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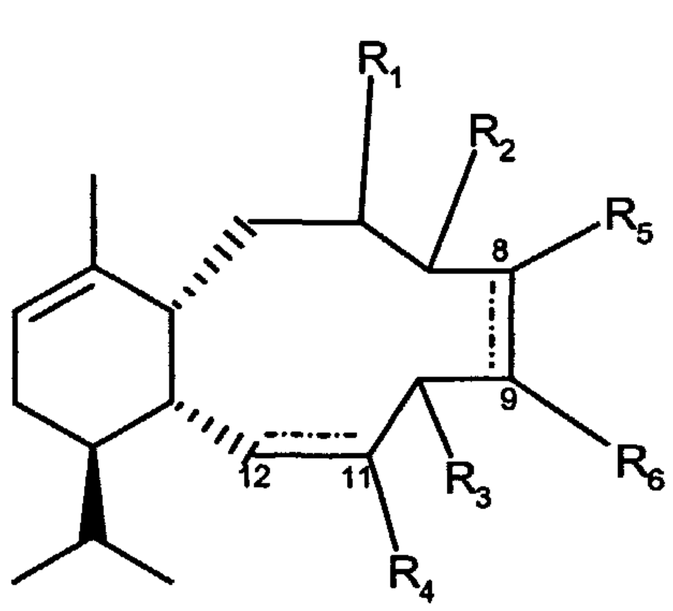
(54) Titre : DERIVES DE SARCODICTYNE A STRUCTURE CHIMIQUE SIMPLIFIEE, UTILISES COMME AGENTS ANTITUMORAUX

(54) Title: SIMPLIFIED SARCODICTYN DERIVATIVES AS ANTI-TUMOR AGENTS



(I)

(57) Abrégé/Abstract:
There are provided sarcodictyin derivatives or pharmaceutically acceptable salts thereof, which are characterized by a simplified chemical structure and have anti-tumor activity. A process for their preparation, the pharmaceutical compositions containing them, and their use in the prevention, control and treatment of cancer are also provided.

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(54) **Title:** SIMPLIFIED SARCODICTYN DERIVATIVES AS ANTI-TUMOR AGENTS

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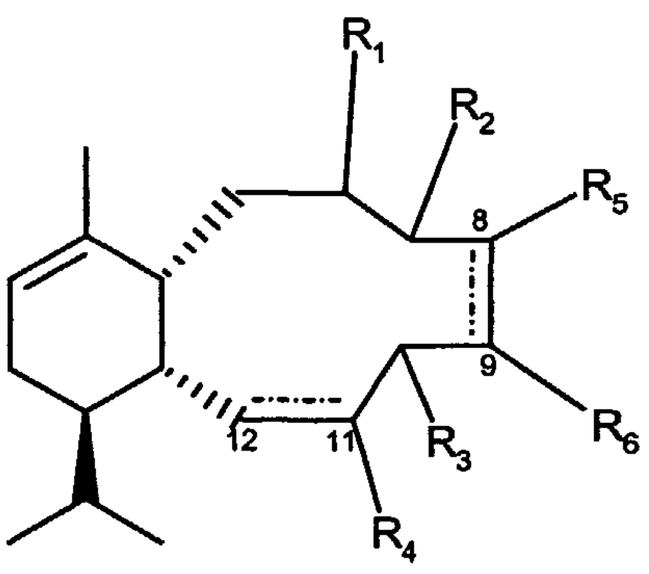


(I)

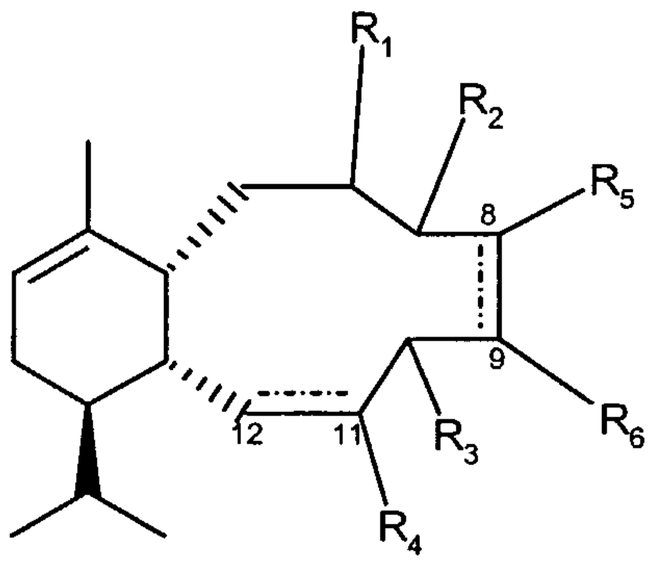
SIMPLIFIED SARCODICTYN DERIVATIVES AS ANTI-TUMOR AGENTS

The present invention relates to new anti-tumor agents, to a process for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in the prevention, control and treatment of cancer. Sarcodictyins A and B were isolated in 1987 by Pietra *et al.* from the Mediterranean stoloniferan coral *Sarcodictyon roseum*, while their anti-tumor activity was recognised about a decade later, and their paclitaxel-like mechanism of action uncovered (Ciomei, M. et al. *Proc. Amer. Ass. Canc. Res.* **1997**, *38*, 5 and WO 96 36 335-A1)

In the meantime, the diterpene glycoside eleutherobin was reported by Fenical *et al.* from an *Eleutherobia* species of australian soft coral, accompanied by disclosure of its potent cytotoxicity. Two years later, in 1997, it was shown that eleutherobin, similarly to sarcodictyins, acted by mitotic arrest through induced tubulin polymerization.

Now, there is a strong need for more simplified molecules, which nevertheless maintain the useful properties referred to above characterizing the natural substances.

The present invention relates to a new class of simplified sarcodictyins. In particular, the present invention provides a compound which is a sarcodictyin derivative of formula (I)

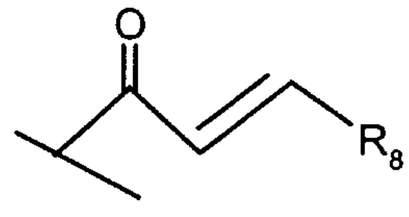


(I)

wherein:

----- at positions 8-9 and 11-12 independently represents a single or double bond,

$-R_1$ represents oxygen (=O), or a residue $-OR_7$, wherein R_7 represents hydrogen, linear or branched C_1-C_7 alkanoyl, benzoyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or a residue of the formula



wherein R_8 is an optionally substituted aryl or heterocyclyl;

one of -R_2 and -R_3 represents hydrogen and the other one is chosen from the group consisting of hydrogen, oxygen (=O) and a residue -OR_9, wherein R_9 represents hydrogen, C_1-C_6 alkanoyl or benzoyl;

when ----- at position 11-12 represents a single bond, then -R_4 represents oxygen (=O), methylene (=CH_2), =$CHCOOR_{10}$, wherein R_{10} represents C_1-C_{10} alkyl or optionally substituted aryl; =$CH(OCH_3)$, or a residue of formula

-OR_9, wherein R_9 is as defined above;

-CH_2OR_{11} wherein R_{11} represents hydrogen or a sugar residue,

-COR_{12} wherein R_{12} represents hydrogen, -OH or -OR_{10}, wherein R_{10} is as defined above; or

when ----- at position 11-12 represents a double bond, then -R_4 represents a residue of formula -CH_2OR_{11} or -COR_{12} as defined above;

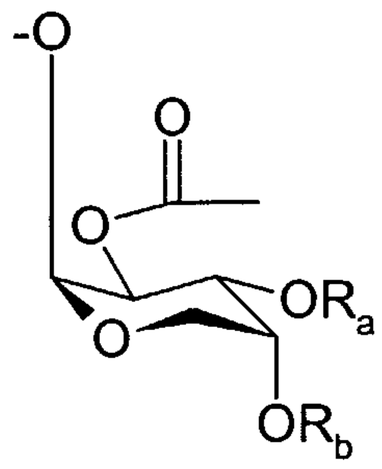
- R_5 and -R_6 are both hydrogen or, when ----- at position 8-9 represents a single bond, taken together with the carbon atoms to which they are attached form a cyclopropane ring; or a pharmaceutically acceptable salt thereof.

As used herein the term "C_1-C_{10} alkyl" refers to a straight or branched chain alkyl moiety having from 1 to 10 carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl and n-octyl. The term "C_2-C_{10} alkenyl" as used herein refers to a straight or branched chain alkenyl moiety having from 2 to 10 carbon atoms and having in addition one double bond of either E or Z stereochemistry where applicable. Examples of alkenyl groups include: vinyl, allyl, metallyl, butenyl and crotyl. The term "aryl" as used herein refers to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms, such as phenyl, naphthyl, indanyl; furthermore, "aryl" as used herein may refer to a diphenyl group (-C_6H_4-C_6H_5). The term "C_1-C_7 alkanoyl" refers to acyl residues such as formyl, acetyl, pivaloyl (PIV), and pentanoyl groups.

The term "heterocyclyl" as used herein refers to a 3- to 7-membered, substituted or unsubstituted, saturated or unsaturated heterocyclyl ring, containing at least one heteroatom selected from O, S and N, any ring carbon may be oxidized as a carbonyl, and wherein said heterocyclyl ring may be optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclyl ring, or to a C_3 -C_7 cycloalkyl ring, or to a benzene or naphthalene ring. Examples of heterocyclyl groups are pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl,

tetrahydrothienyl, furyl, tetrahydrofuryl, aziridinyl, oxiranyl, azetidinyl, succinimido, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyridazinyl, hexahydropyridazinyl, pyrimidinyl, pyranyl, tetrahydropyranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isobenzofuranyl, benzofuranyl, benzimidazolyl, indazolyl, chromenyl, indolyl, oxindolyl, phthalimido, 1-oxo-2-isoindolyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl, indolizinyl, isoindolyl, 2-oxoisoindolyl, 1,2-(methylenedioxy)phenyl, quinuclidinyl, hydantoinyl, saccarinyl, cinnolinyl, purinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl and azepinyl.

Most preferred heterocyclyl groups are N-methyl-imidazolyl, 2-methyl-thiazolyl, 2-methyl-oxazolyl and pyridyl group. Preferably, when OR_{11} is a sugar residue, it has the formula



wherein R_a and R_b independently represent hydrogen, a hydroxy protecting group, or C_1-C_6 alkanoyl.

Substituents which may be present in the aryl or heterocyclyl groups in any of the above definitions of R_1-R_{10} include the following:

- halo (i.e., fluoro, bromo, chloro or iodo);
- hydroxy;
- nitro;
- azido;
- mercapto (i.e., -SH), and acetyl or phenylacetyl esters thereof (i.e., $-SCOCH_3$ and $-SCOCH_2C_6H_5$);
- amino (i.e., $-NH_2$ or $-NHR^I$ or $-NR^IR^{II}$, wherein R^I and R^{II}, which are the same or different, are straight or branched C_1-C_6 alkyl, phenyl, biphenyl (i.e., $-C_6H_4-C_6H_5$), or benzyl groups, optionally substituted by hydroxy, methoxy, methyl, amino, methylamino, dimethylamino, chloro or fluoro; or R^I and R^{II} taken together with the nitrogen atom to which they are attached form a heterocyclic ring such as morpholino, pyrrolidino, piperidino, pyperazino or N-methylpyperazino;
- guanidino, i.e., $-NHC(=NH)NH_2$;

- formyl (i.e. -CHO);

- cyano;

- carboxy (i.e. -COOH), or esters thereof (i.e., -$COOR^I$), or amides thereof (i.e., -$CONH_2$, -$CONHR^I$ or -$CONHR^IR^{II}$), wherein R^I and R^{II} are as defined above, and including morpholino-amides, pyrrolidino-amides, and carboxymethylamides -$CONHCH_2COOH$;

- sulfo (i.e., -SO_3H);

- acyl, i.e., -$C(O)R^I$, wherein R^I is as defined above, including monofluoroacetyl, difluoroacetyl, trifluoroacetyl;

- carbamoyloxy (i.e., -$OCONH_2$) and N-methylcarbamoyloxy;

- acyloxy, i.e., -$OC(O)R^I$ wherein R^I is as defined above, or formyloxy;

- acylamino, i.e., -$NHC(O)R^I$, or -$NHC(O)OR^I$, wherein R^I is as defined above or is a group -$(CH_2)_tCOOH$ where t is 1, 2 or 3;

- ureido, i.e., -$NH(CO)NH_2$, -$NH(CO)NHR^I$, -$NH(CO)NR^IR^{II}$, wherein R^I and R^{II} are as defined above, including -NH(CO)-(4-morpholino), -NH(CO)-(1-pyrrolidino), -NH(CO)-(1-piperazino), -NH(CO)-(4-methyl-1-piperazino);

- sulfonamido, i.e., -$NHSO_2R^I$ wherein R^I is as defined above;

- a group -$(CH_2)_tCOOH$, and esters and amides thereof, i.e., -$(CH_2)_tCOOR^I$ and -$(CH_2)_tCONH_2$, -$(CH_2)_tCONHR^I$, -$(CH_2)_tCONR^IR^{II}$, wherein t, R^I and R^{II} are as defined above;

- a group -$NH(SO_2)NH_2$, -$NH(SO_2)NHR^I$, -$NH(SO_2)NR^IR^{II}$, wherein R^I and R^{II} are as defined above, including -$NH(SO_2)$-(4-morpholino), -$NH(SO_2)$-(1-pyrrolidino), -$NH(SO_2)$-(1-piperazino), -$NH(SO_2)$-(4-methyl-1-piperazino);

- a group -$OC(O)OR^I$, wherein R^I is as defined above;

- a group -OR^I, wherein R^I is as defined above, including -OCH_2COOH;

- a group -SR^I, wherein R^I is as defined above, including -SCH_2COOH;

- a group -$S(O)R^I$, wherein R^I is as defined above;

- a group -$S(O_2)R^I$, wherein R^I is as defined above;

- a group -SO_2NH_2, -SO_2NHR^I, or -$SO_2NR^IR^{II}$, wherein R^I and R^{II} are as defined above;

- C_1 -C_6 alkyl or C_2 -C_6 alkenyl;

- C_3 -C_7 cycloalkyl;

- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl, cyanomethyl, carboxymethyl, sulfomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl,

methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl and guanidinomethyl.

