(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2007 (15.03.2007)

PCT

(10) International Publication Number
WO 2007/029121 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IB2006/003436

(22) International Filing Date: 20 July 2006 (20.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0507769	21 July 2005 (21.07.2005)	FR
60/703,874	1 August 2005 (01.08.2005)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

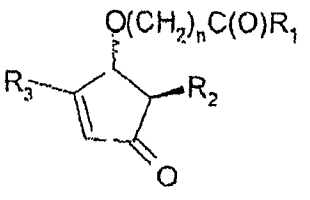
Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/029121 A2

(54) Title: NOVEL CYCLOPENT-2-EN-1-ONE DERIVATIVES WHICH ARE PPAR RECEPTOR MODULATORS, AND USE THEREOF IN PHARMACEUTICAL OR COSMETIC COMPOSITIONS



(I)

(57) Abstract: The invention relates to novel compounds which correspond to general formula (I) below: and also to the method for preparing them, and to their use in pharmaceutical compositions for use in human or veterinary medicine, in particular in dermatology, and also in the field of cardiovascular diseases, immune diseases and/or diseases related to lipid metabolism, or alternatively in cosmetic compositions.

Novel cyclopent-2-en-1-one derivatives which are PPAR receptor modulators, and use thereof in pharmaceutical or cosmetic compositions

The invention relates to novel cyclopent-2-en-1-one derivatives which are modulators of peroxisome proliferator-activated receptors, called PPARs. It also relates to the process for preparing them and to the use thereof in pharmaceutical compositions for use in human or veterinary medicine, or else in cosmetic compositions.

Peroxisome proliferator-activated receptors (PPARs) belong to the superfamily of nuclear hormone receptors (Mangelsdorf, D.J. *et al. Cell* 1995, *83*, 841-850). After activation by a ligand, these proteins act as transcription factors and regulate numerous physiological phenomena, such as reproduction, growth, differentiation, development, metabolic energy and homeostasis. The PPAR subfamily (Kliewer, S.A. *et al. Nature* 1992, *358*, '71-774; Hertz, R. *et al.* J. *Eur J. Biochem.* 1996, *235*, 242-247; Devchand, P.R. *et al. Nature* 1996, *384*, 39-43; Spiegelman, B.M. *Cell* 1998, *93*, 153-155, Kliewer S.A. *et al. Science* 1999, *284*, 757-760; Willson, T.M. *et al. J. Med. Chem.* 2000, *43*, 527-550) comprises three isoforms (α, γ and δ) which have different tissue distributions and exercise various physiological functions, and act as dietary lipid sensors for the control of carbohydrate and fatty acid metabolism (Willson, T.M. *et al. J. Med. Chem.* 2000, *43*, 527-550). PPARα receptors are mainly expressed in the liver and, after binding with one of their ligands, for example a fibrate, stimulate lipid metabolization.

PPARγ receptors are strongly expressed in adipocyte tissues, and activate adipogenesis when they are bound to their natural ligands [(*S*)-15-deoxy-$\Delta^{12,14}$-PGJ$_2$] or synthetic ligands (thiazolidinediones or glitazones).

Together, the α and γ isoforms regulate the balance between catabolism and storage of fatty acid long chains. Interestingly, the PPARδ isoform, largely expressed in the brain, the colon and the skin, is a potential transcription repressor (Oliver, W.R. *et al. Proc. Natl. Acad. Sci. USA* 2001, *98*, 5306-5311), which inhibits the transcription activity induced by the ligands of the α and γ isoforms. The role of PPARδ receptors on anti-lipid oxidation and anti-adipogenesis opens up important and promising perspectives for the therapeutic control of obesity and type II diabetes.

A series of fatty acids and eicosanoids bind and activate PPARγs at micromolar concentrations. Unlike the PPARα receptor, the PPARγ receptor binds preferentially to polyunsaturated fatty acids, such as linoleic acid, linolenic acid, arachidonic acid and eicosapentaenoic acid (EPA).

Similarly, 15-lipooxygenase metabolites, such as 9-HODE or 13-HODE, bind to the PPARγ receptor. The most potent natural ligand of PPARγ receptors is the 15-deoxy-$\Delta^{12,14}$-PGJ_2 prostaglandin. This metabolite of the prostaglandin J series induces adipocyte differentiation at low concentrations, of the order of one micromolar.

Anti-diabetic thiazolidinediones (TZDs) or glitazones, such as rosiglitazone, pioglitazone or troglitazone, have also been identified as PPARγ agonists, and it has been demonstrated that these molecules induce expression of the gene in adipocytes and stimulate differentiation of the latter in cell cultures.

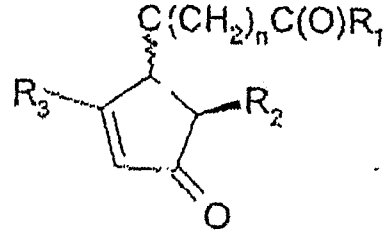
The compounds GI 262570, GW1920 and CW7045, which are tyrosine derivatives, are selective and potent PPARγ antagonists (Henke, B.R. *et al. J. Med. Chem.* 1998, *41*, 5020-5036. Collins, J.L. *et al. J. Med. Chem.* 1998, *41*, 5037-5054. Cobb, J.E. *et al. J. Med. Chem.* 1998, *41*, 5055-5069). Just like the TZDs, the S enantiomers

(derived from natural L-tyrosine) are more potent and more selective PPARγ agonists than the R enantiomers. GW0207, an indole-5-acetic acid derivative, is another PPARγ agonist.

Indomethacin, a cyclooxygenase inhibitor, is also an inhibitor of eicosanoid biosynthesis and also a weak PPARγ agonist, which stimulates adipocyte differentiation at concentrations similar to those required for the activation of PPARγs. Ibuprofen, fenoprofen and flumephenamic acid are also weak PPARγ agonists, but the activation requires higher concentrations than those required for the inhibition of cyclooxygenases.

These compounds have a structure and a method of action (Michael addition on the sulphhydryl groups) similar to those of Δ^7-PGA_1 prostaglandins. However, these compounds are unstable, which limits their use in chemotherapy. Δ^7-PGA_1s and methyl esters thereof are rapidly metabolized in rat serum by the action of PG isomerases (Negishi, M. *et al. J. Lipid Mediators Cell Signalling* 1995, 12, 443-448. Noyori, R. *et al. Science* 1993, *259*, 44-45). Consequently, cyclopentenone derivatives which are more stable, exhibiting a similar PPAR activity, represent considerable stakes with respect to the search for derivatives that are active on PPAR receptors.

In this context, a subject of the present invention is the compounds of formula (I):



(I)

in which:

- R_1 represents an $-OR_4$ or $-NR_4R_5$ group,

R_4 and R_5 having the meaning as defined below;

- R_2 represents a group chosen from the following optionally substituted groups: alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocycloalkyl, heteroaralkyl and heterocycloalkyl-alkyl;

- R_3 represents a hydrogen atom, a halogen atom or a group chosen from the following optionally substituted groups: alkyl, alkenyl, alkynyl, aryl, aralkyl, cyclo-alkyl, cycloalkylalkyl, heteroaryl, heterocycloalkyl, heteroaralkyl and heterocycloalkylalkyl;

R_4 and R_5, which may be identical or different, represent a hydrogen atom or a group chosen from the following optionally substituted groups: alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, alkenyl, alkynyl, aralkyl, cycloalkylalkyl, heteroaralkyl and heterocycloalkylalkyl;

- n is an integer included in the range of from 1 to 6,

in the form of pure optical and/or geometric isomers or as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof.

Advantageously, a subject of the invention is the compounds (I) as defined above, in which:

- R_1 represents an $-OR_4$ or $-NR_4R_5$ group, with R_4 and R_5, which may be identical or different, and which represent a hydrogen atom or an optionally substituted alkyl group, preferably containing from 1 to 5 carbon atoms,
- R_2 represents an alkyl group preferably containing from 1 to 10 carbon atoms,
- R_3 represents a hydrogen atom, a halogen atom or an alkynyl group preferably containing from 2 to 10 carbon atoms,
- n is equal to 4 or 5,

in the form of pure optical and/or geometric isomers or

as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof.

According to preferred variants of the invention, the compounds (I), in the form of pure optical and/or geometric isomers or as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof, will exhibit the characteristics below, alone or in combination:

- R_1 represents an -OH group;
- R_2 represents a heptyl group;
- R_3 represents a hydrogen atom or an iodine atom or an oct-1-yn-1-yl radical;
- n is equal to 4 or 5.

According to the present invention, the term "alkyl radical" is intended to mean a linear or branched, saturated hydrocarbon-based monovalent radical preferably containing from 1 to 12, preferentially from 1 to 10, carbon atoms, unless otherwise specified, and preferably the methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, hexyl, heptyl, octyl, decyl radicals.

The expression "alkyl radical containing from 1 to 5 carbon atoms" is intended to mean in particular the methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and pentyl radicals.

The term "alkenyl and alkynyl radical" is intended to mean an alkyl radical as defined above, but unsaturated, i.e. containing respectively a double or a triple bond, and containing from 2 to 12, preferably from 2 to 10, and preferably from 2 to 8 carbon atoms, unless otherwise specified. Preferably, the alkynyl radical is the oct-1-yn-1-yl radical.

The term "cycloalkyl" denotes a cyclic alkyl group containing from 3 to 12, preferably from 3 to 10, and

preferentially from 3 to 6 carbon atoms, for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl radical, and bridged cycloalkyl groups such as adamantyl or bicyclo[3.2.1]octanyl groups.

The term "aryl radical" is intended to mean mono-, bi or polycyclic carbocycles preferably containing from 6 to 12 carbon atoms, comprising at least one aromatic group, for example a phenyl, biphenyl, cinnamyl or naphthyl radical. The term "substituted aryl radical" is intended to mean such a radical substituted with a halogen atom, a CF_3 radical, an alkyl radical having from 1 to 12 carbon atoms, an alkoxy radical having from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, a nitro function, a polyether radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl radical optionally protected with an acetyl or benzoyl group, or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl having from 1 to 12 carbon atoms.

The term "aralkyl radical" is intended to mean an aryl radical as defined above, connected to the molecule by an alkylene chain, and, for example, a benzyl, phenylethyl or naphthalen-2-ylmethyl radical. The term "substituted aralkyl radical" is intended to mean such a radical substituted with a halogen atom, a CF_3 radical, an alkyl radical having from 1 to 12 carbon atoms, an alkoxy radical having from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl radical optionally protected with an acetyl or benzoyl group, or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl having from 1 to 12 carbon atoms.

The term "alkylene" is intended to mean a divalent alkyl radical having from 1 to 12 carbon atoms, preferably from 1 to 6, and preferentially from 1 to 5 carbon atoms, unless otherwise specified.

The term "heteroaryl radical" is intended to mean an aryl radical interrupted with one or more hetero atoms chosen from a nitrogen, oxygen or sulphur atom, such as the pyridyl, furyl, thienyl, isoxazolyl, oxadiazolyl, oxazolyl, benzimidazolyl, indolyl or benzofuranyl radical. The term "substituted heteroaryl radical" is intended to mean such a radical substituted with at least one halogen, an alkyl having from 1 to 12 carbon atoms, an alkoxy having from 1 to 7 carbon atoms, an aralkoxy, an aryloxy, an aryl radical, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl group, or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl having from 1 to 12 carbon atoms.

The term "heteroaralkyl radical" is intended to mean a heteroaryl radical as defined above, connected to the molecule by an alkylene chain.

The term "heterocycloalkyl" denotes a cycloalkyl as defined above, comprising one or more hetero atoms, selected from nitrogen, oxygen and sulphur atoms. By way of example, mention may be made of a morpholino, piperidino, piperazino, 2-oxopiperidin-1-yl and 2-oxopyrrolidin-1-yl radical. The term "substituted heterocycloalkyl radical" is intended to mean such a radical substituted with at least one alkyl having from 1 to 12 carbon atoms, an alkoxy having from 1 to 7 carbon atoms, an aralkoxy, an aryloxy, an aryl radical, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic

acid, a hydroxyl optionally protected with an acetyl or benzoyl group, or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl having from 1 to 12 carbon atoms.

The term "halogen" is intended to mean a chlorine, bromine, iodine or fluorine atom.

The term "substituted" is intended to mean, unless a more precise definition is given, a radical substituted with one or more substituents chosen from the following: halogens, a cyano, alkyl or trifluoroalkyl radical, an alkenyl radical, an alkynyl radical, a cycloalkyl radical, an aryl or heterocycloalkyl radical, an amino, alkylamino or dialkylamino group, and a hydroxyl, alkoxy or aryloxy radical. In the absence of specification, the substituted radicals will preferably be monosubstituted or disubstituted.

The terms used for the definition of the substituents are those usually recognized by those skilled in the art.

For example, a substituent of the cycloalkylalkyl type means that the substituent consists of an alkyl group which is itself substituted with a cycloalkyl group; similarly, a substituent of the heterocycloalkylalkyl type means that the substituent consists of an alkyl group which is itself substituted with a heterocycloalkyl group.

The salts of the compounds according to the invention are prepared according to techniques well known to those skilled in the art.

When a compound according to the invention has one or more asymmetrical carbons, the optical isomers of this compound are an integral part of the invention. When a

compound according to the invention has a stereoisomerism, for example, of axial-equatorial or Z-E type, the invention comprises all the stereoisomers of this compound. The various compounds according to the invention can therefore be in all of the possible isomeric forms, optionally as a mixture according to any proportions, unless otherwise specified on general formula (I), which is in particular the case of the 5′ carbon of the cyclopent-2-en-1-one group, which is in the (R) configuration. The nomenclature (R) or (S) denotes the (R) or (S) enantiomer in optically pure form. Advantageously, the compounds of formula (I) of the invention are in optically pure form, in particular the carbon in the 1′ position of the cyclopent-2-en-1-one group exhibits an R or S configuration.

The compounds (I) are isolated in the form of pure isomers by means of the conventional separation techniques: for example, fractionated recrystallizations of a salt of the racemic mixture with an optically active acid or base, the principle of which is well known, or conventional techniques of chiral-phase or non-chiral-phase chromatography, could be used.

The invention also relates to the salts of the abovementioned compounds, more particularly with bases. Among the salts of the compounds (I) with bases, mention may be made of the salts with inorganic bases such as a hydroxide of an alkali metal or alkaline earth metal, in particular sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide or ammonium hydroxide, or with organic bases such as alkylamines, methylamine, ethylamine, propylamine, diethylamine, triethylamine, *N,N*-dimethylethanolamine, morpholine, benzylamine, procaine, lysine, arginine, histidine or *N*-methylglucamine, or alkylammoniums such as tetrabutylammonium.

In particular, a subject of the present invention is the compounds of formula (I) below, in the form of a pure isomer or of a mixture, in any proportions, of the (1'R*,5'R*) and (1'S*,5'R*) diastereoisomers, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof:

tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoic acid

tert-butyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

tert-butyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid

(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid

tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate

tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate

(1'*S**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)-hexanoic acid

(1'*R**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)-hexanoic acid

isopropyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

isopropyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

ethyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

ethyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate
ethyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate
ethyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide
(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylhexanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide
(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide
tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoic acid
tert-butyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
tert-butyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoic acid
isopropyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
isopropyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
isopropyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
isopropyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
ethyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-

enyloxy)pentanoate
ethyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
ethyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
ethyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanamide
(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanamide
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylpentanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylpentanamide
(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylpentanamide
tert-butyl (1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate
tert-butyl (1'*S**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate
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ethyl (1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate
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ethyl (1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate
ethyl (1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate
(1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanamide
(1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide
(1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide
(1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylhexanamide
(1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide
(1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide

The compounds according to the present invention can be prepared according to the general process described hereinafter and illustrated on **SCHEME 1**.

