozolomide, procarbazine and hexamethylmelamine

- platinum derivatives such as in particular cisplatin,
30 carboplatin or oxaliplatin

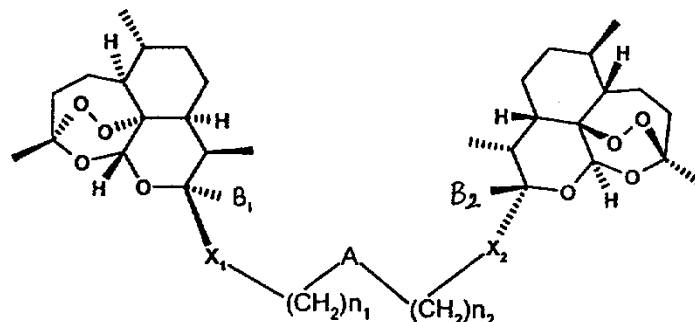
- antibiotic agents such as in particular bleomycin, mitomycin, dactinomycin
- antimicrotubule agents such as in particular vinblastine, vincristine, vindesine, vinorelbine,
5 taxoids (paclitaxel and docetaxel)
- anthracyclines such as in particular doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone, losoxantrone
- groups I and II topoisomerases such as etoposide,
10 teniposide, amsacrine, irinotecan, topotecan and tomudex
- fluoropyrimidines such as 5-fluorouracil, UFT, floxuridine
- cytidine analogues such as 5-azacytidine, cytarabine,
15 gemcitabine, 6-mercaptopurine, 6-thioguanine
- adenosine analogues such as pentostatin, cytarabine or fludarabine phosphate
- methotrexate and folinic acid
- various enzymes and compounds such as L-asparaginase,
20 hydroxyurea, trans-retinoic acid, suramin, dexrazoxane, amifostine, herceptin as well as oestrogenic and androgenic hormones
- antivasular agents such as combretastatin derivatives, for example CA4P, chalcones or colchicine,
25 for example ZD6126, and their prodrugs
- kinase inhibitors such as ertotinib or imatinib
- biotherapeutic agents such as antibodies such as rituximab, bevacizumab, cetuximab, trastuzumab or

- proteasome inhibitors such as bortezomib.

It is also possible to combine the compounds of the present invention with a radiation treatment. These treatments may be administered simultaneously,
5 separately or sequentially. The treatment will be adapted by the practitioner according to the disease to be treated.

CLAIMS

1. A anticancer product corresponding to formula(I):



in which:

- a) A is a divalent group chosen from -S-, -SO-, -SO₂-, -NH-, -N(CH₃)-, -N(CH₂-C(O)O-CH₂CH₃)-, -N(CH₂-COOH)-, epoxide, (C₁-C₆)alkenylene, -NHCO-, 1,2,3-triazole, -NHSO₂-;
- b) X₁ and X₂ are identical and are both O ;
- c) B₁ and B₂ are identical and represent -CF₃;
- d) n₁ and n₂ are identical or different and have the value 1, 2, 3 or 4;

in the form of a base or of an addition salt with an acid.

2. The product of formula (I) as claimed in claim 1, characterized in that n₁ and n₂ are identical and have the value 2, 3 or 4.
3. The product of formula (I) as claimed in claim 1, characterized in that A is -NH-, -N(CH₂C(O)OCH₂CH₃)- or -N(CH₂COOH)- and n₁ and n₂ are identical and have the value 2.
4. The product of formula (I) as claimed in claim 1, characterized in that A is (C₁-C₆)alkenylene or epoxide and n₁ and n₂ are identical and have the value 1.
5. The product of formula (I) as claimed in claim 1, characterized in that A is -NHCO- or 1,2,3-triazole and n₁ and n₂ are different and independently have the value 1 or

2.

6. A product chosen in the following list :

- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [thiobis(2, 1-ethanediyl-oxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluoro-methyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzodioxepine;
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [sulfinylbis(2, 1-ethane-diyloxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluoro-methyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzodioxepine;
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [sulfonylbis(2, 1-ethanediyl-oxy)]bis[decahydro-3, 6, 9-trimethyl-10-tri-fluoromethyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzo-dioxepine;
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [thiobis(3, 1-propanediyl-oxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluorometh-yl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzodioxepine;
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [sulfinylbis(3, 1-propane-diyloxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluoro-methyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzodioxepine;
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [sulfonylbis(3, 1-propane-diyloxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluoro-methyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-benzodioxepine;

- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, -
9'R, 10'R, 12'R, 12'aR) -10, 10' - [thiobis(4, 1-butanediyl-
oxy)]bis[decahydro-3, 6, 9-trimethyl-10-(trifluoro-
methyl)-3, 12-epoxy-12H-pyrano[4, 3-j]-1, 2-
benzodioxepine;