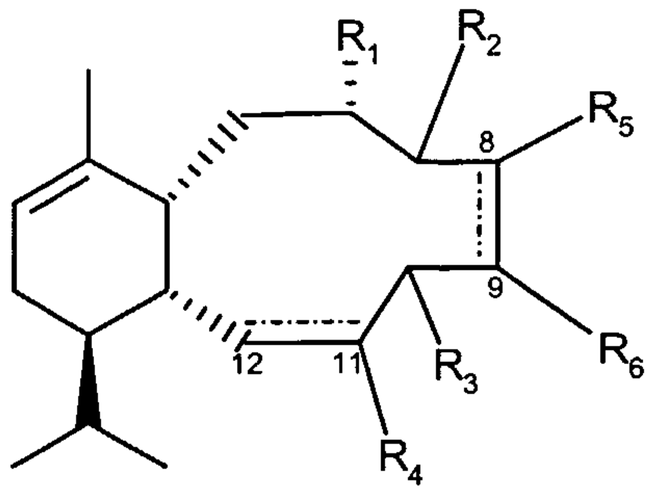
When present, carboxy, hydroxy, mercapto and amino groups may be either free or in a protected form. Protected forms of said groups are any of those generally known in the art. Preferably, carboxy groups are protected as esters thereof, in particular methyl, ethyl, tert-butyl, benzyl, and 4-nitrobenzyl esters. Preferably, hydroxy groups are protected as silyl-ethers, ethers or esters thereof, in particular trimethyl silyl, tert-butyldiphenyl silyl, triethyl silyl, triisopropyl silyl or tert-butyldimethylsilyl ethers, methoxymethyl ethers, tetrahydropyranyl ethers, benzyl ethers, acetates or benzoates. Preferably, mercapto groups are protected as thioethers or thioesters, in particular tert-butyl thioethers, thioacetates or thiobenzoates. Preferably, amino groups are protected as carbamates, e.g. tert-butoxycarbonyl derivatives, or as amides, e.g. acetamides and benzamides.

As stated above, the present invention provides the salts of those compounds of formula (I) that have salt-forming groups, especially the salts of the compounds having a carboxylic group or the salts of the compounds having a basic group, especially an amino. The salts are especially physiologically tolerable salts, for example alkali metal and alkaline earth metal salts (e.g. sodium, potassium, lithium, calcium and magnesium salts), ammonium salts and salts with an appropriate organic amine or amino acid (e.g. arginine, procaine salts), and the addition salts formed with suitable inorganic acids (e.g. hydrochlorides, hydrobromides, sulfates, phosphates) or carboxylic and sulfonic organic acids (e.g. acetates, trifluoroacetates, citrates, succinates, malonates, lactates, tartrates, fumarates, maleates, methanesulfonates, *p*-toluenesulfonates).

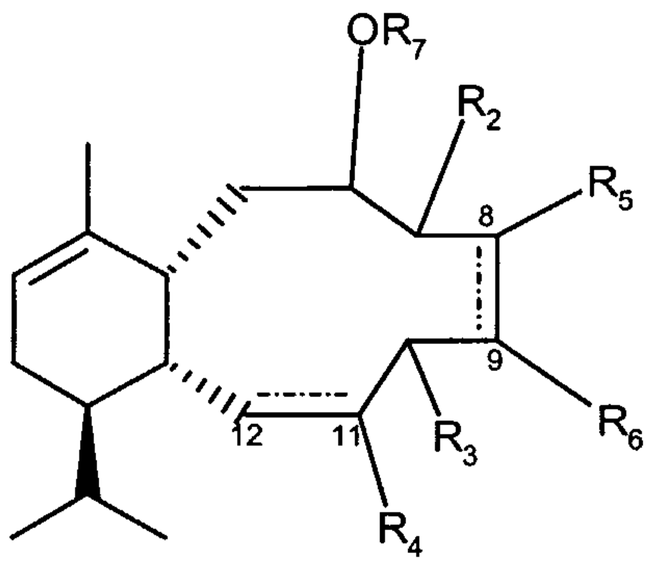
Furthermore, hydrates, solvates of compounds of formula (I), and physiologically hydrolyzable derivatives (i.e., prodrugs) of compounds of formula (I) are included within the scope of the present invention.

It is to be noted that the R_1, R_2, R_3 and R_4 substituents may be above or under the plane, so that the present invention encompasses all the possible stereoisomers (e.g. diastereoisomers, epimers, geometrical isomers) of the compounds of formula (I), as well as their racemic or optically active mixtures related to these substituents.

In the preferred configuration, the substituent R_1 is under the plane:



A preferred sarcodictyin derivative of the present invention has the following formula (Ia)

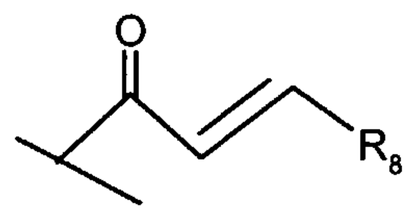


(Ia)

wherein:

----- at positions 8-9 and 11-12 independently represents a single or double bond,

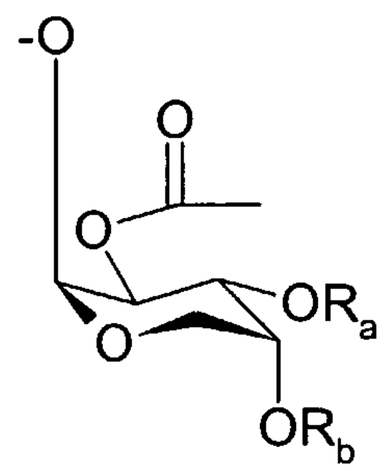
R_7 represents a residue of the formula



wherein R_8 is N-methyl imidazolyl, phenyl, methyl-thiazolyl, methyl-oxazolyl or pyridyl group;

one of -R_2 and -R_3 represents hydrogen and the other one is hydrogen or oxygen (=O), hydroxy, acetoxy ;

when ----- at position 11-12 represents a single bond, then -R_4 represents oxygen (=O), methylene (=CH_2), =$CHCOOR_{10}$, wherein R_{10} represents methyl or ethyl, =$CH(OCH_3)$, –CHO; hydroxy, acetoxy, pivaloyloxy group or -CH_2OR_{11} wherein R_{11} represents hydrogen or a sugar residue having the formula



wherein R_a and R_b independently represent hydrogen, a hydroxy protecting group, or C_1-C_6 alkanoyl,

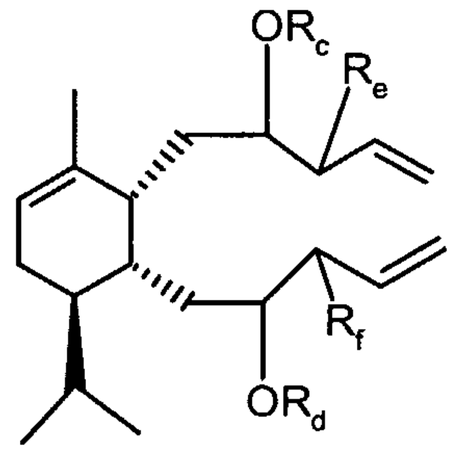
or

when ----- at position 11-12 represents a double bond, then -R_4 represents a residue of formula $-CO_2C_2H_5$; and

- R_5 and -R_6 are both hydrogen atoms or, when ----- at position 8-9 represents a single bond, taken together with the carbon atoms to which they are attached form a cyclopropane ring.

The present invention also provides a process for preparing a compound of the invention as defined above, which process comprises:

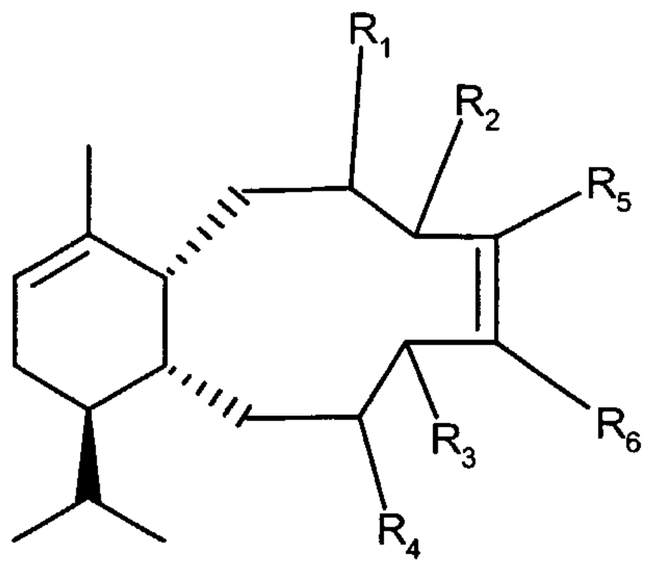
cyclizing a compound of formula II



II

wherein R_c represents hydrogen, a silyl protecting group, C_1-C_6 alkanoyl or benzoyl or , taken together with R_e, forms an acetonide ring; R_d represents hydrogen, C_1-C_6 alkanoyl, or benzoyl, or , taken together with R_f, forms an acetonide ring; either R_e represents H and R_f either represents OH or is linked to the adjacent OR_d substituent as defined above, or R_f represents H and R_e either represents OH or is linked to the adjacent OR_c substituent as defined above;

and, if desired, converting the resulting sarcodictyin derivative of formula I',

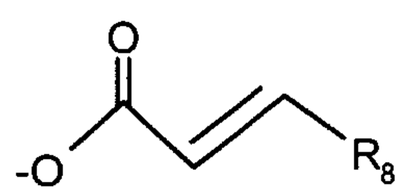


I'

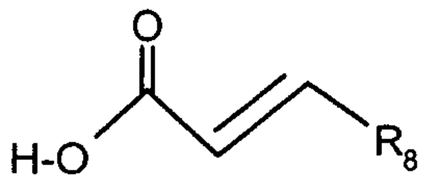
wherein R_1 is OR_c, R_2 is R_e, R_3 is R_f, R_4 is OR_d, in which R_c, R_d, R_e and R_f are as defined above and R_5 and R_6 are hydrogen atoms, into another sarcodicytin derivative of formula I as defined above; and/or if desired, converting a sarcodictyin derivative of formula I' or I into a pharmaceutically acceptable salt therof; and/or, if desired converting a pharmaceutically acceptable salt of a sarcodictyin derivative of formula I or I' into the corresponding free compound.

Preferably, R_c represents a silyl protecting group, more preferably a t-butyldiphenylsilyl group. The cyclization to give the compound of formula I' as single Z isomer can be performed through the Ring Closing Metathesis (RCM) reaction. In particular, the RCM reaction is carried out in the presence of an appropriate catalyst, more preferably a Nolan and Grubb's catalyst, described for example in J.Am.Chem.Soc., 1999, 121, 2674 and in Org. Lett., 1999, 1, 953. The conversion of a compound of formula I' or I into another different final compound of formula I may be carried out in several ways, depending on the meanings of the substituents and the presence of the unsaturated bonds in the ring. Such conversions follow conventional procedures which are known in the art.

For example, a compound of formula I wherein $-R_1$ represents a residue of the formula



wherein R_8 is as defined above, can be obtained by condensing a corresponding compound of the formula I or I' wherein $-R_1$ represents hydroxy group with an activated form of the appropriate derivative of formula



wherein R_8 is as above defined.

A compound of formula I wherein $-R_2$, $-R_3$ or $-R_4$ represents an oxygen atom =O can be obtained from a corresponding compound of formula I or I' as defined above wherein $-R_2$, $-R_3$ or $-R_4$ represents a hydroxy group by means of oxidation, for example with Dess-Martin periodinane, PDC or PCC or under Swern oxidation conditions (DMSO/oxalyl chloride), provided that the other hydroxy groups in the molecule, if any, are protected. A compound of formula I wherein $-R_4$ represents an oxygen atom =O can be conveniently converted into a corresponding compound of formula I wherein $-R_4$ represents methylene ($=CH_2$), $=CHCOOR_{10}$ wherein R_{10} is as defined above, or $=CH(OCH_3)$ by reaction with a suitable Wittig reagent, such as for example, respectively, $Ph_3P=CH_2$, $Ph_3P=CHCOOR_{10}$, wherein R_{10} is as defined above and $Ph_3P=CH(OCH_3)$. A compound of formula I wherein $-R_4$ represents $=CH(OCH_3)$ can be then converted by acidic hydrolysis into a corresponding compound of formula I wherein $-R_4$ represents –CHO, which in turn may be either reacted with a reducing agent to give a compound of formula I wherein $-R_4$ represents $-CH_2OH$, or oxidised with a suitable reagent such as $NaClO_2$ to give a compound of formula I wherein $-R_4$ represents –COOH. A compound of formula I wherein $-R_4$ represents an oxygen atom =O can also be converted into a compound of formula I wherein $-R_4$ represents a $-COOR_{10}$ group wherein R_{10} is as defined above and the bond at position 11-12 is double by treatment with triflic anhydride in the presence of a base followed by reaction of the resultant enol-triflate with CO and R_{10}-OH wherein R_{10} is as defined above in the presence of Palladium catalyst and a base such as triethylamine according to known procedures as those described in J.Chem.Soc.Perkin Trans. I, 1991 (5), 969-979. Such compounds of formula I wherein $-R_4$ represents a –COOH group and the bond at position 11-12 is double can be converted by selective reduction into the corresponding 11-12 unsaturated compounds of formula I wherein $-R_4$ represents a $-CH_2OH$ group, for example by treatment with $ClCOOEt/NaBH_4$.