The synthesis begins with the preparation of the *trans*-4-hydroxycyclopentenone **(2)** substituted in the 5' position, from the alcohol **(1)**, as shown by reaction **b** in accordance with the procedure described by Piancatelli *et al.*, in *Tetrahedron Lett.* 1976, 3555-3558, *Tetrahedron* 1978, 34, 2775-2778, Piancatelli, G. *et al. Synthesis* 1994, 867-889 and *Synth. Commun.* 1997, 116-117. The alcohol **(1)** is obtained by addition of a magnesium compound to furfural according to reaction **a)**.

The conversion of the compound **(1)** to compound **(2)** is carried out by rearrangement of a hydroxypentadienyl carbocation according to a Nazarov-type electrocyclic

reaction (Nieto, O. *et al. Chemistry: Eur. J.*, 2004, 10, 4324-4333). In practice, the following conditions may be used: 2-furylcarbinol **(1)** is heated at 65°C for 48 h in the presence of sub-stoichiometric amounts of PPA (polyphosphoric acid) in a 2/1 (v/v) acetone/water mixture. The starting product is partially recovered and recycled.

The reaction **c** consisting of protection of the alcohol function of the 4-hydroxycyclopentenone **(2)** in the form of a silyl ether **(3)** uses a treatment with TBDMSCl (*tert*-butyldimethylsilyl chloride) and triethylamine catalysed with DMAP (4-dimethylaminopyridine) in dichloromethane (Corey, E.J. *et al. J. Am. Chem. Soc.* 1972, *94*, 6190-6191).

The reaction **d** consisting of formation of the α-iodo-cyclopentenone **(4)** is, for example, carried out by addition of a solution of iodine in a CH_2Cl_2/pyridine mixture to a solution of the compound **(3)** cooled to 0°C (Johnson, C.R. *et al. Tetrahedron Lett.* 1992, *33*, 919-922. Myers, A.G. *et al. J. Am. Chem. Soc.* 1993, *115*, 7021-7022). The iodinated derivative obtained may be converted to a chloride, bromide or fluoride (Bioorganic Med. Chemistry Letters, 2004, 14, 2091-2093) by conventional methods. This reaction **d** is not carried out when it is desired to obtain compounds of formula (I) for which R_3=H.

The reduction (reaction **e**) of the carbonyl group employs the use of an excess of Luche reagent ($NaBH_4$, $CeCl_3 \cdot 7H_2O$ in methanol), as described by Luche, J.L. in *J. Am. Chem. Soc.* 1978, *100*, 2226-2227. Luche, J.L. *et al. J. Am. Chem. Soc.* 1979, *101*, 5848-5849. Gemal, A.L. *et al. J. Am. Chem. Soc.* 1981, *103*, 5454-5459. In practice, the following conditions may be used: after a complexation time of 2 h, and an additional reaction time of 2 h, the (1*S**,4*S**,5*R**) and (1*R**,4*S**,5*R**) diastereoisomer alcohols **(5)** are

obtained. The mixture of diastereoisomers **(5)** is directly used in the subsequent stages.

The *O*-alkylation reaction (reaction **f**) is based on a conventional Williamson reaction (Johnstone, R.A.W. *et al. Tetrahedron* 1979, *35*, 2169). The treatment of the alcohol **(5)**, with an iodide of structure $I-(CH_2)_nC(O)OR_4$ **(6)**, with n and R_4 as defined for the compounds (I) and R_4 other than a hydrogen atom, produces the ether **(7)**. This reaction is advantageously carried out in DMF for 35 min.

The desilylation of the compound **(7)** (reaction **g**) is carried out using a solution of nBu_4NF in THF, advantageously at 25°C for 10 h, and produces the alcohol **(8)** in the form of a mixture of the diastereoisomers.

The oxidation of the alcohol **(8)** with PDC (pyridinium dichromate) according to the reaction **h** is carried out according to the technique described by Corey, E.J. *et al. Tetrahedron Lett.* 1979, *20*, 399, preferably in dichloromethane, for 12 h at 25°C, and produces the mixture of ketones **(A)** and **(B)**, separated by column chromatography.

The hydrolysis of the ester function of the ketones **(A)** and **(B)** according to reaction **i** is carried out in TFA. For example, this hydrolysis produces, respectively, the carboxylic acids **(10)** and **(12)** from the esters **(9)** and **(11)**. Subsequently, the compounds of general formula (I) in which R_3 represents a radical as defined above, with the exception of a hydrogen atom and of a halogen atom, are obtained from the compounds of formula **(A)** or **(B)** for which R_3 = halogen, by means of a Stille coupling reaction [Stille, J.K. *et al. J. Am. Chem. Soc.* **1987**, *109*, 2138-2152, $(CH_3CN)_2PdCl_2$, CuI, $AsPh_3$, NMP, 80°C, 40 min] with a stannane derivative or a boronic acid derivative. By way of example, **SCHEME 1**

illustrates this reaction (reaction **j**) between tributyloct-1-ynylstannane and the iodides **(9)** and **(11)** to give, respectively, the compounds **(13)** and **(14)**. The hydrolysis of the ester function of the compounds **(13)** and **(14)** according to reaction **i** is carried out in TFA, and produces, respectively, the carboxylic acids **(15)** and **(16)**.

By coupling the compounds of formula **(A)** or **(B)** for which $R_4 = H$ with an amine HNR_4R_5 according to a conventional amidation reaction **k**, the compounds **(C)** or **(D)** are respectively obtained.

The set of compounds of general formula **(A)**, **(B)**, **(C)** and **(D)** represents the compounds of general formula (I) of the present invention.

The functional groups possibly present in the reaction intermediates used in the process can be protected, either in permanent form, or in temporary form, with protective groups which ensure one-to-one synthesis of the expected compounds. The protection and deprotection reactions are carried out according to techniques well known to those skilled in the art. The expression "temporary amine-, alcohol- or carboxylic acid-protecting group" is intended to mean protective groups such as those described in "Protective Groups in Organic Chemistry", publisher McOmie J.W.F., Plenum Press, 1973, in "Protective Groups in Organic Synthesis", 2nd edition, Greene T.W. and Wuts P.G.M., publisher John Wiley and Sons, 1991 and in "Protecting Groups", Kocienski P.J., 1994, Georg Thieme Verlag.

A subject of the present invention is therefore also a process for preparing the compounds of formula (I) according to the invention, comprising the following stages:

a) stage consisting of addition between furfural and the compound $BrMgR_2$, in order to obtain the

corresponding 2-furylcarbinol;

b) rearrangement of the carbocation of hydroxypentadienyl obtained from the 2-furylcarbinol obtained in a) according to a Nazarov-type electrocyclic reaction, in order to obtain the corresponding hydroxycyclopentenone;

c) protection of the alcohol function of the hydroxycyclopentenone obtained in b). This protection is carried out in particular by treatment with TBDMSCl;

e) reduction of the carbonyl group of the cyclopentenone obtained, in order to obtain a mixture of the various corresponding diastereoisomeric alcohols;

f) stage consisting of O-alkylation of the diastereoisomeric alcohols obtained in e), with a halide of formula $X-(CH_2)_n-C(O)OR_4$, X being a halogen atom, preferably an iodine atom, and n and R_4 as defined for the compounds of formula (I), R_4 being other than a hydrogen atom;

g) deprotection of the alcohol function of the compound obtained in f);

h) oxidation of the alcohol function deprotected in g), in order to obtain the corresponding ketone.

The compounds derived from this process comprise, as R_3, a hydrogen atom.

When it is desired to obtain compounds comprising, as R_3, a halogen atom, the process comprises, between stages c) and e), a stage d) consisting of α-addition of a halide to the compound obtained in c), in order to obtain the corresponding α-halocyclopentenone. The halide used is in particular an iodide, bromide or chloride.

The compounds thus obtained comprise, as R3, a halogen atom (resulting from the α-addition d)) or a hydrogen atom (without reaction d)), and, as R_1, an $-OR_4$ group.

Since R_4 is other than a hydrogen atom, this process can be continued by means of a stage i) consisting of hydrolysis of the ester function of the ketone compound obtained in h), in order to obtain the corresponding acid (R_4=H).

Alternatively, the process comprises, after stage h), a stage j) consisting of Stille coupling with a tin derivative, or Suzuki coupling with a boron derivative, said tin derivative or boron derivative containing the R_3 group. The compounds derived from this stage thus contain an R_3 group other than a halogen atom or than a hydrogen atom, and, as R_1, an $-OR_4$ group.

This time again, since R_4 is other than a hydrogen atom, this process can be continued by means of a stage i) consisting of hydrolysis of the ester function of the compound obtained in j), in order to obtain the corresponding acid (R_4=H).

Finally, the process according to the invention can comprise, after the hydrolysis stage i), a stage consisting of amidation by coupling of the compound obtained subsequent to the hydrolysis, with an amine of formula HNR_4R_5, R_4 and R_5 being as defined for the compounds of formula (I). In this case, the compounds obtained contain, as R_1, an $-NR_4R_5$ radical.

The compounds (I) according to the invention, and also the salts, solvates and/or hydrates thereof, exhibit PPAR-receptor-modulating properties. This activity on PPARα, δ and γ receptors is measured in a trans-activation test and quantified by virtue of the (apparent) dissociation constant Kdapp, as described hereinafter. The preferred compounds of the present invention have a dissociation constant of less than or equal to 500 nM, and advantageously less than or equal to 100 nM.

A subject of the present invention is also, as a medicament, the compounds of formula (I) as described above, in the form of pure optical and/or geometric isomers or as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof.

A subject of the present invention is the use of the compounds of formula (I), for manufacturing a composition for use in regulating and/or restoring the metabolism of lipids in the skin.

The compounds according to the invention are particularly suitable in the following treatment fields:

1) for treating dermatological conditions linked to a keratinization disorder related to differentiation and proliferation, in particular for treating common acne, comedone-type acne, polymorphic acne, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acne such as solar acne, acne medicamentosa or occupational acne;

2) for treating other types of keratinization disorders, in particular ichthyosis, ichthyosiform states, Darrier's disease, palmoplantar keratoderma, leucoplasia and leucoplasiform states, cutaneous or mucosal (buccal) lichen;

3) for treating other dermatological conditions with an inflammatory immunoallergic component, with or without cell proliferation disorder, and in particular all the forms of psoriasis, whether cutaneous, mucosal or ungual, and even psoriatic rheumatism, or cutaneous atopy, such as eczema or respiratory atopy or gingival hypertrophy;

4) for treating any dermal or epidermal proliferations whether benign or malignant, whether of viral or non-viral origin, such as verruca vulgaris, verruca plana and epidermodysplasia verruciformis, oral or florid papillomatoses, T lymphoma, and proliferations which

may be induced by ultraviolet radiation, in particular in the case of baso- and spinocellular epitheliomas, and any precancerous skin lesion such as keratoacanthomas;

5) for treating other dermatological disorders such as immune dermatoses such as lupus erythematosus, bullous immune diseases and collagen diseases, such as scleroderma;

6) in the treatment of dermatological or general conditions with an immunological component;

7) in the treatment of skin disorders due to exposure to UV radiation and for repairing or combating skin ageing, whether photoinduced or chronological, or for reducing actinic keratoses and pigmentations, or any pathologies associated with chronological or actinic ageing, such as xerosis;

8) for combating sebaceous function disorders such as acne hyperseborrhoea, simple seborrhoea, or seborrhoeic dermatitis;

9) for preventing or treating cicatrization disorders, or for preventing or repairing stretch marks;

10) in the treatment of pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo;

11) in the treatment of lipid metabolism conditions, such as obesity, hyperlipidemia, non-insulin-dependent diabetes or syndrome X;

12) in the treatment of inflammatory conditions such as arthritis;

13) in the treatment or prevention of cancerous or precancerous states;

14) in the prevention or treatment of alopecia of various origins, in particular alopecia due to chemotherapy or to radiation;

15) in the treatment of immune system disorders, such as asthma, diabetes mellitus type I, multiple sclerosis, or other selective dysfunctions of the immune system, or

16) in the treatment of conditions of the cardio-

vascular system such as arteriosclerosis or hypertension.

A subject of the present invention is also a pharmaceutical or cosmetic composition comprising, in a physiologically acceptable medium, at least one compound of formula (I) as defined above. The compositions according to the invention therefore comprise at least one compound of formula (I) in combination with a physiologically acceptable support or at least one pharmaceutically acceptable excipient, chosen according to the desired cosmetic or pharmaceutical form and the chosen method of administration. The expression "physiologically acceptable medium or support" is intended to mean a medium or a support that is compatible with the skin, the mucous membranes and/or the integuments. The term "pharmaceutically acceptable excipient" is intended to mean a substance which is inert with respect to the compounds of formula (I), and compatible with the skin, the mucous membranes and/or the integuments.

The administration of the composition according to the invention may be carried out enterally, parenterally, topically or ocularly. Preferably, the pharmaceutical composition is packaged in a form suitable for topical application.

When administered enterally, the composition, more particularly the pharmaceutical composition, may be in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, lipid or polymeric microspheres or nanospheres or vesicles allowing controlled release. When administered parenterally, the composition may be in the form of solutions or suspensions for perfusion or injection.

The compositions according to the invention contain a

compound according to the invention, in an amount sufficient to obtain the desired cosmetic, prophylactic or therapeutic effect. The compounds according to the invention are generally administered at a daily dose of approximately 0.001 mg/kg to 100 mg/kg of body weight, in 1 to 3 doses. The compounds are used systemically at a concentration generally of between 0.001% and 10% by weight, preferably between 0.01% and 1% by weight, relative to the weight of the composition.

When administered topically, the pharmaceutical composition according to the invention is more particularly for use in the treatment of the skin and the mucous membranes and may be in the form of salves, creams, milks, ointments, powders, impregnated pads, syndets, solutions, gels, sprays, mousses, suspensions, lotions, sticks, shampoos or washing bases. It can also be in the form of suspensions of lipid or polymeric microspheres or nanospheres or vesicles or of polymeric patches and of hydrogels allowing controlled release. This composition for topical administration may be in anhydrous form, in aqueous form or in the form of an emulsion.

The compounds are used topically at a concentration generally of between 0.001% and 10% by weight, preferably between 0.01% and 1% by weight, relative to the total weight of the composition.

The compounds of formula (I) according to the invention, in the form of pure optical and/or geometric isomers or as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof, also find an application in the cosmetics field, in particular in body hygiene and hair care, and more particularly for regulating and/or restoring the metabolism of lipids in the skin. In fact, the regulation and/or the restoration of the metabolism of lipids in the skin makes it possible to

obtain a skin whose surface appearance is embellished.

A subject of the invention is therefore also the cosmetic use of a composition comprising, in a physiologically acceptable support, at least one of the compounds of formula (I), in the form of a pure optical and/or geometric isomer or in the form of a mixture, in any proportions, optionally in the form of a salt, pharmaceutically acceptable solvate and/or hydrate, for body hygiene or hair care.