- 2-[[(3R, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -decahydro-3, 6, 9-
trimethyl-10-(trifluoromethyl)-3, 12-epoxy-12H-
pyrano[4, 3-j]-1, 2-benzodioxepin-10-yl]oxy]-N-[2-
[[(3R, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -decahydro-3, 6, 9-
trimethyl-10-(trifluoromethyl)-3, 12-epoxy-12H-
pyrano[4, 3-j]-1, 2-benzodioxepin-10-yl]oxy]ethyl]-N-
methylethanamine;

- 2-[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-
(trifluoromethyl)decahydro-3, 12-epoxy[1, 2]dioxepino-
[4, 3-i]isochromen-10-yl]oxy]-N-(2-
[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-
(trifluoromethyl)decahydro-3, 12-epoxy[1, 2]dioxepino-
[4, 3-i]isochromen-10-yl]oxy]ethyl)ethanamine;

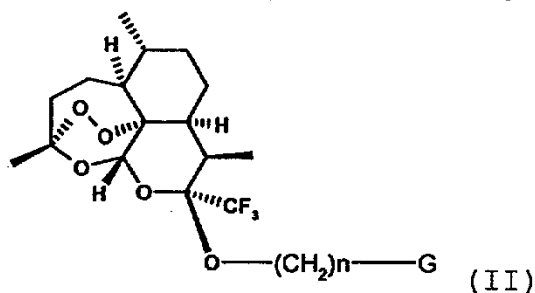
- ethyl N,N-bis(2-[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -
3, 6, 9-trimethyl-10-(trifluoromethyl)decahydro-3, 12-
epoxy[1, 2]dioxepino[4, 3-i]isochromen-10-
yl]oxy]ethyl)glycinate;

- N,N-bis(2-[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-
trimethyl-10-(trifluoromethyl)decahydro-3, 12-
epoxy[1, 2]dioxepino[4, 3-i]isochromen-10-yl]oxy]ethyl)-
glycine;

- 2-[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-
(trifluoromethyl)decahydro-3, 12-epoxy[1, 2]dioxepino[4, 3-i]isochromen-10-yl]oxy]-N-(2-
[[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-
(trifluoromethyl)decahydro-3, 12-epoxy[1, 2]dioxepino-
[4, 3-i]isochromen-10-yl]oxy]ethyl)acetamide;

- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [(2E) -but-2-ene-1, 4-diylbis(oxy)]bis[3, 6, 9-trimethyl-10-(trifluoromethyl) - decahydro-3, 12-epoxy[1, 2]dioxepino[4, 3-i]isochromene];
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [(2Z) -but-2-ene-1, 4-diylbis(oxy)]bis[3, 6, 9-trimethyl-10-(trifluoromethyl) - decahydro-3, 12-epoxy[1, 2]dioxepino[4, 3-i]isochromene];
- (3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR, 3'S, 5'aS, 6'R, 8'aS, - 9'R, 10'R, 12'R, 12'aR) -10, 10' - [(2R, 3R) -oxirane-2, 3-diylbis(methyleneoxy)]bis[3, 6, 9-trimethyl-10-(trifluoromethyl) decahydro-3, 12-epoxy[1, 2]dioxepino-[4, 3-i]isochromene];
- 1-(2-{{{(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-(trifluoromethyl) decahydro-3, 12-epoxy[1, 2]dioxepino[4, 3-i]isochromen-10-yl}oxy)ethyl)-4-({[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-(trifluoromethyl) decahydro-3, 12-epoxy[1, 2]dioxepino-[4, 3-i]isochromen-10-yl}oxy)methyl)-1H-1, 2, 3-triazole;
- 1-(2-{{{(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-(trifluoromethyl) decahydro-3, 12-epoxy[1, 2]dioxepino[4, 3-i]isochromen-10-yl}oxy)ethyl)-5-({[(3S, 5aS, 6R, 8aS, 9R, 10R, 12R, 12aR) -3, 6, 9-trimethyl-10-(trifluoromethyl) decahydro-3, 12-epoxy[1, 2]dioxepino-[4, 3-i]isochromen-10-yl}oxy)ethyl)-1H-1, 2, 3-triazole.

7. A medicament, characterized in that it comprises a product of formula (I) as claimed in any one of claims 1 to 6, or an addition salt of this product with a pharmaceutically acceptable acid, or a hydrate or a solvate of the product of formula (I).
8. Pharmaceutical composition, characterized in that it comprises a product of formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt, a hydrate or a solvate of this product, and at least one pharmaceutically acceptable excipient.
9. As intermediate products, products of general formula



in which n has the value 1, 2, 3 or 4, G represents a bromine atom or $-\text{N}_3$.