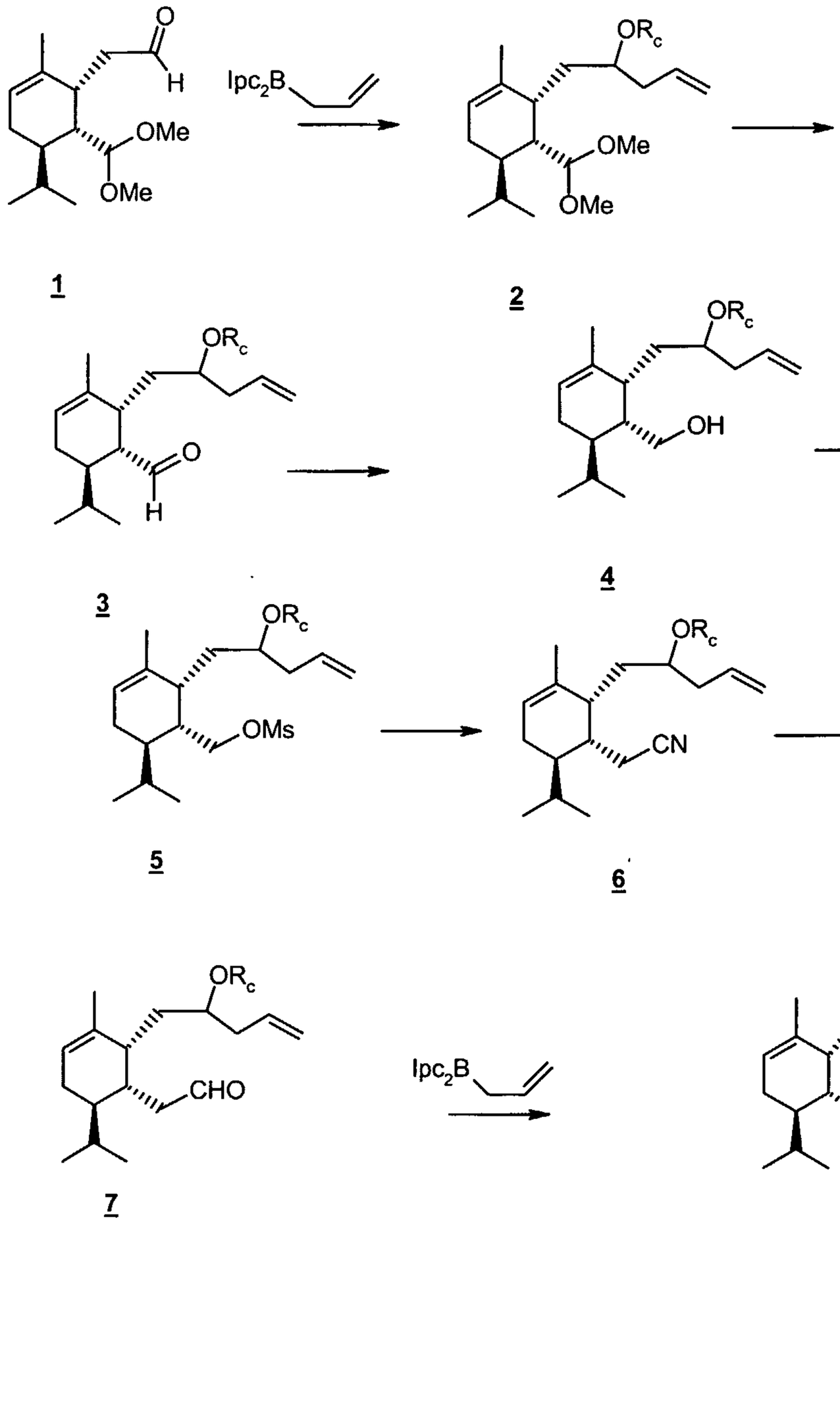
A compound of formula I' or I wherein the bond at position 8-9 is double may be converted into the corresponding compound of formula I with a single bond at the 8-9 position and wherein R_5 and R_6 are hydrogen atoms by hydrogenation, such as by treatment with $H_2/(Ph_3P)_3RhCl$ (Ireland, R. E.; Bey, P. Org. Synth. 1973, 53, 63; Osborn, J. A.; Wilkinson, G. Inorg. Synth. 1977, 28, 77) or with diimide (NH=NH, Org.React. 1991, 40, 91); or into the corresponding compounds of formula I with a single bond at the 8-9 position wherein R_5 and R_6 taken together with the carbon atoms to which they are attached, form a

cyclopropane ring by treatment with a suitable reactant such as a zinc carbenoid (J.Am.Chem.Soc. 2001, 123, 8139-8140).

A sarcodictyin derivative may be converting into a pharmaceutically acceptable salt thereof by salification, using conventional techniques. Suitable salts include those mentioned above.

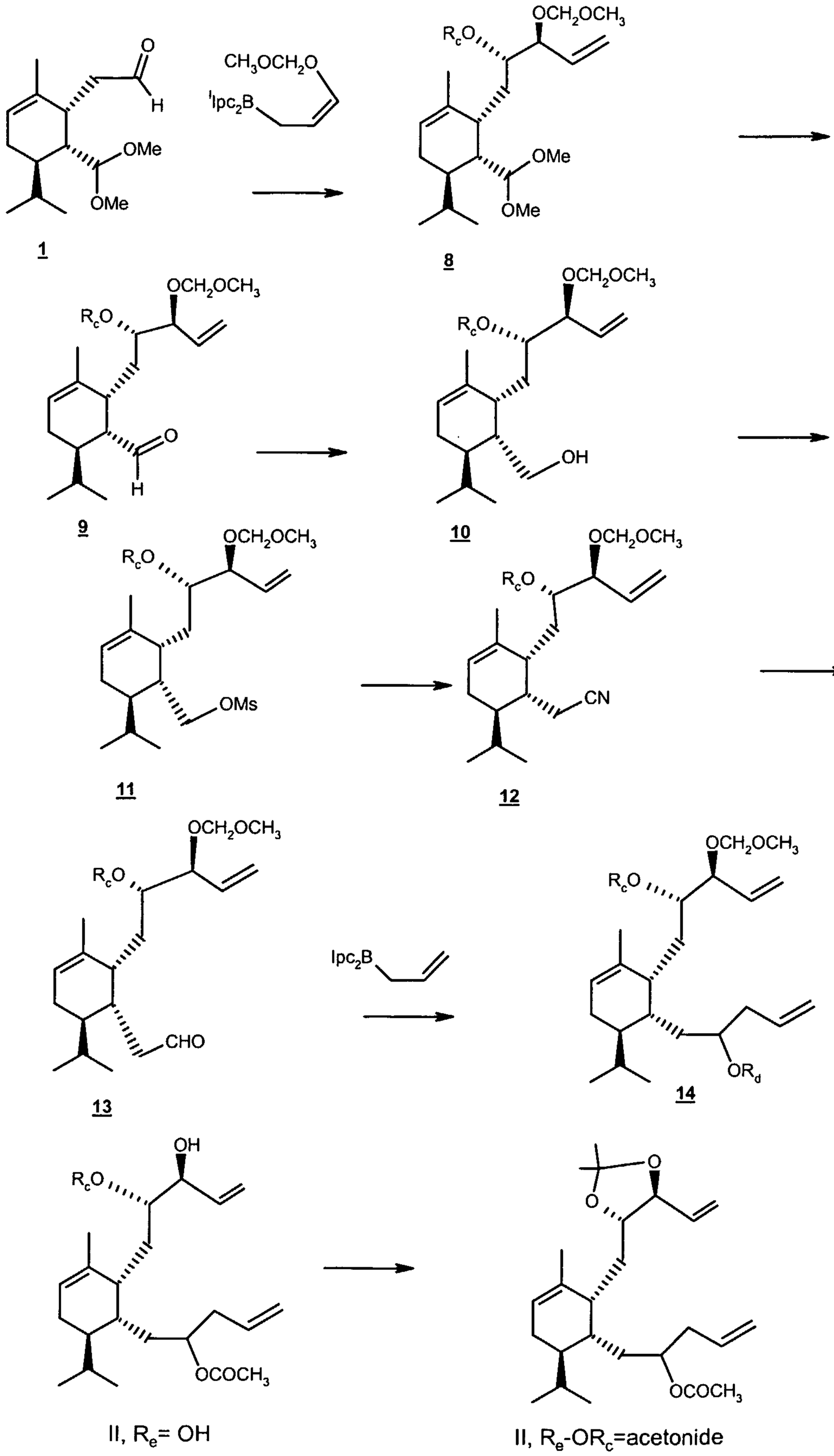
A compound of the formula II may be prepared as described in any one of the following scheme, in which R_c and R_d have the meanings above defined:

SCHEME 1


O
H
OMe
OMe
Ipc2B
ORc
OMe
OMe
1
ORc
O
H
2
ORc
OH
3
ORc
OMs
4
ORc
CN
5
ORc
CHO
7
Ipc2B
6
ORc
ORd
II

The starting compound **1** was submitted to Brown's stereoselective allylation reaction, (J. Org. Chem. ***1982***, 47, *5065*) generating the oxygenated stereocenter of the compound **2**. The allylation reaction proceeds with good to excellent stereocontrol in favor of the desired stereoisomer, just by choosing the suitable absolute stereochemistry of the alpha-pinene-derived reagent [(l-Ipc from (-)-alpha-pinene or d-Ipc from (+)-alpha-pinene]. After standard alcohol protection, such as t-butyldiphenylsilylation, an efficient and well established sequence of steps - dimethylacetal hydrolysis; aldehyde reduction; alcohol mesylation; mesylate substitution with cyanide; nitrile reduction to aldehyde- led to the homologated aldehyde **7**, on which the same allylation procedure described above was applied. The allylation reaction proceeds on aldehyde **7** with good to excellent stereocontrol in favor of the desired stereoisomer, just by choosing the suitable absolute stereochemistry of the alpha-pinene-derived reagent [(l-Ipc from (-)-alpha-pinene or d-Ipc from (+)-alpha-pinene]. The starting compounds of formula **1** are known or can be obtained from known compounds in a manner analogous to that described for example in Tetrahedron Lett. **1999**, 40, 153.