The cosmetic composition according to the invention containing, in a cosmetically acceptable support, at least one compound of formula (I) in the form of a pure optical or geometric isomer or of a mixture of these isomers, or a salt, pharmaceutically acceptable solvate and/or hydrate thereof, can in particular be in the form of a cream, a milk, a lotion, a gel, suspensions of lipid or polymeric microspheres or nanospheres or vesicles, impregnated pads, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

The concentration of compound of formula (I) in the cosmetic composition is between 0.001% and 3% by weight, relative to the total weight of the composition.

The pharmaceutical and cosmetic compositions as described above can also contain inert additives, or even pharmacodynamically active additives as regards the pharmaceutical compositions, or combinations of these additives, and in particular:

- wetting agents;
- flavour enhancers;
- preserving agents such as para-hydroxybenzoic acid esters;
- stabilizers;
- moisture regulators;
- pH regulators;

- osmotic pressure modifiers;
- emulsifiers;
- UV-A and UV-B screening agents;
- antioxidants, such as α-tocopherol, butylhydroxy-anisole or butylhydroxytoluene, superoxide dismutase, ubiquinol or certain metal chelators;
- depigmenting agents, such as hydroquinone, azelaic acid, cafeic acid or kojic acid;
- emollients;
- moisturizers such as glycerol, PEG 400, thia-morpholinone, and its derivatives, or urea;
- antiseborrhoeic or anti-acne agents, such as S-carboxymethylcysteine, S-benzylcysteamine, their salts or their derivatives, or benzoyl peroxide;
- antibiotics such as erythromycin and its esters, neomycin, clindamycin and its esters, tetracyclines;
- antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolidones;
- agents promoting hair regrowth, such as Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and its derivatives, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,4-diphenylimidazolidine-2,4-dione);
- nonsteroidal anti-inflammatory agents;
- carotenoids, and in particular β-carotene;
- antipsoriatic agents such as anthralin and its derivatives;
- 5,8,11,14-eicosatetraynoic acid and 5,8,11-eicosa-triynoic acid, their esters and amides;
- retinoids, i.e. ligands for RAR or RXR receptors, which may be natural or synthetic;
- corticosteroids or oestrogens;
- α-hydroxy acids and α-keto acids or their derivatives, such as lactic acid, malic acid, citric acid, glycolic acid, mandelic acid, tartaric acid, glyceric acid or ascorbic acid, and their salts, amides or esters, or β-hydroxy acids or their derivatives, such as salicylic acid and its salts, amides or esters;
- ion channel blockers, such as potassium channel

blockers;
- or alternatively, more particularly for the pharmaceutical compositions, in combination with medicaments known to interfere with the immune system (for example cyclosporin, FK 506, glucocorticoids, monoclonal antibodies, cytokines or growth factors, etc.).

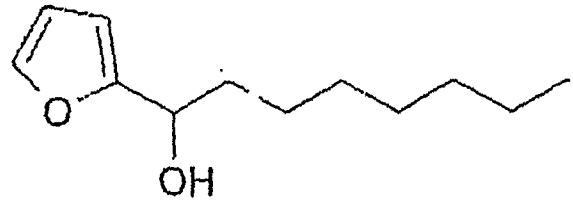
Of course, those skilled in the art will take care to choose the possible compound(s) to be added to these compositions in such a way that the advantageous properties intrinsically associated with the present invention are not, or are not substantially, impaired by the addition envisaged.

Moreover, in general, the same preferences as those indicated above for the compounds of formula (I) apply *mutatis mutandis* to the medicaments, cosmetic compositions, pharmaceutical compositions and use employing the compounds of the invention.

By way of illustration, and without in any way being limiting in nature, several examples of obtaining active compounds of formula (I) according to the invention will now be given, as will results of biological activity of such compounds and various concrete formulations based on these compounds.

EXAMPLE 1: PREPARATION OF THE INTERMEDIATES USED IN SCHEME 1 FOR SYNTHESIZING THE COMPOUNDS OF FORMULA (I)

PREPARATION 1
1-(2-Furyl)octan-1-ol, in racemic form (1)



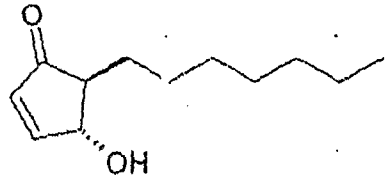
Approximately one tenth of a solution of 1-bromoheptane

(1.14 g, 6.36 mmol) in ether (3.2 ml) is added to a suspension of magnesium (0.23 g, 9.55 mmol) in ether (3.2 ml). A crystal of iodine is added and heating is initiated. The rest of the 1-bromoheptane in ether is added with gentle stirring at reflux. After stirring for 30 min at 25°C, a solution of furfural (0.61 g, 6.36 mmol) in ether (3.2 ml) is added dropwise and the final mixture is stirred for a further 2 hours. The mixture is gently poured into water and cooled to 0°C before the addition of the required amount of a 5% aqueous HCl solution in order to dissolve the white precipitate formed. After the addition of brine, the mixture is extracted with ether (3×) and the combined organic phases are washed with an aqueous solution of $NaHCO_3$ and brine, and dried (Na_2SO_4), and the solvents are evaporated off. The residue is purified by chromatography (SiO_2, hexane/ethyl acetate (ethylOAc), 95/5 v/v) so as to obtain the compound **(1)** (1.07 g, 85%) in the form of a yellow oil.

^1H NMR ($CDCl_3$, 400.13 MHz) δ 0.88 (t, J = 6.7 Hz, 3H, CH_3), 1.2-1.5 (m, 10H), 1.8-1.9 (m, 3H, $2H_2$ + OH), 4.67 (t, J = 6.5 Hz, 1H, H_1), 6.23 (d, J = 3.2 Hz, 1H, H_3-), 6.33 (dd, J = 3.2, 1.7 Hz, 1H, H_4-), 7.37 (dd, J = 1.7, 0.7 Hz, 1H, H_5-) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.6 (t), 25.5 (t), 29.2 (t), 29.3 (t), 31.7 (t), 35.5 (t), 67.8 (d, C_1), 105.7 (d, C_3-), 110.1 (d, C_4-), 141.7 (d, C_5-), 156.9 (s, C_2) ppm. IR (NaCl): p3100-3400 (br, OH), 2931 (m, C-H), 2859 (m, C-H), 1505 (w), 1467 (m), 1227 (w), 1149 (m), 1009 (s), 918 (w), 884 (w), 807 (m), 734 (s), 599 (m) cm^{-1}. MS: m/z (%) 196 (M^+, 10), 97 (100). HRMS: calculated for $C_{12}H_{20}O_2$ (M^+): 196.1463; found: 196.1464.

PREPARATION 2

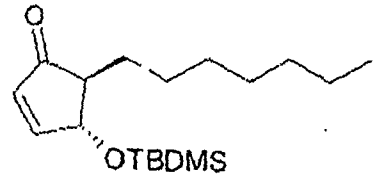
(4*R,5*S**)-5-Heptyl-4-hydroxycyclopent-2-en-1-one (2)**



PPA (0.76 g) is added to a solution of 1-(2-furyl)octan-1-ol **(1)** (4.52 g, 23.09 mmol) in a 2/1, v/v, water/acetone mixture (63 ml), and the solution obtained is stirred for 48 h at 65°C. The reaction mixture is then poured into water and extracted with ether (3 times) and the combined organic phases are washed with a saturated NaCl solution and dried (Na_2SO_4), and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 80/20, v/v hexane/ethylOAc) to give 1.83 g of the compound **(2)**, in the form of a yellow oil, and 0.83 g of the starting alcohol (yield based on the amount of starting product recovered: 50%). **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, *J* = 7.1 Hz, 3H, CH_3), 1.2-1.8 (m, 12H), 2.02 (br s, 1H, OH), 2.23 (ddd, *J* = 8.4, 4.3, 2.3 Hz, 1H, H_5), 4.70 (br s, 1H, H_4), 6.19 (dd, *J* = 5.8, 1.1 Hz, 1H, H_2), 7.50 (dd, *J* = 5.8, 2.2 Hz, 1H, H_3) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.6 (t), 27.3 (t), 28.6 (t), 29.0 (t), 29.6 (t), 31.7 (t), 55.4 (d, C_5), 76.7 (d, C_4), 134.2 (d, C_2), 161.8 (d, C_3), 208.3 (s, C_1) ppm. **IR** (NaCl): υ 3600-3100 (br, OH), 2927 (s, C-H), 2856 (m, C-H), 1708 (s, C=O), 1464 (w), 1341 (w), 1219 (w), 1102 (w), 1026 (w), 773 (s) cm^{-1}. **MS**: m/z(%) 196 (M^+, 18), 126 (7), 111 (17), 98 (100), 80 (15). **HRMS**: calculated for $C_{12}H_{20}O_2$ (M^+): 196.1463; found: 196.1466.

PREPARATION 3

(4*R,5*S**)-4-(tert-Butyldimethylsilyloxy)-5-heptylcyclopent-2-en-1-one (3)**

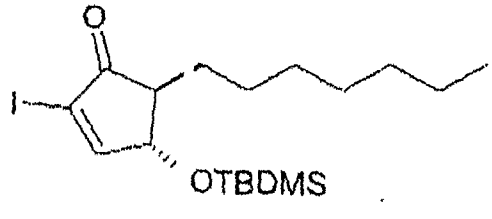


A solution of TBDMSCl (0.17 g, 1.12 mmol) in CH_2Cl_2

(0.3 ml) is added to a solution of cyclopentenone **(2)** (0.110 g, 0.56 mmol) and DMAP (6.8 mg, 0.06 mmol) in CH_2Cl_2 (1 ml) at 0°C. After stirring for 5 min, triethylamine (0.087 ml, 0.62 mmol) is added slowly over a period of 1.5 h. The reaction mixture is then stirred for 1 h at 0°C and then for 12 h at 25°C. This mixture is then poured into water and extracted with ether (3 times). The combined organic phases are washed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 97/3, v/v, hexane/ethylOAc), so as to obtain the compound (4*R**,5*S**)-4-(*tert*-butyldimethylsilyloxy)-5-heptylcyclopent-2-en-1-one **(3)** (0.14 g, yield = 81%) in the form of a yellow oil. **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.14 (s, 3H, Si-CH_3), 0.15 (s, 3H, Si-CH_3), 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.2 [s, 9H, Si-C(CH_3)$_3$], 1.2-1.8 (m, 12H), 2.23 (ddd, J = 7.8, 5.0, 2.2 Hz, 1H, H_5), 4.62 (app td, J = 2.2, 1.1 Hz, 1H, H_4), 6.12 (dd, J = 5.8, 1.1 Hz, 1H, H_2), 7.35 (dd, J = 5.8, 2.2 Hz, 1H, H_3) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ-4.6 (q, Si-CH_3), -4.2 (q, Si-CH_3), 14.0 (q), 17.9 [s, Si-C(CH_3)$_3$], 22.6 (t), 25.7 [q, Si-C($\underline{C}H_3$)$_3$, 3x], 28.3 (t), 29.1 (t), 29.6 (t), 31.8 (t), 55.4 (d, C_5), 76.8 (d, C_4), 133.8 (d, C_2), 162.0 (d, C_3), 208.3 (s, C_1) ppm. **IR** (NaCl): υ 2957 (m, C-H), 2930 (s, C-H), 2858 (s, C-H), 1720 (s, C=O), 1464 (m), 1360 (m), 1257 (m), 1112 (s), 1069 (m), 838 (s) cm^{-1}. **MS**: *m/z*(%) 310 (M^+, 5), 253 (84), 169 (18), 155 (100), 129 (26), 75 (26). **HRMS**: calculated for $C_{18}H_{34}O_2Si$ (M^+): 310.2328; found: 310.2334.

PREPARATION 4

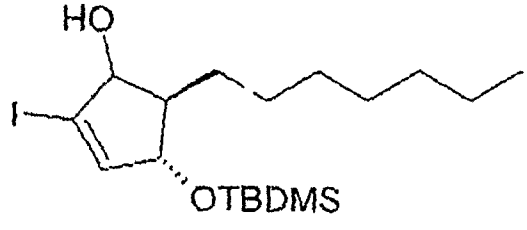
(4*S,5*S**)-4-(*tert*-Butyldimethylsilyloxy)-5-heptyl-2-iodocyclopent-2-en-1-one (4)**



A solution of iodine (0.46 g, 1.80 mmol) in a mixture of CH_2Cl_2/pyridine (50/50 v/v, 10.4 ml) is added, dropwise, for 15 min at 0°C, to the ketone **(3)** (0.33 g, 1.06 mmol). The reaction mixture is stirred for a further 2 h at 25°C, and is then poured into water and extracted with ether. The organic phases are washed with a saturated solution of NaCl and then with a saturated solution of $CuSO_4$, followed by washing with a saturated solution of $Na_2S_2O_3$. They are dried (Na_2SO_4) and the solvent is evaporated off. The residue is purified by chromatography (SiO_2, 98/2, v/v, hexane/ethylOAc), so as to obtain the ketone **(4)** in the form of a yellow oil (0.40 g, yield = 87%). **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.10 (s, 3H, Si-CH_3), 0.12 (s, 3H, Si-CH_3), 0.87 (t, J = 6.9 Hz, 3H, CH_3), 0.91 [s, 9H, Si-$C(CH_3)_3$], 1.2-1.8 (m, 12H), 2.35 (ddd, J = 7.6, 5.3, 2.4 Hz, 1H, H_5), 4.61 (app t, J = 2.4 Hz, 1H, H_4), 7.73 (d, J = 2.4 Hz, 1H, H_3), ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ-4.7 (q, Si-CH_3), -4.3 (q, Si-CH_3), 14.0 (q), 17.9 [s, Si-$\underline{C}(CH_3)_3$], 22.6 (t), 25.6 [q, Si-C($\underline{C}H_3)_3$, 3x], 26.8 (t), 28.5 (t), 29.0 (t), 29.5 (t), 31.7 (t), 53.4 (d, C_5), 77.9 (d, C_4), 104.3 (s, C_2), 167.4 (d, C_3), 201.9 (s, C_1) ppm. **IR** (NaCl): υ 2928 (s, C-H), 2856 (m, C-H), 1726 (s, C=O), 1578 (w), 1461 (w), 1255 (m), 1219 (m), 1075 (m), 838 (s) cm^{-1}. **MS**: *m/z* (%) 436 (M^+, 3), 379 [$(M-tBu)^+$, 55], 322 (10), 281 (39), 252 (100), 224 (19), 195 (32), 181 (13), 75 (26), 73 (21). **HRMS**: calculated for $C_{18}H_{33}IO_2Si$ (M^+): 436.1294; found: 436.1296.

PREPARATION 5

(1*R,4*S**,5*R**) and (1*S**,4*S**,5*R**)-4-(tert-butyldimethylsilyloxy)-5-heptyl-2-iodocyclopent-2-en-1-ol (5)**

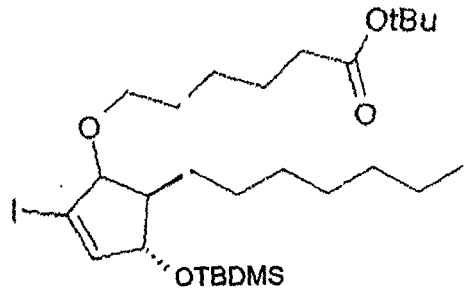


A solution of the ketone **(4)** (0.87 g, 2.00 mmol) and $CeCl_3 \cdot 7H_2O$ (0.75 mg, 2.00 mmol) in methanol (7.1 ml) is added for 2 h at 25°C. $NaBH_4$ (0.26 g, 7.01 mmol) at 0°C is then added in small portions, for 2 h, until the starting products have completely disappeared. A saturated aqueous solution of NH_4Cl (2 ml) is added, and the reaction mixture is then poured into water, extracted with ether (3 times) and washed with a saturated solution of NaCl. The combined organic phases are then dried (Na_2SO_4) and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 97/3, v/v, hexane/ethylOAc), so as to give a mixture of alcohols **(5)** with R_3=I (0.57 g, yield = 64%) in the form of a brown oil. The ^1H NMR spectrum of the compound **(5)** with R_3=I shows a 1:1 mixture of the (1*S**,4*S**,5*S**) and (1*R**,4*S**,5*S**) diastereoisomers.