SCHEME 2

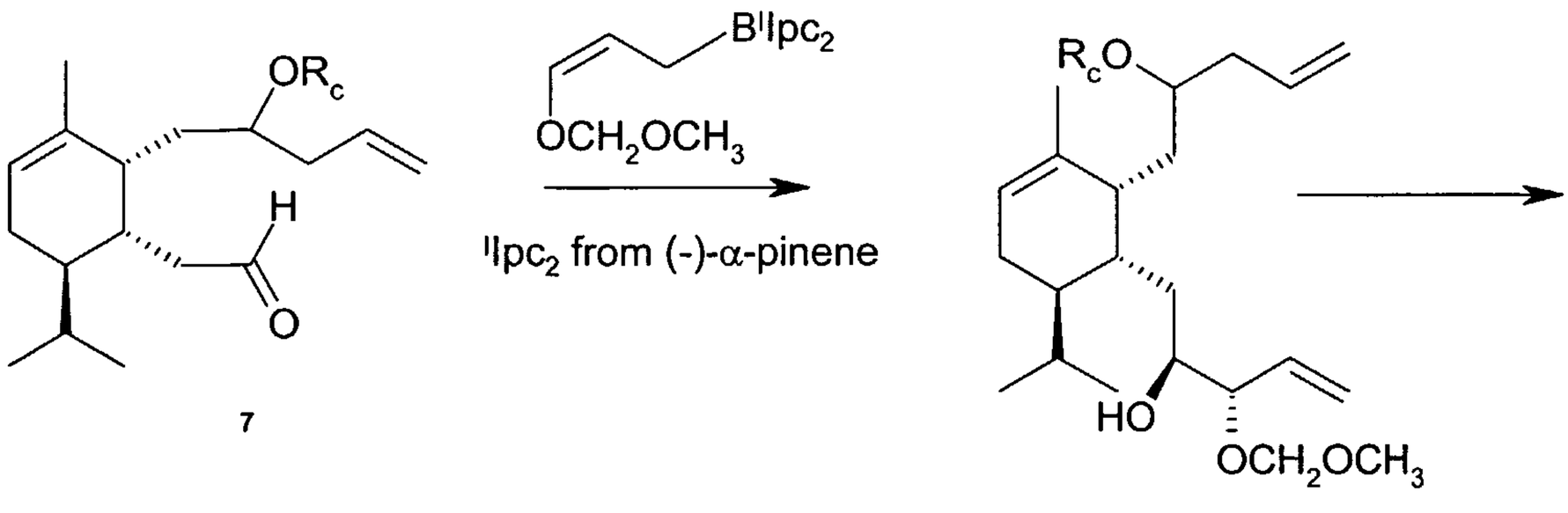


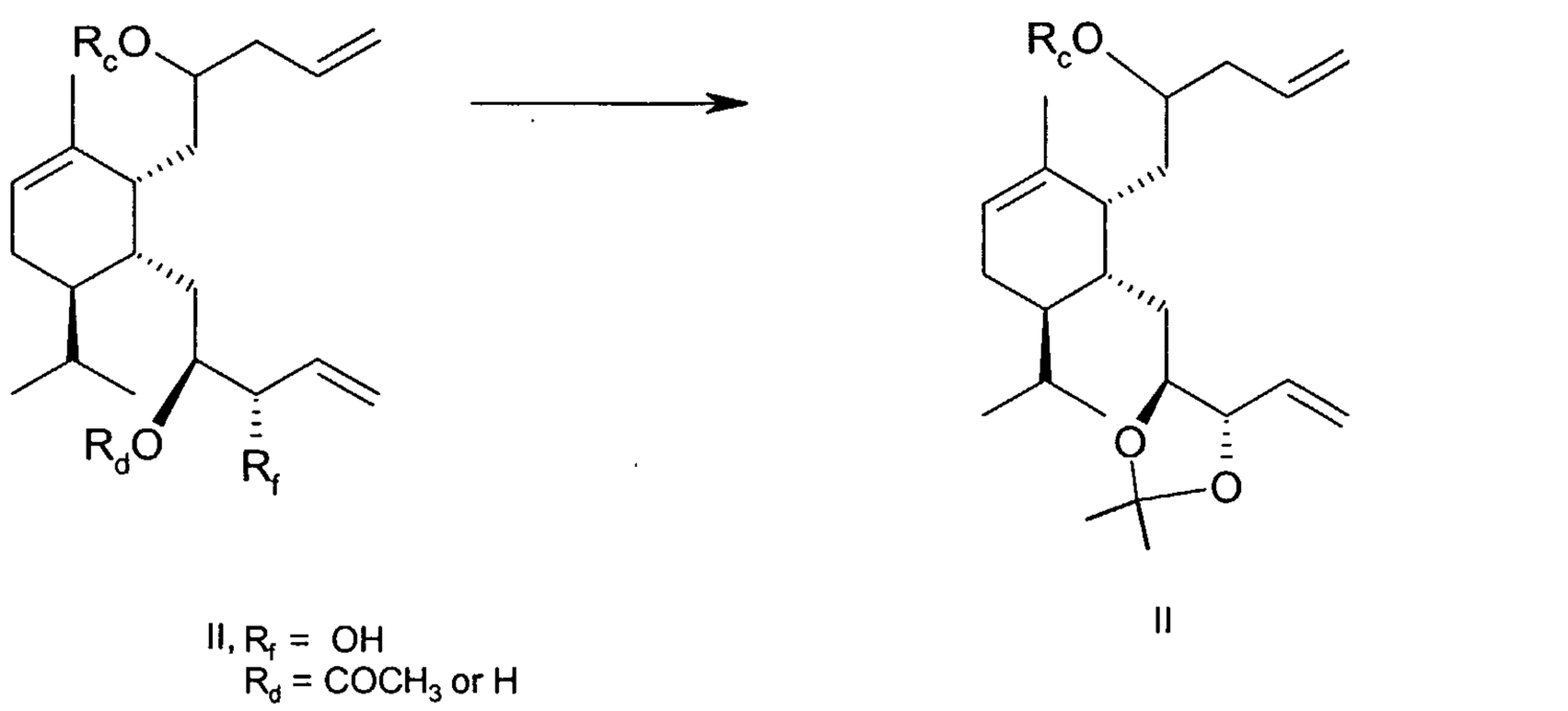
Addition of the oxyallyl borane [(l-Ipc from (-)-alpha-pinene] to aldehyde **1** gave the alcohol **8** (Rc=H) in good to excellent stereocontrol. Choosing the opposite absolute stereochemistry of the alpha-pinene-derived reagent [d-Ipc from (+)-alpha-pinene] gives access to the opposite diastereoisomer (OR_c up, OCH_2OCH_3 down).

Protection of the secondary alcohol as a tert-butyldiphenylsilylether, followed by the reaction sequence already mentioned above for the transformation of **2** to **7** (deprotection of the acetal, reduction of the liberated aldehyde and C_1-chain elongation via substitution of the mesylate by cyanide) gave after reduction the aldehyde **13.** Addition of the desired allyl borane gave the secondary alcohol (**14**, R_d= OH), which was protected with acetic anhydride, yielding the acetate (**14**, R_d= $COCH_3$). Deprotection of the MOM-group (CH_3OCH_2-) leads to free allylic alcohol II (R_e=OH). As stated above, also in this last allylation reaction proceeds with good to excellent stereocontrol in favor of the desired stereoisomer, just by choosing the suitable absolute stereochemistry of the alpha-pinene-derived reagent [(l-Ipc from (-)-alpha-pinene or d-Ipc from (+)-alpha-pinene].

In alternative, an acetonide group is introduced to constrain one side chain. Deprotection of the intermediate and subsequent protection of the resultant diol (II, R_c=H, R_e=OH) gives the acetonide of formula II, wherein R_e and the OR_c group taken together form an acetonide ring.

SCHEME 3





The compounds formula II wherein R_f is hydroxy group are prepared starting from the aldehyde **7** with the desired configuration through reactions analogous to those mentioned above. The compounds of formula II can be converted into the corresponding diol derivative by deprotection (II, R_d=H, R_f=OH), which can be further transformed into the acetonide derivative (II, R_f-OR_d= acetonide).

BIOLOGICAL TESTS

Cytotoxicity

A2780 cells (2000/well) were seeded in multiwell plates (96 wells) in the presence of 200 µl of the complete medium RPMI 1640 + 10% FCS. After 24 h, the cells were treated with the compounds: the compounds' solution (200 x) was prepared in DMSO 100% and 1

µl/well was added. 5 scalar concentrations for each compound were tested in four replicates. The cells were incubated at 37°C, 5% CO_2 for 72 h.

Colorimetric assay (SRB: sulforhodamine B): cell cultures were fixed with trichloroacetic acid, stained with 0.4% SRB dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid and protein-bound dye was extracted with 10mM Tris base for determination of optical density in a 96-well microtiter plate reader. IC_{50} and IC_{90} (concentration inhibiting cell proliferation by 50 or 90 %) were determined by data analysis in the Microsoft Excel 97 program.

Effect on cell cycle progression

Human colon carcinoma HCT116 cells were seeded in culture flasks and treated 24 h after incubation at 37°C. At the end of the treatment (24 or 48 or 72 hours), cells were counted and resuspended in propidium iodide (PI) staining solution (0.1% sodium citrate, 0.1% nonidet P40, 6.5 µg/ml Rnasi A, 50 µg/ml PI). After incubation in the dark at room temperature for at least 30 minutes, samples were then analyzed for cell cycle on FacScan (Becton Dickinson) flow cytometer.

Human colon carcinoma HT29 cells were also used to study the cytotoxicity of the compounds of the present invention.

Table 1 Cytotoxicity tests: IC_{50} values on several different tumor cell lines (A2780; HCT116; HT29)

Compound prepared in Example	IC_{50} [µM] (A2780)	IC_{50} [µM] (HCT116)	IC_{50} [µM] (HT29)
12	4	12	-
16	40	35-60	30
19	4	5	6
27	<5	10-25	7
34	4	4	5

Microtubule assembly and disassembly assay.

Pig brain tubulin was prepared by two cycles of assembly and disassembly and it was stored in liquid nitrogen in Microtubule Assembly Buffer (MAB: 0.1 M MES, 2.5 mM EGTA, 0.5 mM $MgSO_4$, 0.1 mM EDTA, 0.1 mM DTT pH 6.4). Assembly was monitored by the method of Gaskin et al.(Gaskin F, Cantor CR, Shelanski M L, 1974,: Turbidimetric studies of the in vitro assembly and disassembly of porcine neurotubules. J. Mol. Biol. 89:

737-758). The cuvette (1 cm path) containing 0.5 mg/ml tubulin and 1 mM GTP was shifted to 37 °C and continuous turbidity measurements were made at 340 nm on a spectrophotometer equipped with an automatic recorder and a thermostatically regulated sample chamber. After 30 min $CaCl_2$ (5 mM) was added and disassembly was monitored for 10 min as decreased turbidity. Scalar doses of test compounds were monitored at regular intervals of 15 min.

Data were expressed as percentage of reassembly induced by the tested compounds and the dose effecting tubulin assembly by 50% or 90% at 37 °C (ED_{50} and ED_{90}) was calculated on this curve.

Table 2. Tubulin polymerizing activities: ED_{50} = effective dose that induces 50% tubulin polymerisation; ED_{90} = effective dose that induces 90% tubulin polymerisation

Compound prepared in Example	ED_{50} [μM]	ED_{90} [μM]
12	2.0	10.0
16	0.2	1.2
19	5.0	16.0
27	3.0	7.0
30	1.0	1.7
34	1.0	1.8

Compounds of formula I of the invention show enhanced antitumor activity and acceptable toxicity. They are useful as antitumour agents in the prevention, treatment and/or control of cancer, for instance in the treatment of leukemia and solid tumors, such as colon, colo-rectal, ovarian, mammary, prostate, lung, kidney and also melanoma tumors. A human can be treated by a method comprising administering thereto a therapeutically effective amount of a compound of the invention. The invention therefore provides a method of treating a patient in need of an antitumour agent, which method comprises the administration thereto of a compound as defined above. The condition of the human patient can thus be improved. The invention also provides the use of a compound of the invention as defined above in the manufacture of a medicament for use as an antitumour agent.

The dosage range adopted will depend on the route of administration and on the age, weight and condition of the patient being treated. The compound of formula (I) is typically administered by parenteral route, for example intramuscularly, intravenously or by bolus

infusion. A suitable dose range is from 1 to 1000 mg of equivalent per m^2 body surface area of active drug, for instance from 10 to 500 mg/m^2.

The compounds of formula (I) may be formulated into a pharmaceutical composition together with a pharmaceutically carrier or diluent. The invention therefore further provides a pharmaceutical composition which comprises a pharmaceutically acceptable diluent or carrier and, as an active ingredient, a compound as defined above. The pharmaceutical compositions of the invention are prepared by conventional methods and are adminstered in a pharmaceutically acceptable form. For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

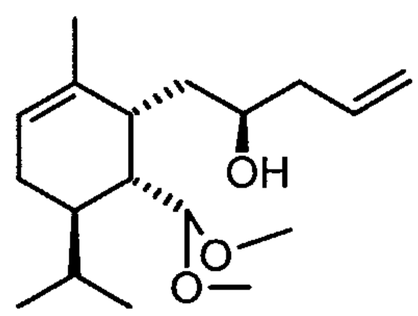
The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty ester surfactant or lecithin.

Typically the pharmaceutical compositions are formulated for parenteral administration, for example by dissolution in water for injection or physiological saline.

Example 1

(R)-1-((1R,5R,6R)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl)-pent-4-en-2-ol .



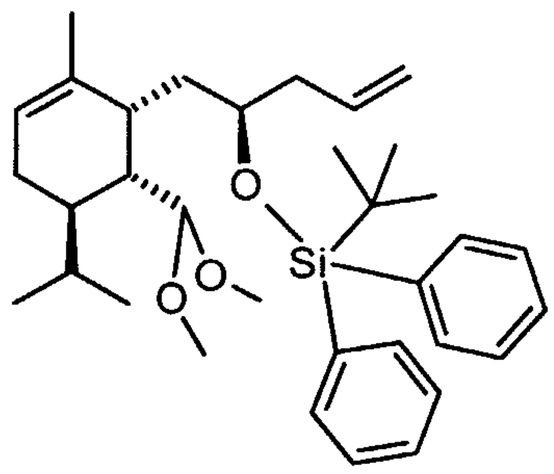
Allyl magnesium bromide (1M in Et_2O, 610 µl, 0.61 mmol, 1.2 eq) was added slowly to a stirred 0.86 M solution of $^{l}Ipc_2BOMe$ (^{l}Ipc derived from (-)-alpha-pinene) in THF (830 µl, 0.71 mmol, 1.4 eq) at 0 °C in an oven dried Schlenck tube under an argon atmosphere. The mixture was stirred at ambient temperature for 1 h, then cooled to –78 °C and a solution of 149 mg (0.51 mmol) of [(1R,5R,6R)-6-dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-acetaldehyde, prepared as described in Ceccarelli S. et al, Tetrahedron Lett. 1999, *40*, 153, dissolved in 2 ml of anhydrous ether, was added dropwise via syringe. The reaction mixture was stirred at –78 °C for 6 h, then warmed to room temperature and quenched with 250 µl of 6M NaOH and 200 µl of 35 % H_2O_2. The mixture became hot spontaneously and was left standing over night. The title product was isolated and purified by intensive flash chromatography (Hex / EtOAc 4 + 1), R_f = 0.43. Yield: 117 mg (0.39 mmol, 77 %) as colourless oil.

R_f = 0.43 (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.98–5.77 (m, 1H), 5.36 (m, 1H), 5.16–5.12 (m, 1H), 5.07 (br s, 1H), 4.36 (d, J = 5.4 Hz, 1H), 3.95–3.86 (m, 1H), 3.38 (s, 6H), 2.46–1.19 (m, 14H), 0.94 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 136.7, 135.6, 121.1, 116.8, 106.9, 68.4, 54.7, 54.4, 42.9, 40.2, 37.1, 36.0, 34.7, 27.0, 24.4, 22.2, 21.0, 17.1; IR (CCl_4): ν = 3590, 3480, 3064, 2945, 2919, 2820, 1516, 1457, 1438, 1380, 1361, 1155, 1105, 1065, 910; $[\alpha]_D^{20}$ = +63.6 (c =

1.16, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{18}H_{32}NaO_3$: 319.2249 $[M+Na]^+$; found: 319.2241.