Mixture of alcohols **(5)** [the data relating to the predominant diastereoisomer (1*S**,4*S**,5*S**) are underlined]: **^1H NMR** ($CDCl_3$, 400.13 MHz) δ 0.09 [s, 12H, 4 x Si-CH_3), 0.7-0.9 [m, 24H, 2 x CH_3 + 2 x Si-C(CH_3)$_3$], 1.2-1.7 (m, 24H), 1.9-2.0 (m, 2 x 1H, 2 x H_5), 4.08 (m, 1H, H_1), 4.24 (ddd, *J* = 4.9, 2.0, 1.2 Hz, 1H, H_4), 4.46 (app dt, *J* = 5.8, 1.7 Hz, 1H, H_4), 4.60 (m, 1H, H_1), 6.22 (dd, *J* = 2.0, 1.2 Hz, 1H, H_3), 6.32 (app t, *J* = 1.7 Hz, 1H, H_3) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ-4.7 (q, Si-CH_3, 2x), -4.4 (q, Si-CH_3), -4.3 (q, Si-CH_3), 14.1 (q, 2x), 17.9 [s, Si-C(CH_3)$_3$, 2x], 22.6 (t, 2x), 25.8 [q, Si-C(CH_3)$_3$, 6x], 27.5 (t), 28.1 (t), 29.2 (t, 2x), 29.7 (t, 2x), 31.7 (t, 2x), 31.8 (t, 2x), 52.4 (d), 57.0 (d), 80.9 (d), 81.4 (d), 81.8 (d), 84.2 (d), 102.2 (s), 105.2 (s), 144.2 (d), 147.5 (d) ppm. **IR** (NaCl): υ 3500-3200 (br, OH), 2955 (m, C-H), 2927 (s, C-H), 2856 (m, C-H), 1462 (w), 1361 (w), 1255 (w), 1220 (w), 1045 (w), 1004 (w), 836 (m), 773 (s) cm^{-1}. **MS**: *m/z* (%) 438 (M^+, 1), 381 (100), 363 (10), 254 (9), 169 (25), 156 (6), 75 (69). **HRMS**: calculated for $C_{18}H_{35}IO_2Si$ (M^+): 438.1451; found: 438.1440.

PREPARATION 6

***tert*-Butyl (1'*R**,4'*S**,5'*S**)-6-[4-(*tert*-butyldimethylsilyloxy)-5-heptyl-2-iodocyclopent-2-enyloxy]hexanoate and *tert*-butyl (1'*S**,4'*S**,5'*S**)-6-[4-(*tert*-butyldimethylsilyloxy)-5-heptyl-2-iodocyclopent-2-enyloxy]hexanoate (7)**

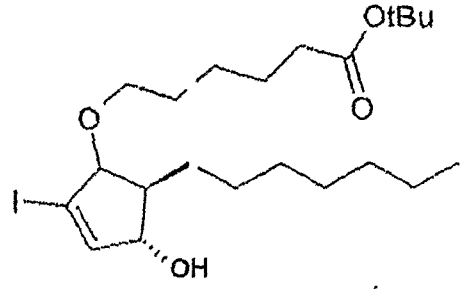


A solution of the alcohol **(5)** with R_3=I (75 mg, 0.17 mmol) in DMF (0.2 ml) is added to NaH (16 mg, 0.68 mmol) cooled to -10°C, and the reaction mixture is stirred for 35 min, before adding, dropwise, over 30 min, the tert-butyl 6-iodohexanoate **(6)** (L. Castellanos et al., Tetrahedron, 1981, vol. 37, 1691-1981), (0.20 g, 0.68 mmol) in solution in DMF (0.2 ml). The reaction mixture is then stirred at 0°C for 4 h, poured into water, and extracted with ether (3 times). The organic phases are washed with a saturated solution of NaCl and dried (Na_2SO_4) and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 98/2, v/v, hexane/ethylOAc), so as to give the compound **(7)** (82 mg, yield = 79%), in the form of a yellow oil, containing the diastereoisomers in a 1:1 ratio.

Spectroscopic data for the mixture (the signals relating to the predominant diastereoisomer (1'*S**,4'*S**,5'*S**) are underlined): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.07 (s, 12H, 4 x Si-CH_3), 0.8-0.9 [m, 24H, 2 x Si-C$(CH_3)_3$ + 2 x CH_3], 1.2-1.8 (m, 36H), 1.45 [s, 18H, 2 x O-C$(CH_3)_3$], 1.9-2.1 (m, 2 x 1H, 2 x H_5-), 2.22 (t, *J* = 7.5 Hz, 2H, $2H_2$), 2.23 (t, *J* = 7.5 Hz, 2H, $2H_2$), 3.4-3.8 (m, 4H, 2 x $2H_6$), <u>3.91</u> (app dt, *J* = 5.2, 1.3 Hz, 1H,

$H_{1'}$), 4.16 (ddd, J = 4.6, 2.0, 1.3 Hz, 1H, $H_{4'}$), 4.27 (dd, J = 6.4, 1.5 Hz, 1H, $H_{1'}$), 4.44 (app dt, J= 5.8, 1.5 Hz, 1H, $H_{4'}$), 6.20 (dd, J = 2.0, 1.5 Hz, 1H, $H_{3'}$), 6.30 (d, J = 1.5 Hz, 1H, $H_{3'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ -4.7 (q, Si-CH_3, 2x), -4.3 (q, Si-CH_3, 2x), 14.1 (q, 2x), 18.0 [s, Si-$\underline{C}(CH_3)_3$, 2x], 22.6 (t, 2x), 24.9 (t, 2x), 25.7 (t, 2x), 25.8 [q, Si-C($\underline{C}H_3)_3$, 6x], 26.6 (t, 2x), 27.3 (t, 2x), 28.1 [q, O-C($\underline{C}H_3)_3$, 6x], 29.1 (t, 2x), 29.7 (t), 29.8 (t), 30.1 (t, 2x), 31.8 (t, 2x), 35.5 (t, 2x), 53.3 (d, $C_{5'}$, 2x), 68.0 (t), 71.5 (t), 79.9 [s, O-$\underline{C}(CH_3)_3$, 2x], 80.8 (d), 81.4 (d), 88.8 (d), 90.8 (d), 98.7 (s), 101.8 (s), 144.8 (d), 147.8 (d), 173.1 (s, 2x) ppm. **IR** (NaCl): υ 2930 (s, C-H), 2857 (s, C-H), 1733 (s, C=O), 1461 (m), 1366 (m), 1255 (m), 1151 (m), 1091 (m), 836 (m) cm^{-1}. **MS**: *m/z* (%) 551 [$(M-t\text{Bu})^+$, 0.2], 421 (16), 190 (14), 189 (100), 171 (19), 73 (10). **HRMS**: calculated for $C_{28}H_{53}IO_4Si$ (M^+): 608.2758; found: 608.2753.

PREPARATION 7: *tert*-Butyl (1'*R,4'*S**,5'*S**)-6-(5-heptyl-4-hydroxy-2-iodocyclopent-2-enyloxy)hexanoate and *tert*-butyl (1'*S**,4'*S**,5'*S**)-6-(5-heptyl-4-hydroxy-2-iodocyclopent-2-enyloxy)hexanoate (8)**

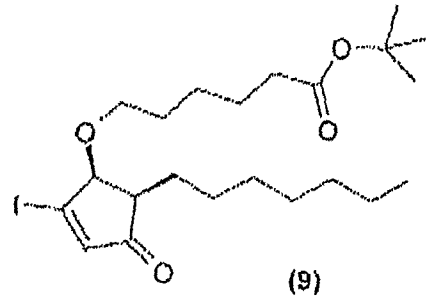


nBu_4NF (0.77 ml, 1.0 M in THF, 0.77 mmol) is added to a solution of the compound **(7)** (0.28 g, 0.45 mmol) in THF (4.5 ml). After stirring for 10 h at 25°C, the reaction mixture is poured into a saturated aqueous solution of $NaHCO_3$, and extracted with ethyl acetate (3 times). The extracted organic phases are combined and then washed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvents are evaporated off. A purification by chromatography (SiO_2, 90/10, v/v, hexane/ethylOAc) is

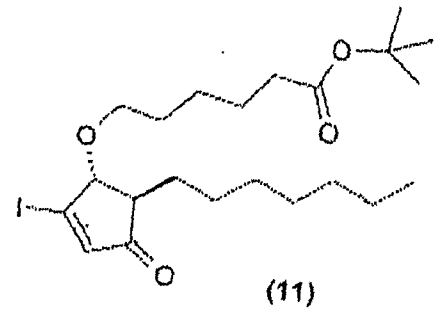
carried out so as to give the mixture of alcohols **(8)** in the form of an oil (0.22 g, yield = 99%).

Spectroscopic data for the mixture (the signals relating to the predominant diastereoisomer (1'*S**,4'*S**,5'*S**) are underlined): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.8-0.9 (m, 6H, 2 x CH_3), 1.2-1.6 (m, 36H), 1.45 [s, 18H, 2 x O-C($\underline{C}H_3$)$_3$], 1.9-2.0 (m, 2 x 1H, 2 x $H_{5'}$), 2.22 (t, *J* = 7.6 Hz, 2H, $2H_2$), 2.23 (t, *J* = 7.5 Hz, 2H, $2H_2$), 3.53 (dt, *J* = 9.1, 6.5 Hz, 1H, H_6), 3.55 (dt, *J* = 9.1, 6.5 Hz, 1H, H_6), 3.63 (dt, *J* = 8.9, 6.5 Hz, 1H, H_6), 3.74 (dt, *J* = 8.9, 6.4 Hz, 1H, H_6), 3.87 (br d, *J* = 4.5 Hz, 1H, $H_{1'}$), 4.14 (br s, 1H, $H_{4'}$), 4.33 (dd, *J* = 6.5, 1.5 Hz, $H_{1'}$), 4.46 (br s, 1H, $H_{4'}$), 6.34 (dd, *J* = 1.9 0.8 H, 1H, $H_{3'}$), 6.39 (d, *J* = 1.7 Hz, 1H, $H_{3'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q, 2x), 22.6 (t, 2x), 24.8 (t, 2x), 25.6 (t, 2x), 26.9 (t, 2x), 27.5 (t, 2x), 28.0 [q, O-C($\underline{C}H_3$)$_3$, 6x], 28.3 (t, 2x), 29.1 (t, 2x), 29.7 (t), 29.8 (t), 31.8 (t), 32.7 (t), 35.4 (t, 2x), 53.1 (d), 54.1 (d), 69.4 (t), 71.4 (t), 79.9 [s, O-$\underline{C}$(CH_3)$_3$, 2x], 80.9 (d), 81.2 (d), 89.1 (d), 91.9 (d), 99.9 (s), 102.2 (s), 144.5 (d), 147.0 (d), 173.1 (s, 2x) ppm. **IR** (NaCl) υ 3600-3100 (br, OH), 2927 (s, C-H), 2856 (m, C-H), 1731 (s, C=O), 1457 (m), 1152 (s), 1092 (m) cm^{-1}. **MS**: *m/z* (%) 437 [(MH_2 - *t*Bu)$^+$, 1], 307 (37), 306 (30), 290 (29), 207 (13), 179 (25), 133 (17), 131 (21), 115 (100), 97 (20), 69 (22). **HRMS**: calculated for $C_{18}H_{24}IO_4$ (MH-*t*Bu)$^+$: 436.1111; found: 436.1116.

EXAMPLE 2: Synthesis of *tert*-butyl (1'*R,5'*R**)-6-(2-iodo-5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate (11) and *tert*-butyl (1'*S**,5'*R**)-6-(2-iodo-5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate (9)**



(9)



(11)

A solution of alcohols **(8)** (0.28 g, 0.57 mmol) in CH_2Cl_2 (2.5 ml) is added to a suspension of PDC (0.28 g, 0.74 mmol) in CH_2Cl_2 (1.5 ml). After stirring for 12 hours at 25°C, the reaction mixture is filtered over silica gel, are eliminated and the residue is purified by chromatography (SiO_2, 95/5, v/v hexane/ethylOAc), to give the ketones **(11)** (1'*R**,5'*R**) (0.13 g, yield = 47%) and **(9)** (1'*S**,5'*R**) (0.13 g, yield = 47%), both in the form of a yellow oil.

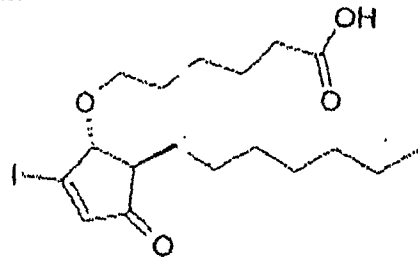
The configuration of the various compounds is evaluated by virtue of the coupling constants obtained for the $H_{1'}$ and H_5 hydrogens. The values of 2.0 Hz and 6.4 Hz for the compounds **(9)** and **(11)**, respectively, correspond to the values obtained using the Karplus equation for the $C_{5'}/C_{1'}$ dihedral (120° and 25°, respectively). PC Spartan with semiempirical AM1. Wavefunction, Inc. 18401 Von Karmen, Suite 370, Irvine, CA 92612.

Data relating to the compound **(11)** (1'*R**,5'*R**): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 1.2-1.8 (m, 18H), 1.45 [s, 9H, O-C$(CH_3)_3$], 2.23 (t, *J* = 7.4 Hz, 2H, $2H_2$), 2.47 (ddd, *J* = 7.5, 5.0, 2.0 Hz, 1H, $H_{5'}$), 3.62 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 3.65 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 4.28 (dd, *J* = 2.0, 1.0 Hz, 1H, $H_{1'}$), 6.68 (d, *J* = 1.0 Hz, 1H, $H_{3'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ14.0 (q), 22.6 (t), 24.8 (t), 25.7 (t), 27.0 (t), 28.1 [q, O-C$(\underline{C}H_3)_3$, 3x], 29.0 (t), 29.2 (t), 29.5 (t), 29.7 (t), 31.8 (t), 35.4 (t), 53.8 (d, $C_{5'}$), 70.0 (t, C_6), 80.0 [s, O-$\underline{C}(CH_3)_3$], 88.8 (d, $C_{1'}$), 137.0 (s, $C_{2'}$), 144.1 (d, C_3-, 173.0 (s, C_1), 204.3 (s, $C_{4'}$)

ppm. **IR** (NaCl): υ 2928 (s, C-H), 2858 (m, C-H), 1720 (s, C=O), 1574 (w), 1458 (w), 1367 (w), 1245 (m), 1153 (s), 1101 (m) cm^{-1}. **MS**: *m/z* (%) 492 (M^+, 2), 437 (18), 436 (78), 435 (31), 419 (11), 323 (12), 322 (86), 321 (18), 309 (17), 306 (21), 304 (40), 224 (54), 221 (13), 211 (11), 208 (20), 207 (30), 195 (16), 179 (21), 177 (50), 131 (10), 115 (100), 97 (30), 69 (33). **HRMS**: calculated for $C_{22}H_{37}IO_4$ (M^+): 492.1737; found: 492.1748.

Data relating to the compound **(9)** (1'S*,5'*R**): ^{1}**H NMR** ($CDCl_3$, 400.13 MHz) δ0.88 (t, *J* = 6.8 Hz, 3H, CH_3), 1.2-1.7 (m, 18H), 1.45 [s, 9H, O-C(CH_3)$_3$], 2.23 (t, *J* = 7.5 Hz, 2H, $2H_2$), 2.58 (app q, *J* = 6.4 Hz, 1H, $H_{5'}$), 3.66 (dt, *J* = 8.9, 6.4 Hz, 1H, H_6), 3.79 (dt, *J* = 8.9, 6.4 Hz, 1H, H_6), 4.49 (dd, *J* = 6.4, 0.8 Hz, 1H, H_1), 6.67 (d, *J* = 0.8 Hz, 1H, H_3) ppm. ^{13}**C NMR** ($CDCl_3$, 100.62 MHz) δ14.1 (q), 22.6 (t), 24.9 (t), 25.7 (t), 26.4 (t), 27.5 (t), 28.1 [q, O-C($\underline{C}H_3$)$_3$, 3x], 29.1 (t), 29.7 (t), 29.8 (t), 31.8 (t), 35.4 (t), 51.7 (d, C_5), 72.8 (t, C_6), 80.0 [s, O-$\underline{C}$(CH_3)$_3$], 85.1 (d, C_1), 137.3 (s, C_2), 143.1 (d, C_3), 173.0 (s, C_1), 205.0 (s, C_4) ppm. **IR** (NaCl): υ 2928 (s, C-H), 2857 (m, C-H), 1718 (s, C=O), 1573 (m), 1459 (m), 1367 (m), 1240 (m), 1152 (s), 1104 (m), 800 (w) cm^{-1}. **MS**: *m/z* (%) 492 (M^+, 0.3), 437 (17), 436 (72), 435 (15), 323 (13), 322 (84), 321 (16), 309 (19), 306 (35), 304 (40), 276 (14), 224 (61), 221 (22), 208 (18), 207 (30), 195 (11), 179 (53), 177 (58), 131 (32), 123 (11), 115 (100), 97 (37), 79 (10), 73 (13), 69 (44), 67 (10). **HRMS**: calculated for $C_{22}H_{37}IO_4$ (M^+): 492.1737; found: 492.1740.

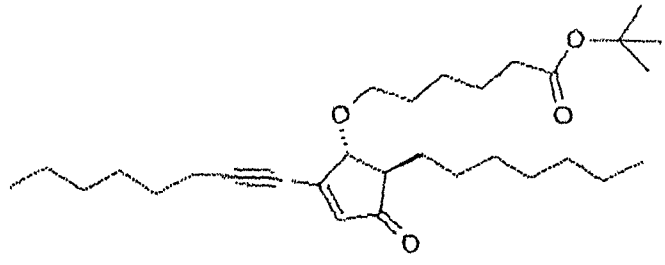
EXAMPLE 3: Synthesis of (1'*R, 5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoic acid (12)**



The ester **(11)** (51 mg, 0.11 mmol) is treated with TFA (0.7 ml) so as to give, after purification by chromatography (SiO_2, 95/5, v/v, CH_2Cl_2/MeOH), the (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoic acid **(12)** (39 mg, yield = 83%), in the form of an oil.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ0.88 (t, *J* = 6.8 Hz, 3H, CH_3), 1.2-1.8 (m, 18H), 2.38 (t, *J* = 7.4 Hz, 2H, $2H_2$), 2.50 (ddd, *J* = 7.6, 5.0, 2.0 Hz, 1H, H_5), 3.63 (dt, *J* = 8.8, 6.3 Hz, 1H, H_6), 3.66 (dt, *J* = 8.8, 6.3 Hz, 1H, H_6), 4.28 (dd, *J* = 2.0, 1.0 Hz, 1H, H_1), 6.69 (d, *J* = 1.0 Hz, 1H, H_3) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ14.0 (q), 22.6 (t), 24.4 (t), 25.6 (t), 27.0 (t), 29.0 (t), 29.2 (t), 29.5 (t), 29.6 (t), 31.7 (t), 33.9 (t), 53.7 (d, C_5), 69.9 (t, C_6), 88.8 (d, C_1), 137.0 (s, C_2), 144.1 (d, C_3), 179.5 (s, C_1), 204.4 (s, C_4) ppm. **IR** (NaCl): υ 3500-2700 (br, OH), 2927 (s, C-H), 2856 (m, C-H), 1716 (s, C=O), 1571 (m), 1457 (w), 1244 (m), 1163 (m), 1101 (m) cm^{-1}. **MS**: *m/z*(%) 436 (M^+, 14), 322 (73), 321 (12), 309 (10), 304 (23), 234 (13), 224 (100), 207 (11), 177 (59), 115 (75), 110 (14), 97 (46), 79 (10), 73 (21), 69 (73), 65 (10). **HRMS**: calculated for $C_{18}H_{29}IO_4$ (M^+): 436.1111; found: 436.1116.

EXAMPLE 4: Synthesis of tert-butyl (1'*R,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-hexanoate (14)**

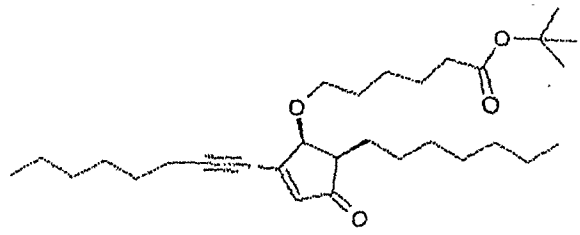


$(CH_3CN)_2PdCl_2$ (2 mg, 0.006 mmol), $AsPh_3$ (4 mg, 0.012 mmol), CuI (3 mg, 0.012 mmol) and tributyloct-1-ynylstannane (59 mg, 0.15 mmol) (E. Shirakawa et al., J. Am. Chem. Soc. 2004, 126, 13614-13615) are added sequentially to a solution of iodide **(11)** (61 mg,

0.12 mmol) in NMP (0.25 ml). After heating at 80°C for 40 min, the reaction mixture is cooled to 25°C, diluted with ethyl acetate (5 ml), poured into a solution of silver acetate (65 mg, 0.36 mmol) in ethyl acetate (4 ml), and vigorously stirred for 2 h. The reaction mixture is then filtered over silica gel, and the filtrate is washed with water and with a saturated solution of NaCl. The aqueous phase is extracted with ether, and the organic phases are combined and then dried (Na_2SO_4), and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 95/5, v/v hexane/ethylOAc), so as to give the ester (**14**) (56 mg, yield = 95%) in the form of a yellow oil.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ0.8-0.9 (m, 6H, 2 x CH_3), 1.2-1.8 (m, 26H), 1.44 [s, 9H, O-C(CH_3)$_3$], 2.22 (t, *J* = 7.5 Hz, 2H, $2H_2$), 2.33 (ddd, *J* = 7.1, 4.8, 2.0 Hz, 1H, H_5), 2.48 (t, *J* = 7.0 Hz, 2H, $2H_3$), 3.58 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 3.77 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 4.22 (d, *J* = 2.0 Hz, 1H, H_1), 6.16 (s, 1H, H_3). **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ14.1 (q, 2x), 20.1 (t, 2x), 22.5 (t), 22.6 (t), 24.8 (t), 25.6 (t), 27.0 (t), 28.0 [q, O-C($\underline{C}H_3$)$_3$, 3x], 28.5 (t), 29.0 (t), 29.4 (t), 29.5 (t), 29.7 (t), 31.2 (t), 31.7 (t), 35.4 (t), 52.5 (d, C_5), 70.1 (t, C_6), 76.1 (s, C_1-), 79.9 [s, O-$\underline{C}$(CH_3)$_3$], 85.3 (d, C_1), 109.2 (s, $C_{2'}$), 135.4 (d, C_3), 155.4 (s, C_2), 172.9 (s, C_1), 207.5 (s, C_4). **MS**: *m/z* (%) 474 (M^+, 6), 419 (21), 418 (77), 417 (38), 320 (24), 304 (18), 303 (23), 288 (61), 287 (100), 286 (46), 285 (19), 258 (22), 234 (19), 216 (14), 206 (26), 203 (28), 190 (15), 136 (24), 115 (31), 105 (12), 97 (11), 91 (35), 77 (10), 69 (26). **HRMS**: calculated for $C_{30}H_{50}O_4$ (M^+): 474.3709; found: 474.3688.

EXAMPLE 5: Synthesis of *tert*-butyl (1'*S, 5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-hexanoate (13)**

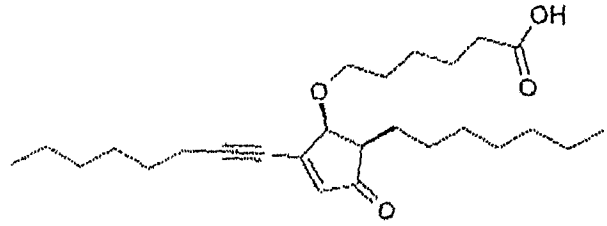


By following the procedure described above in EXAMPLE 4, the iodide (**9**) (58 mg, 0.12 mmol) is treated with $(CH_3CN)_2PdCl_2$ (2 mg, 0.006 mol), $AsPh_3$ (4 mg, 0.012 mmol), CuI (3 mg, 0.012 mmol) and tributyloct-1-ynylstannane (56 mg, 0.14 mmol) in NMP (0.25 ml), for 40 min at 80°C. After purification by chromatography (SiO_2, 95/5, v/v, hexane/ethylOAc), 51 mg (yield = 89%) of the ester (**13**), which is partly isomerized in the form of the compound (**14**) (with a **13:14** ratio of 3.3:1), are obtained, in the form of a yellow oil. An analytical sample is obtained after purification by HPLC (Waters Spherisorb® 5 µm, 97/3, v/v, hexane/ethylOAc, 1 ml/min, t_R (**13**) = 31.25 min, t_R (**14**) = 32.75 min.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ0.8-0.9 (m, 6H, 2 x CH_3), 1.2-1.6 (m, 26H), 1.45 [s, 9H, O-C$(CH_3)_3$], 2.22 (t, J = 7.5 Hz, 2H, $2H_2$), 2.3-2.4 (m, 3H, $2H_{3''}$ + H_5), 3.60 (dt, J = 9.1, 6.5 Hz, 1H, H_6), 3.88 (dt, J = 9.1, 6.5 Hz, 1H, H_6), 4.43 (d, J = 6.2 Hz, 1H, H_1), 6.16 (s, 1H, H_3). **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ14.1 (q, 2x), 20.1 (t), 22.5 (t), 22.6 (t), 24.8 (t), 25.6 (t), 25.9 (t), 27.7 (t), 28.0 [q, O-C($\underline{C}H_3)_3$, 3x], 28.1 (t), 28.5 (t), 29.1 (t), 29.7 (t), 31.2 (t), 31.8 (t), 35.4 (t), 50.2 (d, C_5), 72.0 (t, C_6), 76.5 (s, C_1), 79.9 [s, O-$\underline{C}(CH_3)_3$], 81.1 (d, C_1), 108.8 (s, $C_{2''}$), 134.7 (d, C_3), 156.0 (s, C_2), 172.9 (s, C_1), 208.7 (s, C_4). **IR** (NaCl): υ 2929 (s, C-H), 2858 (m, C-H), 2217 (w, C≡C), 1731 (s, C=O), 1707 (s, C=O), 1653 (w), 1458 (m), 1367 (m), 1153 (m), 1106 (w) cm^{-1}. **MS**: *m/z* (%) 474 (M^+, 8), 419 (23), 418 (80), 417 (35), 320 (24), 304 (18), 303 (21), 288 (48), 287 (100), 286 (45), 234 (14), 206 (24), 203 (24), 190 (20), 136 (20), 115 (40), 97 (10), 91 (13), 69 (23).

HRMS: calculated for $C_{30}H_{50}O_4$ (M^+): 474.3709; found: 474.3706.

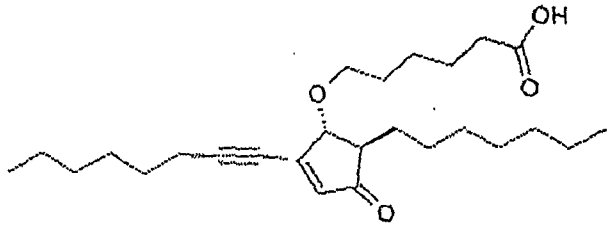
EXAMPLE 6: Synthesis of (1'*R,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid (15)**



The ester (**13**) (29 mg, 0.06 mmol) is treated with TFA (0.4 ml) so as to obtain, after purification by chromatography (SiO_2, 95/5, v/v, CH_2Cl_2/MeOH), 25 mg (99%) of acid (**15**) in the form of a yellow oil.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ0.8-0.9 (m, 6H, 2 x CH_3), 1.2-1.8 (m, 26H), 2.3-2.4 (m, 1H, H_5), 2.37 (t, J = 7.5 Hz, 2H, $2H_2$), 2.48 (t, J = 7.1 Hz, 2H, $2H_{3'}$), 3.59 (dt, J = 8.8, 6.4 Hz, 1H, H_6), 3.79 (dt, J = 8.8, 6.4 Hz, 1H, H_6), 4.22 (d, J = 1.7 Hz, 1H, H_1), 6.17 (s, 1H, H_3). **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ14.1 (q, 2x), 20.1 (t, 2x), 22.5 (t), 22.6 (t), 25.7 (t), 27.0 (t), 28.1 (t), 28.6 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.7 (t, 2x), 31.2 (t), 31.8 (t), 33.9 (t), 52.5 (d, C_5), 69.9 (t, C_6), 76.1 (s, C_1), 85.3 (d, $C_{1'}$), 109.3 (s, C_2), 135.5 (d, C_3), 155.4 (s, C_2), 179.2 (s, C_1), 207.7 (s, C_4). **IR** (NaCl): υ 3500-2700 (br, OH), 2928 (s, C-H), 2857 (m, C-H), 2219 (w, C≡C), 1709 (s, C=O), 1589 (w), 1458 (m), 1283 (w), 1104 (m) cm^{-1}. **MS**: *m/z* (%) 418 (M^+, 100), 320 (35), 304 (22), 303 (50), 287 (32), 286 (28), 258 (30), 234 (53), 218 (24), 216 (22), 206 (64), 205 (38), 203 (33), 190 (27), 136 (95), 115 (27), 105 (19), 97 (18), 91 (31), 69 (51). **HRMS**: calculated for $C_{26}H_{42}O_4$ (M^+): 418.3083; found: 418.3074.