Example 2

tert-Butyl-[(R)-1-((1R,5R,6R)-6-dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl)-but-3-enyloxy]-diphenyl-silane

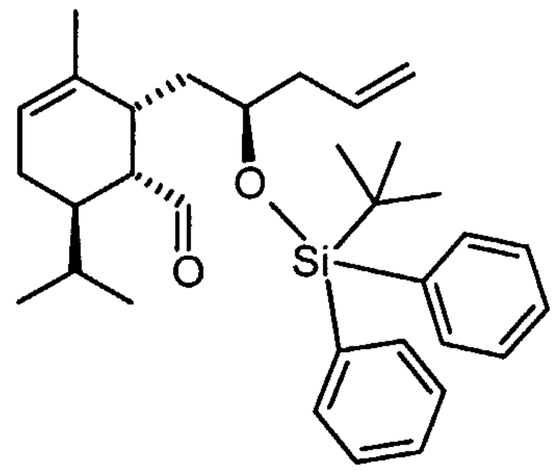


184 mg (0.62 mmol) of the compound prepared in example 1 were dissolved in 5 ml of dry CH_2Cl_2 and imidazole (211 mg, 3.11 mmol, 5 eq) is added. The solution was cooled to 0 °C and 318 µl (1.24 mmol, 2.0 eq) of TBDPSCl (tert-butyl-diphenyl-silylchloride) were slowly added. The reaction mixture was stirred at 0 °C for 90 min, then left stirring at room temperature over night, until complete reaction (TLC control). Then, the solvent was evaporated and the residue submitted to flash chromatography (Hex / EtOAc 25+1), R_f = 0.4. Yield: 332 mg (0.62 mmol, quant.) of the title compound as colourless oil.

R_f = 0.40 (hexane/EtOAc 25:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.76 (m, 4H), 7.72–7.49 (m, 6H), 5.76–5.59 (m, 1H), 5.24 (m, 1H), 4.90–4.73 (m, 2H), 4.09 (d, J = 5.6 Hz, 1H), 4.06–3.98 (m, 1H), 3.19 (s, 3H), 3.17 (s, 3H), 2.47–2.41 (m, 1H), 2.14–2.07 (m, 2H), 1.93–1.72 (m, 6H), 1.65 and 1.64 (s, 3H), 1.42–1.22 (m, 1H), 1.06 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 138.6, 136.1 (2C), 136.0 (2C), 135.3, 135.1, 134.8, 129.2 (2C), 127.3 (2C), 127.2 (2C), 120.5, 116.1, 107.6, 72.5, 54.7, 54.6, 42.3, 41.3, 38.1, 35.5, 35.1, 27.1, 27.1 (3C), 24.1, 22.9, 21.5, 19.4, 16.3; IR (CCl_4): ν = 3060, 3040, 2943, 2917, 2840, 1465, 1420, 1381 1320, 1105, 1075, 905; $[\alpha]_D^{20}$ = +46.4 (c = 1.04, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{34}H_{50}NaO_3Si$: 557.3427 $[M+Na]^+$; found: 557.3413.

Example 3

(1R,2R,6R)-2-[(R)-2-(tert-Butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enecarbaldehyde.

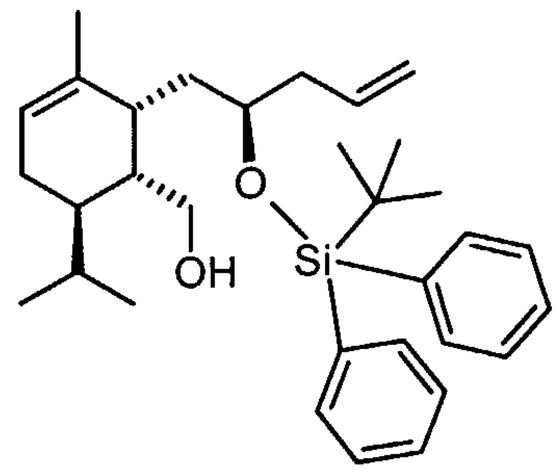


264 mg (0.49 mmol) of the compound prepared in example 2 were dissolved in 5 ml of a mixture of AcOH / H_2O / THF 3+1+1. The mixture was stirred at ambient temperature for 15 h until TLC analysis showed complete conversion (Hex / EtOAc 9+1, $R_f = 0.68$). Ether, 5 g of $NaHCO_3$ and 10 ml of water were added and vigorous stirring was continued until no more gas evolves. The product was extracted with 3 portions of ether, the combined organic layers dried (Na_2SO_4), the solvent was distilled and pure title compound was obtained. Yield: 242 mg (0.49 mmol, quant.), colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.55$ (d, $J = 3.6$ Hz, 1H), 7.71–7.58 (m, 4H), 7.48–7.29 (m, 6H), 5.72–5.51 (m, 1H), 5.30 (m, 1H), 4.99–4.79 (m, 2H), 3.79–3.69 (m, 1H), 2.43–1.01 (m, 22H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 206.5$, 136.1, 135.9 (4C), 134.2, 134.1, 134.0, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 121.6, 117.5, 72.1, 53.1, 41.6, 36.9, 35.7, 35.3, 27.1 (3C), 26.3, 23.8, 22.3, 20.6, 19.3, 16.9; IR (CCl_4): $\nu = 3060$, 2945, 2918, 2842, 2700, 1713, 1465, 1458, 1420, 1382, 1363, 1105, 1061, 910; $[\alpha]_D^{20} = +28.4$ (c = 1.22, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{32}H_{44}NaO_2Si$: 511.3008 $[M+Na]^+$; found: 511.2996.

Example 4

{(1R,2R,6R)-2-[(R)-2-(tert-Butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-methanol

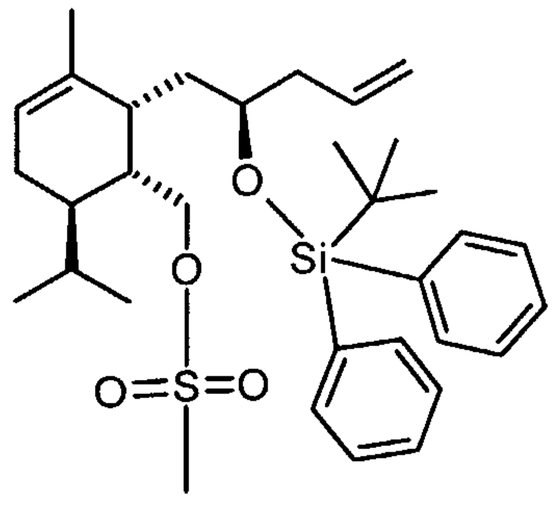


242 mg (0.49 mmol) of the compound prepared in example 3 were dissolved in 2 ml of EtOH. 28 mg (0.75 mmol, 1.5 eq) of $NaBH_4$ were added and the reaction mixture stirred at ambient temperature for 45 min. Then, another 10 mg (0.26 mmol, 0.5 eq) of $NaBH_4$ were added and stirring continued for 70 min. Then, 270 mg (5 mmol) of NH_4Cl were added, after 5 min, this mixture was diluted with ether. The ethereous phase was dried (Na_2SO_4), filtered over Celite, and the filtrate evaporated. The residue was purified by flash chromatography (Hex / EtOAc 4+1, $R_f = 0.31$). Yield: 176 mg (0.358 mmol, 73 %) of the title compound as colourless oil.

R_f = 0.21 (hexane/EtOAc 25:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77–7.57 (m, 4H), 7.45–7.34 (m, 6H), 5.92–5.75 (m, 1H), 5.26 (br s, 1H), 5.05–4.92 (m, 2H), 4.08–3.95 (m, 1H), 3.65 (dd, J = 10.9, 5.6 Hz, 1H), 3.48–3.38 (m, 1H), 2.30 (t, J = 5.8 Hz, 2H), 1.90–0.91 (m, 21H), 0.85 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.4, 136.0 (4C), 135.2, 134.7, 134.4, 129.6 (2C), 127.5 (4C), 121.5, 117.2, 72.3, 62.4, 41.7, 41.3, 36.9, 36.0, 34.7, 27.1 (4C), 24.1, 23.4, 21.2, 19.4, 16.2; IR (CCl_4): ν = 3615, 3060, 2945, 2918, 2880, 2842, 1422, 1381, 1363, 1105, 1058; $[\alpha]_D^{20}$ = +67.5 (c = 0.99, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{32}H_{47}O_2Si$: 491.3345 $[M+H]^+$; found: 491.3341.

Example 5

<u>Methanesulfonic acid (1R,2R,6R)-2-[(R)-2-(tert-butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl ester</u>

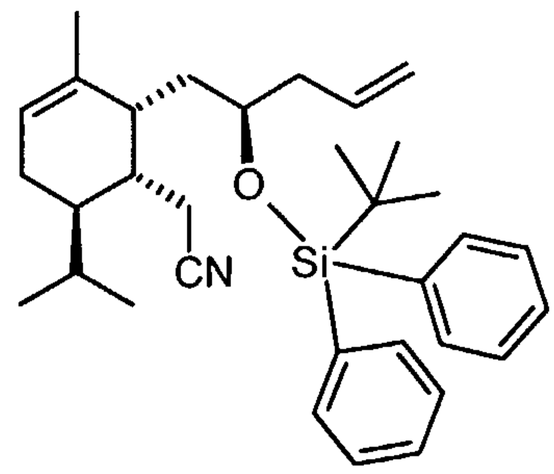


162 mg (0.33 mmol) of the compound prepared in example 4 were dissolved in 3 ml of dry CH_2Cl_2. The mixture was cooled to – 40 °C, 91 µl (67 mg, 0.66 mmol, 3 eq) of Et_3N and 40 µl (0.50 mmol, 1.5 eq) of MsCl (mesyl chloride) were added via syringe and the reaction was warmed to room temperature over 75 min. Then, $NaHCO_3$ sat. was added, the acqueous phase was extracted with 3 portions of CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, the solvent was distilled and the product was purified by flash chromatography (Hex / EtOAc 4+1, $R_f = 0.63$). Yield: 188 mg of the title compound (0.33 mmol, quant.) as colourless oil.

$R_f = 0.63$ (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.65–7.59$ (m, 4H), 7.44–7.30 (m, 6H), 5.88–5.67 (m, 1H), 5.23 (br s, 1H), 5.02–4.88 (m, 2H), 4.21 (dd, J = 10.0, 6.5 Hz, 1H), 3.98 (dd, J = 10.0, 8.5 Hz, 2H), 2.86 (s, 3H), 2.31–2.26 (m, 3H), 2.04–0.99 (m, 19H), 0.82 (d, J = 6.0 Hz, 3H), 0.80 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 136.3$, 135.9 (4C), 134.7, 134.4 (2C), 129.6 (2C), 127.6 (4C), 121.5, 117.5, 72.1, 70.1, 41.3, 39.0, 37.3, 37.0, 36.3, 34.8, 27.3, 27.1 (3C), 23.7, 23.2, 21.0, 19.4, 17.0; IR (CCl_4): $\nu = 3070$, 2960, 2930, 2858, 1471, 1428, 1389, 1368, 1348, 1329, 1180, 1110, 1062; $[\alpha]_D^{20}$ = +58.1 (c = 0.92, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{33}H_{52}NO_4SiS$: 586.3386 $[M+NH_4]^+$; found: 586.3368.

Example 6

{(1R,2R,6R)-2-[(R)-2-(tert-Butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-acetonitrile.

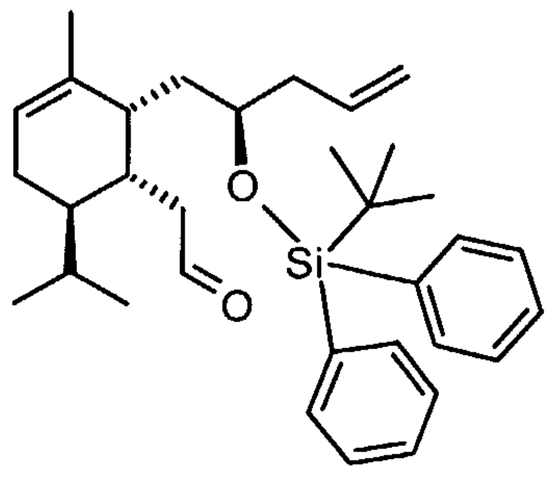


162 mg (285 µmol) of the compound prepared in example 5 were dissolved in 3 ml of dry acetonitrile. 56 mg (855 µmol, 3 eq) of KCN and 226 mg (855 µmol, 3 eq) of 18-crown-6 were added. The reaction mixture was heated to 80 °C for 6 h. The solvent was evaporated under reduced pressure, the residue was dissolved in Hex / EtOAc 9+1 and purified by flashchromatography (Hex / EtOAc 9+1, R_f = 0.60), yield: 136 mg (272 µmol, 95 %) of the title compound as colourless oil.

R_f = 0.40 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.69 (m, 4H), 7.47–7.33 (m, 6H), 5.84–5.70 (m, 1H), 5.22 (br s, 1H), 5.05–4.92 (m, 2H), 3.95–3.86 (m, 1H), 2.27–1.27 (m, 15H), 1.05 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 135.8 (4C), 135.4, 134.3, 134.2, 134.1, 129.5 (2C), 127.4 (4C), 121.2, 119.4, 117.6, 71.8, 40.9, 38.5, 36.3, 36.1, 35.9, 27.2, 27.0 (3C), 23.4, 22.8, 20.8, 19.2, 17.8, 17.5; IR (CCl_4): ν = 3070, 2955, 2922, 2890, 2856, 1715, 1470, 1460, 1425, 1388, 1369, 1110, 1070, 915; $[\alpha]_D^{20}$ = +66.4 (c = 1.28, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{33}H_{45}NaNOSi$: 522.3168 $[M+Na]^+$; found: 522.3179.

Example 7

{(1R,2R,6R)-2-[(R)-2-(tert-Butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-acetaldehyde.