EXAMPLE 7: Synthesis of (1'*S,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid (16)**

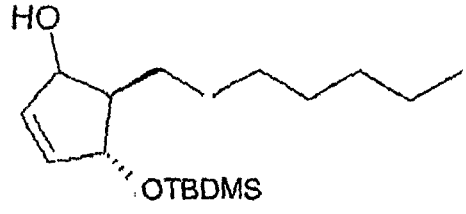


In accordance with the general hydrolysis procedure, the ester (**14**) (40 mg, 0.08 mmol) is treated with TFA (0.6 ml) so as to obtain, after purification by chromatography (SiO_2, 95/5, v/v, CH_2Cl_2/MeOH), 35 mg (99%) of acid (**16**) in the form of a brown oil.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ0.8-0.9 (m, 6H, 2 x CH_3), 1.2-1.8 (m, 26H), 2.37 (t, *J* = 7.5 Hz, 2H, $2H_2$), 2.4-2.5 (m, 1H, $H_{5'}$), 2.48 (t, *J* = 7.0 Hz, 2H, $2H_3$), 3.61 (dt, *J* = 9.0, 6.3 Hz, 1H, H_6), 3.79 (dt, *J* = 9.0, 6.3 Hz, 1H, H_6), 4.44 (d, *J* = 6.2 Hz, 1H, H_1), 6.17 (s, 1H, H_3). **IR** (NaCl): υ 3500-2700 (br, OH), 2928 (s, C-H), 2857 (m, C-H), 2218 (w, C≡C), 1708 (s, C=O), 1590 (w), 1458 (m), 1278 (w), 1107 (m) cm^{-1}. **MS**: *m/z* (%), 418 (M^+, 100), 320 (30), 303 (39), 287 (31), 286 (32), 273 (19), 234 (32), 229 (18), 218 (21), 216 (21), 215 (19), 206 (52), 205 (31), 203 (32), 190 (32), 136 (74), 115 (42), 105 (18), 97 (18), 91 (28), 69 (52). **HRMS**: calculated for $C_{26}H_{42}O_4$ (M^+): 418.3083; found: 418.3098.

EXAMPLE 8: Synthesis of *tert*-butyl (1'*S,5'*R**) and (1'*R**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)-hexanoate (17) and (18)**

Preparation of (1*R,4*R**,5*R**) and (1*S**,4*R**,5*R**)-4-(tert-butyldimethylsilyloxy)-5-heptylcyclopent-2-en-1-ol (5)**

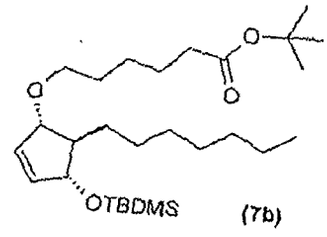


A solution of the ketone (**3**) (0.80 g, 2.59 mmol) and $CeCl_3 \cdot 7H_2O$ (0.96 g, 2.59 mmol) in methanol (5.1 ml) is

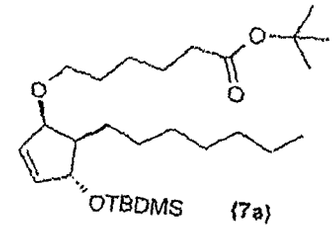
stirred for 15 min at 25°C. $NaBH_4$ (98 mg, 2.59 mmol) at 0°C is then added in small portions, and the stirring is maintained for 10 min. A saturated aqueous solution of NH_4Cl (2 ml) is added, and the reaction mixture is then poured into water, extracted with ether (3 times) and washed with a saturated solution of NaCl. The combined organic phases are then dried (Na_2SO_4), and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 90:10 hexane/EtOAc) so as to give a mixture of alcohols (**5**) with R_3=H (0.70 g, 87%) in the form of a yellow oil. The ^1H NMR spectrum of the compound (**5**) with R_3=H shows a 1:4 proportion of the (1*R**,4*R**,5*R**) and (1*S**,4*R**,5*R**) diastereoisomers.

Spectroscopic data for the mixture (the signals relating to the predominant diastereoisomer (1*S**,4*R**,5*R**) are underlined): **^1H NMR** ($CDCl_3$, 400.13 MHz) δ 0.09 (s, 12H, 4 x Si-CH_3), 0.8-0.9 (m, 6H, 2 x CH_3), 0.90 [s, 18H, 2 x Si-C(CH_3)$_3$], 1.2-1.6 (m, 24H), 1.6-1.8 (m, 2 x 1H, 2 x H_5), 4.18 (m, 1H, H_4), 4.26 (m, 1H, H_1), 4.59 (app dq, *J* = 5.9, 1.5 Hz, 1H, H_4), 4.70 (app dt, *J* = 6.1, 1.5 Hz, 1H, H_1), 5.82 (app dt, *J* = 5.6, 1.4 Hz, 1H, H_3), 5.87 (app dt, *J* = 5.6, 1.4 Hz, 1H, H_2), 5.97 (dd, *J* = 5.8, 1.5 Hz, 1H, H_3), 6.00 (app dq, *J* = 5.8, 1.5 Hz, 1H, H_2) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ -4.3 (q, Si-CH_3, 2x), -4.6 (q, Si-CH_3, 2x), 14.1 (q, 2x), 18.0 [s, Si-C(CH_3)$_3$, 2x], 22.6 (t, 2x), 25.8 [q, Si-C(CH_3)$_3$, 6x], 26.8 (t), 27.5 (t), 28.2 (t), 29.2 (t, 2x), 29.7 (t), 29.8 (t), 31.7 (t), 31.8 (t, 2x), 52.3 (d, C_5), 58.6 (d, C_5), 75.3 (d, C_4), 80.4 (d, C_4), 80.8 (d, C_1), 81.4 (d, C_1), 133.9 (d, C_3), 134.9 (d, C_3), 136.3 (d, C_2), 140.2 (d, C_2) ppm. **IR** (NaCl): υ 3600-3100 (br, OH), 3060 (w), 2957 (s, C-H), 2929 (s, C-H), 2858 (s, C-H), 1463 (M), 1362 (m), 1254 (s), 1120 (m), 1075 (s), 872 (m), 837 (s), 775 (s) cm^{-1}. **MS**: *m/z* (%) 313 [(M+1)$^+$, 1], 255 [(M-*t*Bu)$^+$, 100], 157 (9), 75 (52). **HRMS**: calculated for $C_{18}H_{36}O_2Si$ (M^+): 312.2484; found: 312.2486.

tert-Butyl (1'S*,4'R*,5'R*) and (1'R*,4'R*,5'R*)-6-[4-(tert-butyldimethylsilyloxy)-5-heptylcyclopent-2-enyloxy]hexanoate (7b) and (7a)



(7b)



(7a)

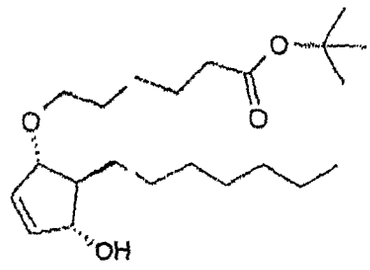
A solution of the alcohol (**5**) with R_3=H (0.59 g, 1.89 mmol) in DMF (2.3 ml) is added to NaH (0.18 g, 7.57 mmol) and cooled to -10°C, and the reaction mixture is stirred for 35 min before adding, dropwise, over 30 min, the iodide (**6**) (2.26 g, 7.57 mmol) in solution in DMF (2.4 ml). The reaction mixture is then stirred at 0°C for 4 h, poured into water, and extracted with ether (3x). The extracted organic phases are combined and then washed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvents are evaporated off. A purification by chromatography (SiO_2, 98:2 hexane/EtOAc) is carried out so as to give the compound (**7b**) (0.50 g) and (**7a**) (0.17 g) in the form of a yellow oil, with a yield of 84%.

Data relating to the compound (**7b**) (1'S*,4'R*,5'R*): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.07 (s, 6H, 2 x Si-CH_3), 0.8-0.9 (m, 3H, CH_3), 0.89 [s, 9H, Si-C(CH_3)$_3$], 1.3-1.6 (m, 18H), 1.44 [s, 9H, O-C(CH_3)$_3$], 1.92 (m, 1H, $H_{5'}$), 2.21 (t, J = 7.5 Hz, 2H, $2H_2$), 3.40 (dt, J = 9.1, 6.4 Hz, 1H, H_6), 3.51 (dt, J = 9.1, 6.4 Hz, 1H, H_6), 3.91 (app dq, J = 5.4, 1.5 Hz, 1H_1-), 4.25 (app dq, J = 5.0, 1.5 Hz, $H_{4'}$), 5.79 (app dt, J = 5.8, 1.5 Hz, 1H, H_3-), 5.89 (app dt, J = 5.8, 1.5 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ -4.6 (q, Si-CH_3), -4.2 (q, Si-CH_3), 14.1 (q), 18.0 [s, Si-C(CH_3)$_3$], 22.7 (t), 24.9 (t), 25.7 (t), 25.8 [q, Si-C(CH_3)$_3$, 3x], 27.7 (t), 28.1 [q, O-C(CH_3)$_3$, 3x], 29.2 (t), 29.8 (t), 29.9 (t), 31.9 (t), 32.5 (t), 35.5 (t), 54.5 (d, $C_{5'}$), 68.2 (t, C_6), 79.9 [s, O-

$\underline{C}(CH_3)_3$], 80.7 (d, $C_{4'}$), 87.3 (d, $C_{1'}$), 132.0 (d, $C_{2'}$), 136.5 (d, $C_{3'}$), 173.1 (s, C_1) ppm. **IR** (NaCl): υ 2929 (s, C-H), 2857 (s, C-H), 1733 (s, C=O), 1462 (m), 1365 (m), 1254 (m), 1151 (s), 1076 (s), 871 (m), 837 (m), 774 (s) cm^{-1}. **MS**: *m/z* (%) 482 (M^+, 0.03), 425 (1), 369 (2), 295 (18), 189 (100), 171 (19), 75 (11). **HRMS**: calculated for $C_{28}H_{54}O_4Si$ (M^+): 482.3791; found: 482.3777.

Data relating to the compound (**7a**) (1'*R**,4'*R**,5'*R**): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.08 (s, 6H, 2 x Si-CH_3), 0.8-0.9 (m, 3H, CH_3), 0.90 [s, 9H, Si-$C(CH_3)_3$], 1.2-1.6 (m, 18H), 1.45 [s, 9H, O-$C(CH_3)_3$], 1.86 (app dq, *J* = 9.5, 6.3 Hz, 1H, $H_{5'}$), 2.21 (t, *J* = 7.5 Hz, 2H, $2H_2$), 3.32 (dt, *J* = 9.1, 6.5 Hz, 1H, H_6), 3.46 (dt, *J* = 9.1, 6.5 Hz, 1H, H_6), 4.28 (app dt, *J* = 6.3, 1.5 Hz, 1H, $H_{1'}$), 4.59 (app dq, *J* = 5.9, 1.5 Hz, 1H, $H_{4'}$), 5.95 (dd, *J* = 5.8, 1.5 Hz, 1H, $H_{3'}$), 6.06 (app dt, *J* = 5.8, 1.5 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ -4.6 (q, Si-CH_3), -4.2 (q, Si-CH_3), 14.1 (q), 17.9 [s, Si-$\underline{C}(CH_3)_3$], 22.6 (t), 24.9 (t), 25.8 (t), 25.9 [q, Si-$C(\underline{C}H_3)_3$, 3x], 27.6 (t), 28.1 [q, O-$C(\underline{C}H_3)_3$, 3x], 29.2 (t), 29.8 (t), 29.9 (t), 31.8 (t), 32.5 (t), 35.5 (t), 54.5 (d, $C_{5'}$), 68.2 (t, C_6), 79.9 [s, O-$\underline{C}(CH_3)_3$], 80.7 (d, $C_{4'}$), 87.3 (d, $C_{1'}$), 132.0 (d, $C_{2'}$), 136.5 (d, $C_{3'}$), 173.1 (s, C_1) ppm. **IR** (NaCl): υ 2928 (s, C-H), 2856 (s, C-H), 1732 (s, C=O), 1461 (m), 1366 (m), 1254 (m), 1152 (s), 1096 (s), 862 (m), 837 (m), 774 (s) cm^{-1}. **MS**: *m/z* (%) 482 (M^+, 0.04), 425 (5), 369 (7), 295 (30), 255 (9), 189 (100), 171 (36), 115 (10), 97 (6), 73 (15). **HRMS**: calculated for $C_{28}H_{54}O_4Si$ $(M)^+$: 482.3791; found: 482.3793.

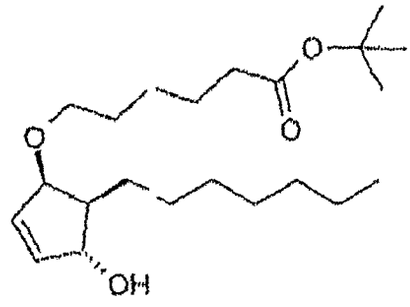
***tert*-Butyl (1'*S**,4'*R**,5'*S**)-6-(5-heptyl-4-hydroxycyclopent-2-enyloxy)hexanoate (8b)**



n-Bu_4NF (0.69 ml, 1.0 M in THF, 0.69 mmol) is added to a solution of the compound (**7b**) (0.19 g, 0.39 mmol) in THF (3.5 ml). After stirring for 10 h at 25°C, the reaction mixture is poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3x). The organic extract is then washed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvent is evaporated off. The residue obtained is purified by chromatography (SiO_2, 90:10 hexane/EtOAc) so as to give the alcoholic compound (**8b**) in the form of a yellow oil (0.123 g, 87%). **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.87 (t, *J* = 7.0 Hz, 3H, CH_3), 1.2-1.8 (m, 18H), 1.45 [s, 9H, O-C$(CH_3)_3$], 1.7-1.8 (m, 1H, $H_{5'}$), 2.22 (t, *J* = 7.5 Hz, 2H, $2H_2$), 3.43 (dt, *J* = 9.6, 6.5 Hz, 1H, H_6), 3.49 (dt, *J* = 9.6, 6.5 Hz, 1H, H_6), 3.91 (br s, 1H, $H_{1'}$), 4.22 (br s, 1H, $H_{4'}$), 5.94 (d, *J* = 5.7 Hz, 1H, $H_{3'}$), 5.98 (d, *J* = 5.7 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.6 (t), 24.8 (t), 25.6 (t), 27.7 (t), 28.0 [q, O-C$(CH_3)_3$, 3x], 29.1 (t), 29.7 (t), 29.8 (t), 31.8 (t), 32.8 (t), 35.4 (t, C_2), 54.8 (d, $C_{5'}$), 68.7 (t, C_6), 79.9 [s, O-C$(CH_3)_3$], 80.6 (d, C_4-) 87.8 (d, $C_{1'}$), 133.0 (d, $C_{2'}$), 136.3 (d, C_3-), 173.0 (s, C_1) ppm. **IR** (NaCl) υ 3600-3100 (br, OH), 2926 (m, C-H), 2855 (w, C-H), 1731 (m, C=O), 1625 (w), 1530 (w), 1458 (m), 1366 (m), 1219 (m), 1152 (w), 1092 (d), 773 (s), 669 (w) cm^{-1}. **MS**: *m/z* (%) 369 [$(M + 1)^+$, 0.6], 368 (M^+, 0.3), 351 [$(M - OH)^+$, 7], 312 (7), 295 (12), 197 (10), 182 (23), 181 (39), 180 (25), 179 (21), 131 (21), 115 (100), 97 (26), 83 (12), 81 (19), 69 (21). **HRMS**: calculated for $C_{22}H_{40}O_4$ (M^+): 368.2927; found: 368.2911.

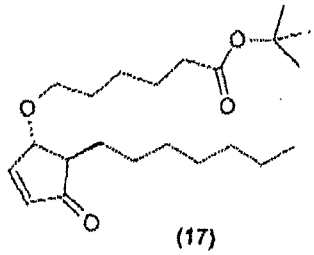
***tert*-Butyl (1'*R**,4'*R**,5'*S**)-6-(5-heptyl-4-hydroxycyclo-**

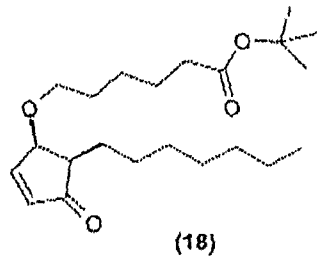
pent-2-enyloxy)hexanoate (8a)



n-Bu_4NF (0.60 ml, 1.0 M in THF, 0.60 mmol) is added to a solution of the compound (**7a**) (0.16 g, 0.33 mmol) in THF (3.0 ml). After stirring for 10 h at 25°C, the reaction mixture is poured into a saturated aqueous solution of $NaHCO_3$, and extracted with ethyl acetate (3 times). The extracted organic phases are combined and then washed with a saturated solution of NaCl and dried (Na_2SO_4), and the solvents are evaporated off. A purification by chromatography (SiO_2, 90/10, v/v, hexane/ethylOAc) is carried out so as to give the alcohol (**8a**) in the form of a yellow oil (0.12 g, 96%). **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 1.2-1.6 (m, 18H), 1.44 [s, 9H, O-C$(CH_3)_3$], 1.8-1.9 (m, 1H, $H_{5'}$), 2.20 (t, *J* = 7.5 Hz, 2H, $2H_2$), 3.33 (dt, *J* = 9.1, 6.4 Hz, 1H, H_6), 3.46 (dt, *J* = 9.1, 6.4 Hz, 1H, H_6), 4.33 (app dt, *J* = 6.4, 1.7 Hz, 1H, $H_{1'}$), 4.60 (br s, 1H, $H_{4'}$), 6.02 (dd, *J* = 5.8, 1.7 Hz, 1H, $H_{3'}$), 6.10 (app dt, *J* = 5.8, 1.7 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.6 (t), 24.8 (t), 25.7 (t), 26.8 (t), 28.0 [q, O-C($\underline{C}H_3)_3$, 3x], 28.5 (t), 29.2 (t), 29.7 (t), 29.9 (t), 31.8 (t), 35.4 (t, C_2), 52.5 (d, $C_{5'}$), 69.3 (t, C_6), 79.9 [s, O-$\underline{C}(CH_3)_3$], 81.4 (d, $C_{4'}$), 82.7 (d, $C_{1'}$), 133.1 (d, $C_{2'}$), 139.3 (d, $C_{3'}$), 173.1 (s, C_1) ppm. **IR** (NaCl): υ 3600-3100 (br, OH), 2928 (s, C-H), 2856 (m, C-H), 1732 (S, C=O), 1457 (w), 1367 (m), 1252 (w), 1152 (s), 1100 (m), 847 (w) cm^{-1}. **MS**: *m/z* (%) 368 ($M^{+\cdot}$ 0.1), 350 (0.1), 311 (4), 294 (3), 213 (2), 181 (35), 158 (7), 131 (16), 115 (100), 97 (21), 81 (11), 69 (19). **HRMS**: calculated for $C_{18}H_{31}O_4$ [M - tBu]$^+$: 311.2222; found: 311.2226.

tert-Butyl (1'S*,5'R*) and (1'R*,5'R*)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate (17) and (18)


(17)


(18)

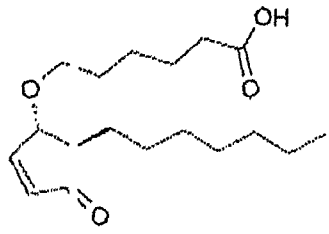
A solution of alcohols **8a/8b** (0.63 g, 1.70 mmol) in CH_2Cl_2 (7 ml) is added to a suspension of PDC (0.77 g, 2.04 mmol) in CH_2Cl_2 (5.0 ml). After stirring for 12 h at 25°C, the reaction mixture is filtered over a silica gel, the solvent is evaporated off and the residue is purified by chromatography (SiO_2, 90:10 hexane/EtOAc), so as to give the ketones (**17**) [**(B)** with n=5; R_2= $-(CH_2)_6-CH_3$; R_3=H and R_4=tBu]; (0.45 g, 73%) and (**18**) [**(A)** with n=5; R_2= $-(CH_2)_6-CH_3$; R_3=H and R_4=tBu] (0.13 g, 21%) in the form of yellow oils.

Data relating to the compound (**17**) (1'S*,5'R*): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, J = 6.7 Hz, 3H, CH_3), 1.2-1.8 (m, 18H), 1.44 [s, 9H, O-C$(CH_3)_3$], 2.22 (t, J = = 7.3 Hz, 2H, $2H_2$), 2.27 (ddd, J = 8.2, 5.1, 2.2 Hz, $H_{5'}$), 3.54 (dt, J = 8.9, 6.5 Hz, 1H, H_6), 3.60 (dt, J = 8.9, 6.5 Hz, 1H, H_6), 4.30 (app td, J = 2.2, 1.1 Hz, 1H, $H_{1'}$), 6.21 (dd, J = 5.8, 1.1 Hz, 1H, $H_{3'}$), 7.57 (dd, J = 5.8, 2.2 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 13.9 (q), 22.5 (t), 24.7 (t), 25.6 (t), 27.0 (t), 28.0 [q, O-C($\underline{C}H_3)_3$, 3x], 29.0 (t), 29.1 (t), 29.5 (t), 29.6 (t), 31.7 (t), 35.3 (t), 52.3 (d, $C_{5'}$), 69.3 (t, C_2), 79.9 [s, O-$\underline{C}(CH_3)_3$], 83.5 (d, C_1-), 134.7 (d, $C_{3'}$), 159.3 (d, $C_{2'}$), 172.9 (s, C_1), 208.2 (s, $C_{4'}$). **IR** (NaCl): υ 2929 (s, C-H), 2857 (m, C-H), 1722 (s, C=O), 1459 (m), 1367 (m), 1319 (w), 1255 (w), 1153 (s), 1113 (m), 848 (w), 773 (m) cm^{-1}. **MS:** *m/z* (%) 366 (M^+, 1), 310 (55), 240 (7), 212 (7), 196 (40), 180 (74), 179 (100), 179 (79), 165 (10), 131 (12), 115 (70), 98 (36), 97 (30), 81 (39). **HRMS:** calculated for $C_{22}H_{38}O_4$ (M^+):

366.2770; found: 366.2761.

Data relating to the compound (**18**) (1'*R**,5'*R**): **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.2-1.6 (m, 18H), 1.44 [s, 9H, O-C(CH_3)$_3$], 2.22 (t, *J* = 7.5 Hz, 2H, $2H_2$), 2.45 (app dt, *J* = 7.6, 6.1 Hz, 1H, H_5-), 3.53 (dt, *J* = 9.0, 6.5 Hz, 1H, H_6), 3.62 (dt, *J* = 9.0, 6.5 Hz, 1H, H_6), 4.53 (ddd, *J* = 6.1, 2.2, 1.3 Hz, 1H, H_1-), 6.21 (dd, *J* = 5.8, 1.3 Hz, 1H, H_3-), 7.61 (dd, *J* = 5.8, 2.2 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.6 (t), 24.8 (t), 25.6 (t), 26.2 (t), 27.6 (t), 28.0 [q, O-C($\underline{C}H_3$)$_3$, 3x], 29.1 (t), 29.6 (t), 29.7 (t), 31.8 (t), 35.4 (t), 49.5 (d, $C_{5'}$), 70.3 (t, C_6), 79.0 (d, $C_{1'}$), 79.9 [s, O-$\underline{C}$(CH_3)$_3$], 134.2 (d, $C_{3'}$), 160.2 (d, $C_{2'}$), 172.9 (s, C_1), 209.2 (s, $C_{4'}$). **IR** (NaCl): υ 2928 (s, C-H), 2857 (s, C-H), 1721 (s, C=O), 1459 (w), 1367 (m), 1220 (m), 1152 (s), 773 (m) cm^{-1}. **MS** *m/z* (%) 366 (M^+, 2), 310 (72), 240 (7), 212 (14), 196 (52), 195 (21), 180 (41), 179 (100), 178 (81), 165 (13), 115 (79), 98 (40), 69 (23). **HRMS**: calculated for $C_{22}H_{38}O_4$ (M^+): 366.2770; found: 366.2767.

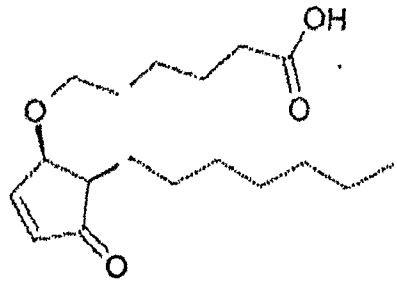
EXAMPLE 9: Synthesis of (1'*S,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoic acid (19)**



TFA (0.9 ml) is added slowly to a solution of the ester (**17**) (49 mg, 0.13 mmol) and the resulting mixture is stirred for 5 min at 23°C. The mixture is poured into water and extracted with ether (3x). The extracted organic phases are combined and then washed with a saturated solution of $NaHCO_3$ and of NaCl and dried (Na_2SO_4), and the solvent is evaporated off. The residue is purified by chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH), so as to give 41 mg (99%) of the compound (**19**) [**(B)**

with n=5, R_2= -$(CH_2)_6$-CH_3; R_3=H and R_4=H] in the form of a yellow oil. **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3H, CH_3), 1.0-1.8 (m, 18H), 2.28 (ddd, *J* = 8.0, 4.9, 2.2 Hz, 1H, $H_{5'}$), 2.37 (t, *J* = 7.4 Hz, $2H_2$), 3.54 (dt, *J* = 9.0, 6.3 Hz, 1H, H_6), 3.61 (dt, *J* = 9.0, 6.3 Hz, 1H, H_6), 4.31 (app td, *J* = 2.2, 1.2 Hz, 1H, $H_{1'}$), 6.21 (dd, *J* = 5.8, 1.2 Hz, 1H, $H_{3'}$), 7.57 (dd, *J* = 5.8, 2.2 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.0 (q), 22.5 (t), 24.4 (t), 25.6 (t), 27.0 (t), 29.0 (t), 29.1 (t), 29.5 (t, 2x), 31.7 (t), 33.9 (t), 52.3 (d, $C_{5'}$), 69.2 (t, C_6), 83.6 (d, $C_{1'}$), 134.7 (d, $C_{3'}$), 159.4 (d, C_2-), 179.4 (s, C_1), 208.4 (s, $C_{4'}$). **IR** (NaCl): υ 3000-2700 (br, OH), 2926 (s, C-H), 2857 (s, C-H), 1714 (s, C=O), 1457 (w), 1351 (w), 1220 (m), 1113 (m), 773 (s) cm^{-1}. **MS**: *m/z* (%) 310 (M^+, 21), 240 (7), 212 (5), 196 (60), 179 (28), 178 (72), 165 (18), 115 (79), 98 (100), 97 (57), 82 (28), 81 (36), 69 (87). **HRMS**: calculated for $C_{18}H_{30}O_4$ (M^+): 310.2144; found: 310.2143.

EXAMPLE 10: Synthesis of (1'*R,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoic acid (20)**



According to the method of preparation described for the compound (**19**), the ester (**18**) (30 mg, 0.08 mmol) is treated with TFA (0.5 ml) so as to give, after purification by chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH), 21 mg (84%) of the compound (**20**) [**(A)** with n=5, R_2= -$(CH_2)_6$-CH_3; R_3=H and R_4=H] in the form of a yellow oil. **^{1}H NMR** ($CDCl_3$, 400.13 MHz) δ 0.88 (t, *J* = 6.3 Hz, 3H, CH_3), 1.2-1.7 (m, 18H), 2.37 (t, *J* = 7.3 Hz, 2H, $2H_2$), 2.4-2.5 (m, 1H, $H_{5'}$), 3.53 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 3.63 (dt, *J* = 8.8, 6.4 Hz, 1H, H_6), 4.54 (ddd, *J* = 5.8, 2.1, 1.0 Hz, 1H, $H_{1'}$), 6.21 (app dt, *J* = 5.8, 1.0

Hz, 1H, $H_{3'}$), 7.61 (dd, J = 5.8, 2.1 Hz, 1H, $H_{2'}$) ppm. **^{13}C NMR** ($CDCl_3$, 100.62 MHz) δ 14.1 (q), 22.6 (t), 24.4 (t), 25.7 (t), 26.2 (t), 27.7 (t), 29.1 (t), 29.6 (t), 29.8 (t), 31.8 (t), 33.8 (t), 43.6 (d, $C_{5'}$), 70.3 (t, C_6), 79.1 (d, $C_{1'}$), 134.3 (d, $C_{3'}$), 169.3 (d, C_2-), 179.2 (s, C_1), 209.4 (s, $C_{4'}$). **IR** (NaCl): υ 3500-2700 (broad, OH), 2928 (s, C-H), 2857 (s, C-H), 1713 (s, C=O), 1460 (w), 1350 (w), 1110 (m) cm^{-1}. **MS**: *m/z* (%) 310 (M^+, 18), 196 (32), 179 (22), 178 (63), 165 (18), 121 (15), 115 (69), 108 (16), 107 (16), 99 (12), 98 (100), 97 (55), 95 (32), 94 (21), 84 (15), 83 (27), 82 (39), 81 (41), 79 (23), 73 (25), 69 (96), 67 (29), 66 (18). **HRMS**: calculated for $C_{18}H_{30}O_4$ (M^+): 310.2144; found: 310.2137.

EXAMPLE 11: CROSSED CURVE PPAR TRANSACTIVATION TEST

The activation of receptors with an agonist (activator) in HeLN cells leads to the expression of a reporter gene, luciferase, which, in the presence of a substrate, generates light. The modulation of the receptors is measured by quantifying the luminescence produced after incubation of the cells in the presence of a reference agonist. The ligands will displace the agonist from its site. The activity is measured by quantifying the light produced. This measurement makes it possible to determine the modulating activity of the compounds according to the invention by determining the constant which represents the affinity of the molecule for the receptor. This value, which can fluctuate according to the basal activity and expression of the receptor, is called the apparent Kd (KdApp in nM).

To determine this constant, "crossed curves" of the product to be tested, against a reference agonist, are realized in a 96-well plate: 10 concentrations of the product to be tested plus a concentration 0 are arranged in rows, and 7 concentrations of the agonist plus a concentration 0 are arranged in columns. This represents 88 points of measurement for 1 product and 1 receptor. The remaining 8 wells are used for

repeatability controls.

In each well, the cells are in contact with a concentration of the product to be tested and a concentration of the reference agonist, 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenylsulphanyl)-2-methylpropionic acid for PPARα, {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulphanyl]phenoxy}acetic acid for PPARδ and 5-{4-[2-methylpyridin-2-ylamino)ethoxy]benzyl}-thiazolidine-2,4-dione for PPARγ. Measurements are also carried out for the total agonist controls with the same products.

The HeLN cell lines used are stable transfectants containing the plasmids ERE-βGlob-Luc-SV-Neo (reporter gene) and PPAR (α, δ, γ) Gal-hPPAR. These cells are seeded into 96-well plates in a proportion of 10 000 cells per well, in 100 µl of DMEM medium without phenol red and supplemented with 10% of defatted calf serum. The plates are then incubated at 37°C, 7% CO_2, for 16 hours.

The various dilutions of the test compounds and of the reference ligand are added in a proportion of 5 µl per well. The plates are then incubated for 18 hours at 37°C, 7% CO_2.

The culture medium is removed by inverting the plates and 100 µl of a 1:1 PBS/luciferin mixture are added to each well. After 5 minutes, the plates are read by means of the luminescence reader.