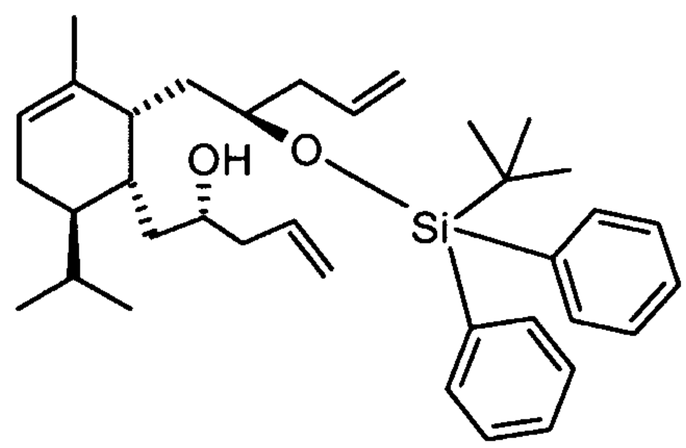


136 mg of the compound prepared in example 6 were dissolved in 3 ml of toluene / hexane 1+2. At –78 °C, 2.7 ml (2.7 mmol, 10 eq) of DIBAlH (Di-isobutyl aluminium hydride, 1.0 M in hexane) were added. After stirring 45 min at –78 °C the reaction was quenched with 1.5 ml of EtOAc and 5 ml of 1 M tartaric acid. Extraction with 3 portions of CH_2Cl_2, washing the combined organic phases with 1N HCl, drying (Na_2SO_4) and purification by flash chromatography (Hex / EtOAc 9+1, $R_f = 0.60$), 107 mg (121 mmol, 78 %) of the title compound were obtained as colourless oil.

$R_f = 0.39$ (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.66$ (s, 1H), 7.78–7.71 (m, 4H), 7.457.35 (m, 6H), 5.91–5.71 (m, 1H), 5.26 (br s, 1H), 5.07–4.90 (m, 2H), 3.91 (q, $J = 5.9$ Hz, 1H), 2.38–2.03 (m, 5H), 1.99–0.93 (m, 19H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 203.1$, 136.6, 135.9 (4C), 134.6, 134.5, 134.3, 129.6 (2C), 127.5 (4C), 121.3, 117.4, 72.1, 44.2, 41.2, 38.9, 37.0, 36.4, 34.3, 27.4, 27.1 (3C), 23.7, 23.1, 21.2, 19.4, 17.2; IR (CCl_4): $\nu = 3060$, 2943, 2917, 2880, 2842, 2695, 1720, 1465, 1455, 1420, 1382, 1365, 1103, 1095, 1060, 910; $[\alpha]_D^{20} = +53.3$ (c = 1.14, EtOAc).

Example 8

(R)-1-{(1R,2R,6R)-2-[(R)-2-(tert-Butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol.



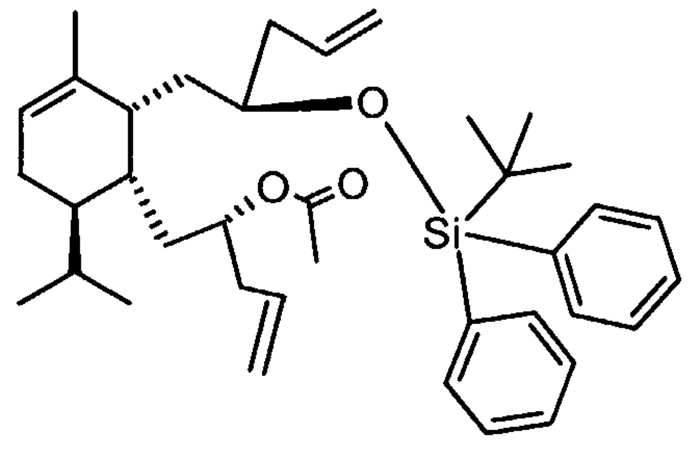
Allyl magnesium bromide (1.0 M in Et_2O, 150 µl, 0.15 mmol, 3 eq) was added to a solution of 170 µl (0.17 mmol, 3.3 eq) of ^{l}Ipc$_2$BOMe (^{l}Ipc derived from (-)-alpha-pinene, 1.0 M in THF) at 0 °C. The mixture was stirred at room temperatur for 1 h. After 1 h, it was cooled to – 78 °C and a solution of 25 mg (50 µmol) of the compound prepared in example 7 in 200 µl of dry ether were added. The mixture was stirred at –78 °C for 3 h 45

min, then it was warmed to room temperature and quenched with 200 µl of 30 % H_2O_2 and 250 µl of 6M NaOH. Stirring was continued at ambient temperature for 40 min, water and ether were added and the product was isolated by extraction with 3 portions of ether, drying (Na_2SO_4) and intensive flash chromatography (Hex / EtOAc 4+1, $R_f = 0.59$). Yield: 15 mg (28 µmol, 55 %) of the title compound as a colourless oil.

$R_f = 0.59$ (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.73–7.56$ (m, 4H), 7.46–7.27 (m, 6H), 5.91–5.70 (m, 2H), 5.49–4.92 (m, 5H), 4.17–3.89 (m, 1H), 3.67–3.62 (m, 1H), 2.51–1.92 (m, 5H), 1.82–1.19 (m, 13H), 1.09 (s, 9H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ□ = 136.9, 135.9 (4C), 135.0, 134.9, 134.6, 134.5, 129.5 (2C), 127.4 (4C), 121.1, 118.0, 117.0, 72.2, 68.3, 41.9, 41.5, 38.5, 37.1, 35.8, 35.4, 35.2, 27.1, 27.0 (3C), 23.9, 23.1, 21.2, 19.3, 17.5; IR (CCl_4): $\nu = 3595$, 3078, 2960, 2934, 2899, 2860, 1642, 1475, 1465, 1430, 1389, 1371, 1110, 1069, 917; $[\alpha]_D^{20} = +38.8$ (c = 0.84, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{36}H_{52}NaO_2Si$: 567.3634 $[M+Na]^+$; found: 567.3665.

Example 9

Acetic acid (R)-1-{(1R,2R,6R)-2-[(R)-2-(tert-butyl-diphenyl-silyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl ester.

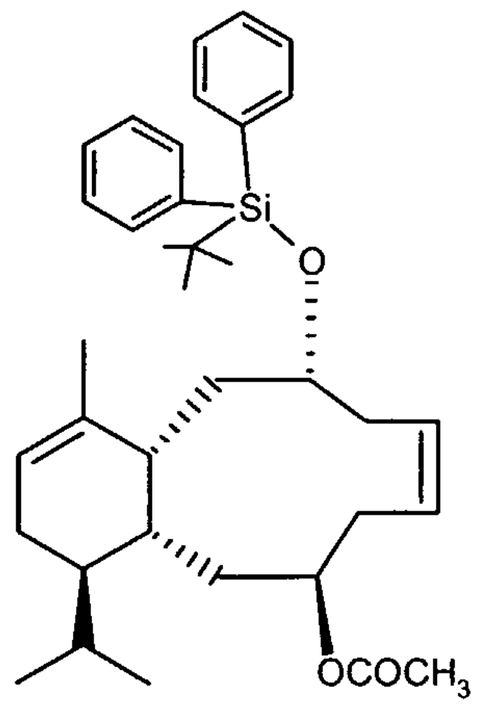


78 mg (0.14 mmol) of the compound prepared in example 8 were treated with acetic anhydride (41 µl, 0.44 mmol, 3 eq) and 4-DMAP (4-dimethylaminopyridine, 2 mg) in 500 µl of pyridine at 0 °C. Stirring was continued until the reaction was complete by TLC (3 h). The mixture was diluted with EtOAc, washed with saturated $KHSO_4$ aqueous solution, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (Hexane / EtOAc 14+1, $R_f = 0.65$). Yield: 75 mg (0.13 mmol, 93 %) of the title compound as colourless oil.

R_f = 0.58 (hexane/EtOAc 14:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.99–7.65 (m, 4H), 7.45–7.28 (m, 6H), 5.91–5.62 (m, 2H), 5.19–4.87 (m, 6H), 3.91 (q, J = 5.7 Hz, 1H), 2.30–2.01 (m, 5H), 1.97 (s, 3H), 1.85–1.14 (m, 11H), 1.06 (s, 9H), 0.95–0.84 (m, 1H), 0.76 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.4, 135.8 (4C), 135.0, 134.5, 134.4 (2C), 133.6, 129.4 (2C), 127.3 (4C), 121.1, 117.6, 117.0, 71.9, 71.2, 41.4, 39.2, 39.0, 36.6, 34.8, 33.5, 31.5, 27.2, 27.0 (3C), 23.6, 22.9, 21.1, 20.9, 19.3, 19.2; IR (CCl_4): ν = 3050, 2934, 2911, 2831, 1726, 1460, 1450, 1415, 1375, 1359, 1096, 1090, 1052, 900; $[\alpha]_D^{20}$ = +27.9 (c = 1.26, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{38}H_{54}NaO_3Si$: 609.3740 $[M+Na]^+$; found: 609.3746.

Example 10

11-Acetoxy-1-isopropyl-4-methyl-6-(tert-butyl-diphenyl-silyloxy)-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecene.

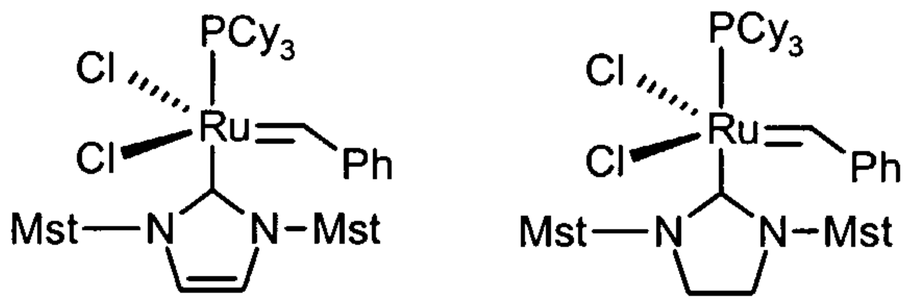


6 mg (10 µmol) of the compound prepared in example 9 was dissolved in 1 ml of dry degassed dichloromethane. 2 mg (2 µmol, 0.2 eq) of RCM catalyst **A** were dissolved in 500 µl of dry degassed dichloromethane and this solution was slowly added to the solution of the compound prepared in example 9 over 2 h under an argon atmosphere. The mixture was then stirred over night under an argon atmosphere. Another 1 mg (1 µmol, 0.1 eq) was dissolved in 250 µl of DCM and slowly added via syringe pump over 30 min. Stirring at ambient temperature was continued until no more starting material can be detected by TLC. Then, the solvent was distilled and the residue was submitted to flash chromatography (Hexane/EtOAc 9+1, Rf = 0.53). Yield of the title compound: 5 mg (9 µmol, 90 %).

R_f = 0.43 (hexane/EtOAc 14:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.62 (m, 4H), 7.44–7.33 (m, 6H), 5.86 (dt, J = 11.1, 4.7 Hz, 1H), 5.51 (ddd, J = 11.7, 3.9 Hz, 1H), 5.20 (m, 1H), 5.13 (m, 1H), 4.17 (m, 1H), 2.77–2.49 (m, 2H), 2.29–2.25 (m, 1H), 2.15 (m, 1H), 2.05–0.85 (m, 23H), 0.89–0.85 (m, 1H), 0.81 (d, J = 6.6 Hz, 3H), 0.77–0.65 (m, 1H), 0.61 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.4, 138.5, 135.7 (4C), 134.4 (2C), 129.5 (2C), 127.5 (4C), 126.9 (2C), 120.4, 72.8 (2C), 37.8, 37.0, 36.6, 34.7, 31.9, 31.6, 26.9 (4C), 26.2, 24.2, 23.9, 21.2, 20.9, 19.2, 14.9; IR (CCl_4): ν = 3070, 2958, 2926, 2856, 1740, 1460, 1427, 1368, 1110, 1067; $[\alpha]_D^{20}$ = +41.0 (c = 1.26, EtOAc); HRMS [EI (70 eV)]: *m/z*: calcd for $C_{36}H_{50}O_3Si$: 558.3529 $[M]^+$; found: 558.3532.

Assignment of the olefinic $^3J_{cis}$ coupling constant (11.5 Hz between the protons at δ = 5.51 and δ = 5.86 ppm, respectively) by a 400 MHz H,H-COSY experiment.

Unequivocal assignment of *cis* stereochemistry of the double bond by detection of a NOE contact between olefinic protons in a 400 MHz NOESY experiment.

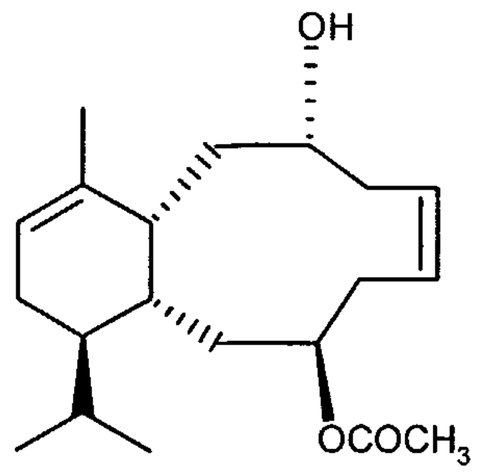


RCM Catalyst **A** RCM Catalyst **B**

[Mst=C_6H_2-2,4,6-$(CH_3)_3$]

The same reaction was repeated with the RCM catalyst **B** (7% mol), in CH_2Cl_2 at room temperature, and after 168 h the title compound was isolated in 88% yield (95% after recovering starting material, stereochemistry of the double bond: 100% *Z*).

Example 11
11-Acetoxy-6-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecene.