These crossed curves make it possible to determine the AC50 values (concentration at which 50% activation is observed) of the reference ligand at various concentrations of product to be tested. These AC50 values are used to calculate the Schild regression by plotting a straight line corresponding to the Schild

equation ("*quantitation in receptor pharmacology*" *Terry P. Kenakin, Receptors and Channels,* **2001,** 7, 371-385) which results in the Kd app values being obtained (in nM).

Transactivation results:

	PPAR alpha	PPARs delta	PPAR gamma
Compounds	Kd app (nM)	Kd app (in nM)	Kd app (in nM)
Reference 1: 2-(4-{2-[3-(2,4-Difluorophenyl)-1-heptylureido]ethyl}phenylsulphanyl)-2-methyl-propionic acid	200	n.a.	n.a.
Reference 2: {2-Methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulphanyl]phenoxy}-acetic acid	n.a.	10	n.a.
Reference 3: 5-{4-[2-(Methylpyridin-2-ylamino)-ethoxy]benzyl}thiazolidine-2,4-dione	n.a.	n.a.	30
Compound **Example 3**	1000	500	30
Compound **Example 7**	500	2000	8000
Compound **Example 6**	500	n.a.	4000

n.a. signifies not active.

These results show the affinity of the compounds for PPAR receptors, and more particularly for the PPARα or PPARδ subtypes.

EXAMPLES 12 : EXAMPLES OF COMPOSITIONS

Various concrete formulations based on the compounds according to the invention are given hereinafter.

A - ORAL ADMINISTRATION

(a) 0.2 g tablet
- Compound Example 4 0.001 g
- Starch 0.114 g
- Dicalcium phosphate 0.020 g
- Silica 0.020 g
- Lactose 0.030 g
- Talc 0.010 g
- Magnesium stearate 0.005 g

(b) Oral suspension in 5 ml ampoules
- Compound Example 3 0.001 g
- Glycerol 0.500 g
- 70% sorbitol 0.500 g
- Sodium saccharinate 0.010 g
- Methyl para-hydroxybenzoate 0.040 g
- Flavouring qs
- Purified water qs for 5 ml

B - TOPICAL ADMINISTRATION

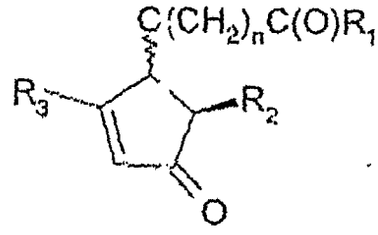
(a) Ointment
- Compound Example 5 0.300 g
- White petroleum jelly codex qs for 100 g

(b) Non-ionic water-in-oil cream
- Compound Example 9 0.100 g
- Mixture of emulsive lanolin alcohols, of waxes and of oils ("Eucerine anhydre" [anhydrous eucerin] sold by BDF) 39.900 g
- Methyl para-hydroxybenzoate 0.075 g
- Propyl para-hydroxybenzoate 0.075 g
- Sterile demineralized water qs for 100 g

(c) Lotion
- Compound Example 3 0.100 g
- Polyethylene glycol (PEG 400) 69.900 g
- 95% ethanol 30.000 g

CLAIMS

1. Compounds of formula (I):



(I)

in which:

- R_1 represents an $-OR_4$ or $-NR_4R_5$ group,

R_4 and R_5 having the meaning as defined below;

- R_2 represents a group chosen from the following optionally substituted groups: alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocycloalkyl, heteroaralkyl and heterocycloalkyl-alkyl;

- R_3 represents a hydrogen atom, a halogen atom or a group chosen from the following optionally substituted groups: alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocycloalkyl, heteroaralkyl and heterocycloalkylalkyl;

R_4 and R_5, which may be identical or different, represent a hydrogen atom or a group chosen from the following optionally substituted groups: alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, alkenyl, alkynyl, aralkyl, cycloalkylalkyl, heteroaralkyl and heterocycloalkylalkyl;

- n is an integer included in the range of from 1 to 6;

in the form of pure optical and/or geometric isomers or as a mixture, in any proportions, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof.

2. Compounds according to Claim 1, characterized in that:

- R_1 represents an $-OR_4$ or $-NR_4R_5$ group, with R_4 and R_5, which may be identical or different, and which represent a hydrogen atom or an alkyl group preferably containing from 1 to 5 carbon atoms,
- R_2 represents an alkyl group preferably containing from 1 to 10 carbon atoms,
- R_3 represents a hydrogen atom, a halogen atom or an alkynyl group preferably containing from 2 to 10 carbon atoms,
- n is equal to 4 or 5.

3. Compounds according to Claim 1 or 2, characterized in that R_1 represents an -OH group.

4. Compounds according to one of Claims 1 to 3, characterized in that R_2 represents a heptyl group.

5. Compounds according to one of Claims 1 to 4, characterized in that R_3 represents hydrogen, an iodine atom or an oct-1-yn-1-yl radical.

6. Compounds according to one of Claims 1 to 5, characterized in that n is equal to 4 or 5.

7. Compounds according to Claim 1 in the form of a pure isomer, or of a mixture, in any proportions, of the (1'*R**,5'R*) and (1'*S**,5'*R**) diastereoisomers, and also the salts, pharmaceutically acceptable solvates and/or hydrates thereof, from one of the following compounds:

tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoic acid

tert-butyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

tert-butyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid

(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid

tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate

tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)hexanoate

(1'*S**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)-hexanoic acid

(1'*R**,5'*R**)-6-(5-heptyl-4-oxocyclopent-2-enyloxy)-hexanoic acid

isopropyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

isopropyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

ethyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

ethyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

ethyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

ethyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanamide

(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide

(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide

(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylhexanamide

(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide

(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-

oxocyclopent-2-enyloxy]-*N*-propylhexanamide
tert-butyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
tert-butyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoic acid (14)
tert-butyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
tert-butyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoic acid
isopropyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
isopropyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
isopropyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
isopropyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
ethyl (1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
ethyl (1'*S**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanoate
ethyl (1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
ethyl (1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanoate
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)pentanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanamide
(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]pentanamide
(1'*R**,5'*R**)-6-(5-heptyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylpentanamide
(1'*R**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylpentanamide

(1'*S**,5'*R**)-6-[5-heptyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylpentanamide

tert-butyl (1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

tert-butyl (1'*S**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

(1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoic acid

tert-butyl (1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

tert-butyl (1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

(1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoic acid

isopropyl (1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*S**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

isopropyl (1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

isopropyl (1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

ethyl (1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

ethyl (1'*S**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanoate

ethyl (1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

ethyl (1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanoate

(1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)hexanamide

(1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide

(1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]hexanamide

(1'*R**,5'*R**)-6-(5-hexyl-2-iodo-4-oxocyclopent-2-enyloxy)-*N*-propylhexanamide

(1'*R**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-

oxocyclopent-2-enyloxy]-*N*-propylhexanamide
(1'*S**,5'*R**)-6-[5-hexyl-2-(oct-1-yn-1-yl)-4-oxocyclopent-2-enyloxy]-*N*-propylhexanamide

8. Compounds according to one of the preceding claims, as medicaments.

9. Pharmaceutical composition comprising at least one compound of formula (I) according to one of Claims 1 to 7, in combination with at least one pharmaceutically acceptable excipient.

10. Composition according to Claim 9, characterized in that the concentration of compound(s) of formula (I) is between 0.001% and 10% by weight relative to the total weight of the composition.

11. Composition according to Claim 10, characterized in that the concentration of compound(s) of formula (I) is between 0.01% and 1% by weight relative to the total weight of the composition.

12. Cosmetic composition, characterized in that it comprises, in a physiologically acceptable medium, at least one compound of formula (I) according to any one of Claims 1 to 7.

13. Composition according to Claim 12, characterized in that the concentration of compound(s) of formula (I) is between 0.001% and 3% by weight relative to the total weight of the composition.

14. Cosmetic use of a composition as defined in either one of claims 12 or 13, for body hygiene or hair care.

15. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a composition for use in regulating and/or restoring the metabolism of lipids in the skin.

16. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a composition for use in the treatment:

- of dermatological conditions linked to a keratinization disorder related to differentiation and proliferation, in particular common acne, comedone-type acne, polymorphic acne, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acne such as solar acne, acne medicamentosa or occupational acne;
- of ichthyosis, ichthyosiform states, Darrier's disease, palmoplantar keratoderma, leucoplasia and leucoplasiform states, cutaneous or mucosal (buccal) lichen;
- of dermatological conditions with an inflammatory immunoallergic component, with or without cell proliferation disorder, in particular cutaneous, mucosal or ungual psoriasis, psoriatic rheumatism, or cutaneous atopy, such as eczema, respiratory atopy or gingival hypertrophy;
- of benign or malignant dermal or epidermal proliferations of viral or non-viral origin, in particular verruca vulgaris, verruca plana and epidermodysplasia verruciformis, oral or florid papillomatoses, T lymphoma;
- of proliferations which may be induced by ultraviolet radiation, in particular baso- and spinocellular epitheliomas;
- of precancerous skin lesions, in particular keratoacanthomas;
- of immune dermatoses, in particular lupus erythematosus;
- of bullous immune diseases;
- of collagen diseases, in particular scleroderma;
- of dermatological or general conditions with an immunological component;
- of skin disorders due to exposure to UV radiation, photoinduced or chronological skin ageing, or actinic keratoses and pigmentations, or any pathologies

associated with chronological or actinic ageing, in particular xerosis;
- of sebaceous function disorders, in particular acne hyperseborrhoea, simple seborrhoea, or seborrhoeic dermatitis;
- of cicatrization disorders, or stretch marks;
- of pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo;
- of lipid metabolism conditions, such as obesity, hyperlipidemia, non-insulin-dependent diabetes or syndrome X;
- of inflammatory conditions such as arthritis;
- of cancerous or precancerous states;
- of alopecia of various origins, in particular alopecia due to chemotherapy or to radiation;
- of immune system disorders, such as asthma, diabetes mellitus type I, multiple sclerosis, or other selective dysfunctions of the immune system, or
- of conditions of the cardiovascular system such as arteriosclerosis or hypertension.

17. Process for preparing the compounds of formula (I) according to any one of Claims 1 to 7, comprising the following stages:

a) stage consisting of addition between furfural and the compound $BrMgR_2$, in order to obtain the corresponding 2-furylcarbinol;
b) rearrangement of the carbocation of hydroxypentadienyl obtained from the 2-furylcarbinol obtained in a) according to a Nazarov-type electrocyclic reaction, in order to obtain the corresponding hydroxycyclopentenone;
c) protection of the alcohol function of the hydroxycyclopentenone obtained in b);
e) reduction of the carbonyl group of the cyclopentenone obtained, in order to obtain a mixture of the various corresponding diastereoisomeric alcohols;
f) stage consisting of O-alkylation of the

diastereoisomeric alcohols obtained in e), with a halide of formula $X-(CH_2)_n-C(O)OR_4$, X being an iodine atom, n and R_4 being as defined for the compounds of formula (I), R_4 being other than a hydrogen atom;

g) deprotection of the alcohol function of the compound obtained in f);

h) oxidation of the alcohol function deprotected in g), in order to obtain the corresponding ketone.

18. Process according to Claim 17, characterized in that it comprises, between stages c) and e), a stage d) consisting of α-addition of a halide to the compound obtained in c), in order to obtain the corresponding α-halocyclopentenone.

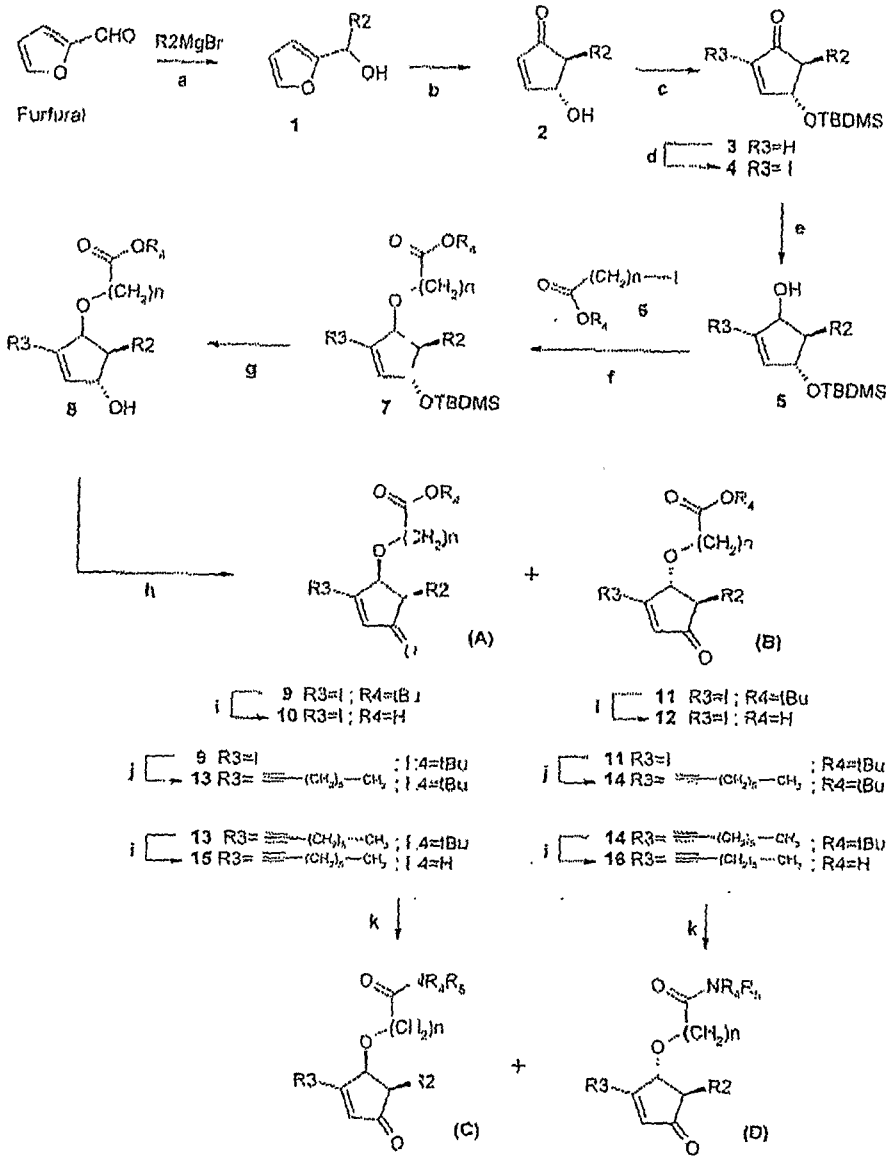
19. Process according to Claim 17 or 18, characterized in that it comprises a stage i) consisting of hydrolysis of the ketone obtained in h).

20. Process according to Claim 17 or 18, characterized in that it comprises, after stage h), a stage j) consisting of Stille coupling with a tin derivative, or Suzuki coupling with a boron derivative, in order to obtain the corresponding compound of formula (I).

21. Process according to Claim 20, characterized in that it comprises a stage i) consisting of hydrolysis of the compound obtained in j).

22. Process according to Claim 19 or 21, characterized in that it comprises, after stage i), a stage consisting of amidation by coupling of the compound obtained subsequent to the hydrolysis, with an amine HNR_4R_5.

SCHEME 1


CHO
R2MgBr
a
Furfural
1
b
2
c
OTBDMS
d
3 R3=H
4 R3= I
e
5
f
6
g
7
8
OH
h
(A)
(B)
i
9 R3=I ; R4=tBu
10 R3=I ; R4=H
11 R3=I ; R4=tBu
12 R3=I ; R4=H
j
13
14
15
16
k