A solution of the compound prepared in example 10 (19 mg, 0.034 mmol) in THF (550 µl) was treated with 1 M TBAF in THF (170 µl, 5 eq.) at room temperature. The mixture was stirred for 16 h, then treated with pH 7 phosphate buffer, and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated to give a crude mixture, which was purified by flash-chromatography (hexane-EtOAc 4+1) to yield the title compound (10 mg, 94%).

R_f = 0.27 (hexane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.72 (dt, J = 11.2, 3.9 Hz, 1H), 5.53 (dt, J = 11.7, 4.0 Hz, 1H), 5.31–5.12 (m, 2H), 4.26–4.19 (m, 1H), 2.85–2.66 (m, 2H), 2.42–1.16 (m, 19H), 0.85 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.4, 138.4, 127.9, 126.2, 121.1, 72.6, 71.3, 38.0, 37.4, 36.8, 34.7, 31.9, 31.8, 27.0, 26.4, 24.4, 24.3, 21.2, 21.0, 15.1; IR (CCl_4): ν = 3634, 3621, 2924, 2843, 1739, 1460, 1382, 1364; $[\alpha]_D^{20}$ = +4.6 (c = 0.46, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{20}H_{32}NaO_3$: 343.2249 $[M+Na]^+$; found: 343.2241.

Preparation step A: (*E*)-3-(1*H*-Imidazol-4-yl)-2-propenoic Acid Ethyl Ester.
(*E*)-3-(1*H*-Imidazol-4-yl)-2-propenoic Acid (2.0 g, 14.48 mmol) was dissolved in absolute EtOH (10 mL) under N_2. H_2SO_4 (conc., 1 ml) was added and the mixture was refluxed for 3 h until the solution was clear. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution (pH = 7). The solution was extracted with EtOAc (3 x 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the title compound (2.19 g, 13.19 mmol, 91%) as a white solid.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.31 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.22 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.44 (d, J = 15.7 Hz, 1H, CH=C*H*-$CO_2CH_2CH_3$), 7.29 (s, 1H, Ar-

H), 7.60 (d, J = 15.7 Hz, 1H, C*H*=CH-$CO_2CH_2CH_3$), 7.71 (s, 1H, Ar-H), 8.30 (br s, 1H, N*H*).

Preparation step B (*E*)-3-(1-Methyl-Imidazol-4-yl)-2-propenoic Acid Ethyl Ester

The compound prepared in preparation step A (2.19 g, 13.19 mmol) was dissolved in absolute CH_3CN (20 ml) under N_2. K_2CO_3 (1.0 eq., 13.19 mmol, 1.82 g) and MeI (1.0 eq., 13.19 mmol, 1.87 g) were added. The solution stirred for 24 h at room temperature in a closed flask (TLC showed starting material left). MeI (0.5 eq., 6.60 mmol, 0.91 g) were added and the solution stirred for another 48 h at room temperature in a closed flask (TLC showed minimal starting material left). $CHCl_3$ (20 mL) and H_2O (20 mL) were added. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (CH_2Cl_2/EtOH 97:3) to yield the title compound (714 mg, 3.96 mmol, 30%) as a white solid. R_f = 0.55 (CH_2Cl_2/EtOH 97:3); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.28 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.68 (s, 3H, N-C*H*$_3$), 4.21 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.50 (d, J = 15.7 Hz, 1H, CH=C*H*-$CO_2CH_2CH_3$), 7.05 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.51 (d, J = 15.7 Hz, 1H, C*H*=CH-$CO_2CH_2CH_3$).

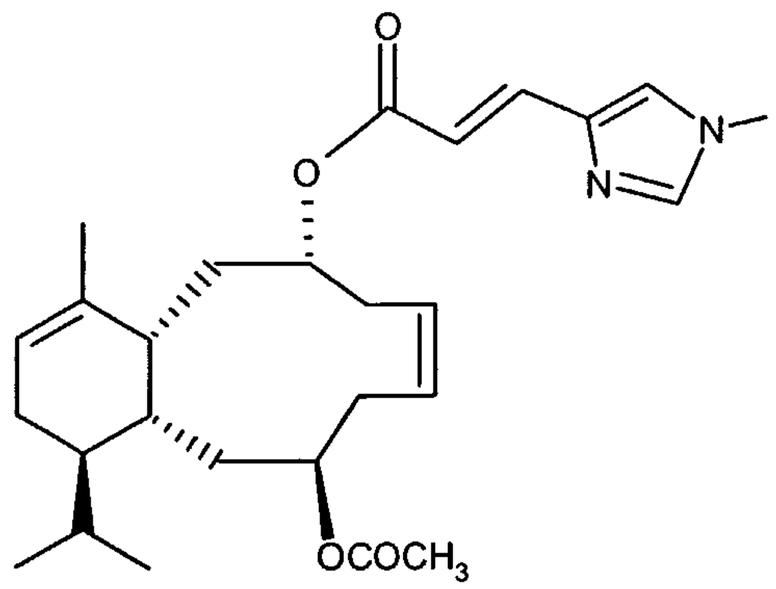
Preparation step C (*E*)-3-(1-Methyl-Imidazol-4-yl)-2-propenoic Acid Sodium Salt

The compound prepared in preparation step B (187 mg, 1.038 mmol) was dissolved in THF/H_2O (1:1, 8 ml). NaOH (1.0 eq., 1.038 mmol, 41.5 mg) was added and the solution stirred 48 h at room temperature (TLC showed minimal starting material left and the pH was neutral, between 7-8). The solvent was evaporated under reduced pressure, coevaporated with benzene (5 x 5 mL) and dried at a high vacuum pump to yield the title compound as a grey-white solid, that was used without further purification.

^{1}H-NMR (DMSO-D_6, 200 MHz): δ = 3.60 (s, 3H, N-C*H*$_3$), 6.20 (d, J = 15.7 Hz, 1H, CH=C*H*-$CO_2CH_2CH_3$), 6.96 (d, J = 15.7 Hz, 1H, C*H*=CH-$CO_2CH_2CH_3$), 7.16 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H).

Example 12

3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester .



The compound prepared in the preparation step C (15.0 eq., 0.515 mmol, 90 mg) was dissolved in dry THF (5 mL) under Ar. Pivaloylchloride (15.0 eq, 0.515 mmol, 62 mg) was added and the solution stirred for 24 h at room temperature in a closed flask. The solution was filtered under Ar to separate the precipitated NaCl, the precipitate was washed with dry THF (2 x 5mL) and the solvent carefully evaporated under reduced pressure to give the corresponding crude mixed anhydride as a white suspension (checked by ^{1}H-NMR in $CDCl_3$). The alcohol prepared in example 11 (1.0 eq., 0.0343 mmol, 11.0 mg) was dissolved in dry CH_2Cl_2 (2 ml) and added to the solution of the crude mixed anhydride under Ar. NEt_3 (15.0 eq., 0.515 mmol, 52 mg) and DMAP (1.0 eq., 0.0343 mmol, 4 mg) were added and the the solution stirred for 3 d at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (Hexane/EtOAc 1:4) to yield the title compound (9.2 mg, 0.020 mmol, 59%) as an oil.

R_f = 0.25 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 15.6 Hz, 1H), 7.47 (s, 1H), 7.09 (s, 1H), 6.54 (d, J = 15.6 Hz, 1H), 5.74–5.66 (m, 1H), 5.62–5.55 (m, 1H), 5.45–5.39 (m, 1H), 5.34 (br s, 1H), 5.24–5.18 (m, 1H), 3.72 (s, 3H), 2.88–2.77 (m, 2H), 2.40–2.25 (m, 2H), 2.23–2.18 (m, 1H), 2.07 (s, 3H), 2.05–1.26 (m, 12H), 0.87 (d, J = 6.7 Hz, 3H), 0.70 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.4, 166.7, 137.9, 138.4, 135.9, 127.9, 126.4, 122.2, 121.0, 116.4, 73.6, 72.5, 37.5, 37.3, 34.6, 33.5, 32.7, 31.6, 29.6, 29.2, 26.9, 26.2, 24.3, 24.2, 21.2, 20.9, 15.1; IR (CCl_4): ν = 2960, 2850, 1745, 1705, 1640, 1450, 1440, 1380, 1345, 1295, 905; $[\alpha]_D^{20}$ = –29 (c = 0.71, EtOAc); HRMS [EI (30 eV)]: *m/z*: calcd for $C_{27}H_{38}N_2O_4$: 454.2832 $[M]^+$; found: 454.2802.

Example 13

(4*R*,4a*R*,6*R*,11*R*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanoxy)-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol

The compound prepared in Example 10 (30 mg, 0.05 mmol) was dissolved in MeOH (1 mL). K_2CO_3 (17 mg, 0.10 mmol) was added and the solution stirred for 15 h at room temperature. H_2O (2mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL), the combined organic layers were washed with a saturated aqueous NaCl solution (2x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (26 mg, 94 %) as a colourless oil. R_f = 0.25 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74–7.61 (m, 4H), 7.46–7.31 (m, 6H), 5.82 (dt, J = 11.3, 5.1 Hz, 1H), 5.52 (dt, J = 11.3, 5.1 Hz, 1H), 5.13 (br s, 1H), 4.23–4.04 (m, 2H), 2.70–2.49 (m, 2H), 2.33–2.04 (m, 3H), 1.99–1.18 (m, 13H), 1.08 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 138.5, 135.7 (4C), 134.5, 134.4, 129.4 (2C), 127.9, 127.5 (4C), 126.6, 120.4, 72.7, 71.0, 37.9, 37.3, 36.6, 35.5, 33.7, 32.0, 29.1, 27.0 (4C), 24.3, 23.9, 21.0, 19.2, 15.3; IR (CCl_4): ν = 3611, 2942, 2921, 2842, 1472, 1458, 1427, 1389, 1369, 1109, 1067, 909; $[\alpha]_D^{20}$ = +25.3 (c = 0.73, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{34}H_{48}NaO_2Si$: 539.3321 $[M+Na]^+$; found: 539.3306.

Example 14

(4*R*,4a*R*,11*R*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanoxy)-4-isopropyl-1-methyl-3,4a,5,7,10,11,12,12a-octahydro-4*H*-benzocyclodecen-6-one:

$(COCl)_2$ (91 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to –60 °C. DMSO (77 mg, 0.98 mmol) was added and the solution stirred for 10 min at –60 °C. The compound prepared in Example 13 (62 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added and the solution stirred for further 30 min at –60 °C. NEt_3 (199 mg, 1.97 mmol) was added, the solution was allowed to warm to 0 °C over 1 h and stirred additional 10 min at 0 °C. An aqueous phosphate buffer solution (3 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide unreacted starting compound (9 mg) and the title compound (50 mg, 81 %,

95 % after recovering starting material) as colourless oils. R_f = 0.55 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77–7.59 (m, 4H), 7.47–7.29 (m, 6H), 6.19–6.06 (m, 1H), 5.97–5.84 (m, 1H), 5.06 (br s, 1H), 3.96–3.82 (m, 1H), 3.20–2.87 (m, 3H), 2.32–1.95 (m, 4H), 1.89–1.61 (m, 5H), 1.41–1.18 (m, 5H), 1.07 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 213.0, 139.2, 135.8 (4C), 134.0 (2C), 131.4, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 123.7, 116.7, 73.0, 44.1, 38.7, 36.0, 36.7 (2C), 36.5, 32.1, 27.0 (3C), 26.6, 24.1, 22.6, 21.1, 19.2, 14.3, IR (CCl_4): ν = 3022, 2955, 2922, 2899, 2860, 1708, 1705, 1469, 1427, ;$[\alpha]_D^{20}$ = +49.0 (c = 0.79, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{34}H_{46}NaO_2Si$: 537.3165 $[M+Na]^+$; found: 537.3139.

Example 15

(4*R*,4a*R*,11*R*,12a*R*)-11-Hydroxy-4-isopropyl-1-methyl-3,4a,5,7,10,11,12,12a-octahydro-4*H*-benzocyclodecen-6-one

The compound prepared in example 14 (16 mg, 0.03 mmol) was dissolved in THF (0.50 mL) and TBAF (0.06 mL, 0.06 mmol, 1.0 M in THF) was added. The reaction mixture stirred 23 h at room temperature. Additional TBAF (0.06 mL, 0.06 mmol, 1.0 M in THF) was then added and the solution stirred for further 5 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 8:2) to yield the title compound (10 mg, quant.) as a colourless oil. R_f = 0.17 (hexane/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.01–5.84 (m, 2H), 5.23 (br s, 1H), 4.07–3.93 (m, 1H), 3.24–2.87 (m, 3H), 2.42–2.08 (m, 4H), 1.92–1.01 (m, 11H), 0.87 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 212.8, 139.0, 130.3, 124.6, 119.5, 71.9, 44.2, 39.0, 38.0, 37.1, 37.0, 36.9, 32.1, 26.6, 24.2, 23.3, 21.2, 14.4; IR (CCl_4): ν = 3627, 2960, 2951, 2904, 1709, 1460, 1442, 1389, 1371, 909; $[\alpha]_D^{20}$ = –4.7 (c = 0.51, EtOAc).

Example 16

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,12a*R*)-1-isopropyl-4-methyl-11-oxo-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-enyl] ester

The compound prepared in Example 15 (9 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to Mixed Anhydride (110 mg, 0.47 mmol). NEt_3 (48 mg, 0.47 mmol) and DMAP (4 mg, 0.03 mmol) were added and the solution stirred for 3 d at 40 °C. The

solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:5) to yield the title compound (7 mg, 52 %) as a colourless oil. R_f = 0.18 (hexane/EtOAc 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 15.6 Hz, 1H), 7.47 (s, 1H), 7.09 (s, 1H), 6.55 (d, J = 15.6 Hz, 1H), 5.97–5.88 (m, 2H), 5.26 (br s, 1H), 5.15 (d, J = 12.0 Hz, 1H), 3.72 (s, 3H), 3.25–3.15 (m, 1H), 3.09–2.96 (m, 2H), 2.46–2.14 (m, 4H), 1.94–1.55 (m, 7H), 1.48–1.17 (m, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H);^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 212.7, 166.6, 139.1, 139.0. 138.6, 136.0, 130.6, 124.7, 122.3, 119.2, 116.3, 73.7, 44.1, 39.1, 37.0, 36.8 (2C), 34.1, 33.5, 29.7, 26.7, 24.2, 23.1, 21.1, 14.4; IR (CCl_4): ν = 2945, 2920, 2890, 1703, 1640, 1452, 1381, 1390, 1153, 1104, 905; $[\alpha]_D^{20}$ = –15.6 (c = 0.34, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{25}H_{35}N_2O_3$: 411.2648 $[M+H]^+$; found: 411.2648.

Example 17

(1*R*,4a*R*,6*R*,12a*R*)-*tert*-Butyl-(1-isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yloxy)-diphenyl-silane

Ph_3PCH_3Br (17 mg, 0.047 mmol) was dissolved in THF (0.2 mL). n-BuLi (13 µL, 0.020 mmol, 1.6 M in *n*-hexane) was added and the solution stirred for 1 h at room temperature. The compound prepared in Example 14 (8 mg, 0.016 mmol) was added in THF (600 µL) and the solution was heated to 50 °C for 12 h. H_2O (2.0 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane) to yield the title compound (8 mg, 94 %) as a colourless oil. R_f = 0.32 (hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4H), 7.46–7.33 (m, 6H), 6.03–5.87 (m, 1H), 5.73–5.61 (m, 1H), 5.11 (br s, 1H), 4.94 (br s, 1H), 4.75 (br s, 1H), 4.04–3.93 (m, 1H), 3.08 (dd, J = 16.1, 5.9 Hz, 1H), 2.84–2.70 (m, 2H), 2.19–1.44 (m, 8H), 1.41–1.17 (m, 6H), 1.09 (s, 9H), 0.88 (d, J = 5.8 Hz, 3H), 0.75 (d, J = 5.8 Hz, 3H);^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 138.4, 135.9 (4C), 134.5 (2C), 133.8, 129.6, 129.5, 128.8, 128.6 (2C), 127.6, 127.5 (2C), 119.2, 111.1, 73.3, 39.4, 37.7, 37.3, 37.1, 36.3, 32.1, 30.7, 27.1 (3C), 26.6, 24.5, 23.1, 21.1 (2C), 19.3; IR (CCl_4): ν = 3070, 3018, 2955, 2925, 2856, 1470, 1459, 1423, 1385, 1366, 1308, 1108, 1071; $[\alpha]_D^{20}$ = +68.4 (c = 0.25, EtOAc).

Example 18

(1*R*,4a*R*,6*R*,12a*R*)-1-Isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol

The compound prepared in Example 17 (8 mg, 0.015 mmol) was dissolved in THF (1.0 mL) and TBAF (73 µL, 0.075 mmol, 1.0 M in THF) was added. The reaction mixture stirred 12 h at room temperature. Additional TBAF (73 µL, 0.075 mmol, 1.0 M in THF) was added and the reaction mixture stirred for another 12 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 9:1) to yield the title compound (4 mg, quant.) as a colourless oil. R_f = 0.28 (hexanes/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.76–5.62 (m, 2H), 5.26 (br s, 1H), 4.98 (s, 1H), 4.80 (s, 1H), 4.08–3.97 (m, 1H), 3.24–3.12 (m, 1H), 2.98–2.74 (m, 2H), 2.29–1.67 (m, 9H), 1.61–1.34 (m, 5H), 0.87 (d, J = 6.7 Hz, 4H), 0.77 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 133.8, 129.8, 127.0, 123.3, 120.0, 111.7, 72.0, 39.7, 37.7, 37.5, 36.9, 36.7, 32.2, 31.1, 26.8, 24.6, 23.6, 21.1 (2C); IR (CCl_4): ν = 3632, 3080, 3024, 2967, 2930, 1461, 1455, 1440, 1389, 1370; $[\alpha]_D^{20}$ = +36.4 (c = 0.17, EtOAc).

Example 19

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,12a*R*)-(1-isopropyl-4-methyl-11-methylene-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 18 (4 mg, 0.0091 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and added to Mixed Anhydride (51 mg, 0.137 mmol). NEt_3 (22 mg, 0.219 mmol) and DMAP (1 mg, 0.008 mmol) were added and the solution stirred for 3 d at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield the title compound (3 mg, 47 %) as a colourless oil. R_f = 0.30 (hexane/EtOAc 1:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62 (br s, 1H), 7.54 (d, J = 15.7 Hz, 1H), 7.08 (br s, 1H), 6.59 (d, J = 15.7 Hz, 1H), 5.74–5.62 (m, 2H), 5.30–5.11 (m, 2H), 5.04 (br s, 1H), 4.72 (br s, 1H), 3.73 (s, 3H), 3.25–2.73 (m, 3H), 2.34–1.55 (m, 7H), 1.44–1.21 (m, 6H), 0.87 (d, J = 6.7 Hz, 4H), 0.77 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 164.3, 148.2, 138.2, 135.4, 131.5, 131.3, 129.6, 127.6, 119.7, 113.8, 111.6, 74.7, 39.3, 37.4, 36.9, 36.2, 34.8, 33.7, 30.9, 29.7, 29.5,

26.5, 24.5, 23.4, 21.0 (2C); IR (CCl_4): ν = 3380, 3075, 2956, 2922, 2856, 1766, 1709, 1645, 1460, 1428, 1382, 1368, 1305, 1159, 1099; $[\alpha]_D^{20}$ = +6.0 (c = 0.05, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{26}H_{37}N_2O_2$: 409.2855 $[M+H]^+$; found: 409.2855.

Examples 20 and 21

(2*S*,3*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-3-methoxymethoxy-pent-4-en-2-ol (20) and (2*R*,3*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enyl}-3-methoxymethoxy-pent-4-en-2-ol (21)

Methoxymethyl allyl ether (180 mg, 1.75 mmol) in THF (4.0 mL) was cooled to –78 °C and *sec*-BuLi (1.10 mL, 1.45 mmol, 1.3 M in cyclohexane) was added. The reaction solution was stirred at –78 °C for 30 min and $^{l}Ipc_2BOMe$ (1.60 mL, 1.45 mmol, 0.93 M in THF) was then added. Stirring was maintained for 1 h, BF_3*Et_2O (263 mg, 1.86 mmol) was then added, followed by the compound prepared in example 7 (293 mg, 0.58 mmol) in THF (2.0 mL). The mixture was stirred at –78 °C for 5 h and then slowly warmed to room temperature. An aqueous NaOH solution (4.0 mL, 6.0 M) and H_2O_2 (4.0 mL, 35 %) were then added and the mixture left stirring overnight. H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3x10 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 6:1) to provide unreacted starting compound (56 mg), the title compound **20** (246 mg, 70 %) and **21** (25 mg, 7 %) as colourless oils (total yield 77 %, 84 % after recovering starting material, de 82 %, **20**:**21** 10:1). **20**: R_f = 0.43 (hexane/EtOAc 6:1); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.95–7.66 (m, 4H), 7.45–7.30 (m, 6H), 5.91–5.51 (m, 2H), 5.32–5.16 (m, 3H), 5.01–4.90 (m, 2H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 3.95 (q, *J* = 5.9 Hz, 1H), 3.79–3.72 (m, 1H), 3.58–3.47 (m, 1H), 3.38 (s, 3H), 2.35–2.14 (m, 5H), 1.93–1.14 (m, 11H), 1.05 (s, 9H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): μ = 136.4, 135.9 (4C), 135.1, 134.9, 134.7, 134.6, 129.4 (2C), 127.4 (4C), 120.9, 119.9, 117.0, 93.9, 81.9, 72.2, 71.4, 55.7, 41.3, 39.3, 37.1, 35.8, 34.3, 31.3, 27.5, 27.1 (3C), 23.9, 22.9, 21.2, 19.3, 19.2; IR (CCl_4): ν = 3590, 3078, 2955, 2893, 2860, 1473, 1462, 1430, 1390, 1369, 1152, 1108, 935, 915; $[\alpha]_D^{20}$ = +43.8 (c = 0.90, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{38}H_{56}NaO_4Si$: 627.3845 $[M+Na]^+$; found: 627.3828; **21**: R_f = 0.37 (hexane/EtOAc 6:1); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.60 (m, 4H), 7.47–7.30 (m,

6H), 5.96–5.77 (m, 1H), 5.65–5.49 (m, 1H), 5.38–5.21 (m, 2H), 5.16 (br s, 1H), 5.07–4.92 (m, 2H), 4.73 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 6.7 Hz, 1H), 3.98–3.83 (m, 1H), 3.81–3.69 (m, 1H), 3.65–3.50 (m, 1H), 3.39 (s, 3H), 2.46–1.95 (m, 4H), 1.90–0.98 (m, 20H), 0.90–0.87 (m, 1H), 0.83 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 137.3, 135.9 (4C), 135.1, 134.8, 134.7 (2C), 129.4 (2C), 127.4 (4C), 121.9, 120.2, 117.0, 93.7, 82.4, 72.1, 70.3, 55.8, 40.8, 37.5, 37.1, 35.8, 35.4, 31.3, 29.7, 27.0 (3C), 26.8, 24.3, 23.9, 21.1, 19.3; IR (CCl_4): ν = 3600, 3080, 2960, 2938, 2899, 2862, 1475, 1432, 1391, 1372, 1158, 1108, 912; $[\alpha]_D^{20}$ = +48.1 (c = 1.09, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{38}H_{56}NaO_4Si$: 627.3846 $[M+Na]^+$; found: 627.3860.

Example 22

2,2-Dimethyl-propionic acid {(1*S*,2*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-methoxymethoxy-but-3-enyl} ester.

The compound prepared in Example 20 (173 mg, 0.29 mmol) was dissolved in pyridine (2.0 mL). DMAP (4 mg, 0.03 mmol) and PivCl (172 mg, 1.43 mmol) were added. The mixture stirred at room temperature for 72 h. EtOAc (10 mL) were added, the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2x10 mL), the combined aqueous layers were back extracted with EtOAc (3x10 mL) and the combined organic layers were dried over Na_2SO_4 The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (158 mg, 80 %) as a colourless oil. R_f = 0.52 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 4H), 7.45–7.28 (m, 6H), 5.85–5.59 (m, 2H), 5.29–5.17 (m, 3H), 5.03–4.90 (m, 3H), 4.65 (d, J = 6.3 Hz, 1H), 4.56 (d, J = 6.3 Hz, 1H), 4.09–3.87 (m, 2H), 3.35 (s, 3H), 2.30–2.12 (m, 3H), 1.85 (br s, 1H), 1.72–1.22 (m, 11H), 1.18 (s, 9H), 1.04 (s, 9H), 0.82 (d, J = 6.3 Hz, 3H), 0.72 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 177.6, 135.9 (4C), 135.3, 134.8, 134.6 (2C), 134.1, 129.5 (2C), 127.5 (4C), 121.0, 119.0, 117.2, 94.4, 77.8, 72.2, 71.7, 55.6, 41.4, 39.4, 36.8, 34.8, 32.7, 27.4, 27.3 (3C), 27.2, 27.0 (3C), 23.6, 22.5, 21.0, 20.6, 19.3 (2C); IR (CCl_4): ν = 3061, 2942, 2920, 2882, 2842, 1722, 1455, 1467, 1458, 1423, 1392, 1385, 1362, 1150, 1107, 1098, 909; $[\alpha]_D^{20}$ = +25.5 (c = 0.78, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{43}H_{64}NaO_5Si$: 711.4420 $[M+Na]^+$; found: 711.4412.

Example 23

2,2-Dimethyl-propionic acid {(1*S*,2*S*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanoxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-hydroxy-but-3-enyl} ester.

The compound prepared in Example 22 (10 mg, 0.015 mmol) was dissolved in CH_2Cl_2 (0.3 mL) and cooled to –78 °C. PhSH (2 mg, 0.015 mmol) and BF_3*Et_2O (4 mg, 0.029 mmol) were added and the solution was allowed to warm to –10 °C and stirred at –10 °C for 2 h. Then a saturated aqueous $NaHCO_3$ solution (2 mL) was added and the solution was warmed up to room temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 8:2) to provide the title compound (6 mg, 64 %) as a colourless oil. R_f = 0.54 (hexane/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 4H), 7.41–7.31 (m, 6H), 5.89–5.72 (m, 2H), 5.34 (br s, 1H), 5.25–5.14 (m, 2H), 5.03–4.91 (m, 3H), 4.08 (br s, 1H), 3.93–3.87 (m, 1H), 2.27–2.16 (m, 3H), 2.01–1.22 (m, 14H), 1.18 (s, 9H), 1.04 (s, 9H), 0.93–0.88 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 176.1, 137.1 (2C), 136.4, 135.9 (2C), 135.0 (2C), 134.7, 129.5 (2C), 127.4 (4C), 121.0, 117.2, 116.4, 74.4, 73.4, 72.3, 41.4, 39.2, 36.7, 35.0, 33.3, 28.0, 27.5, 27.3 (3C), 27.0 (3C), 23.8, 22.6, 20.9 (2C), 20.0, 19.3 (2C); IR (CCl_4): ν = 3618, 3582, 3060, 2942, 2918, 2842, 1724, 1472, 1465, 1458, 1421, 1382, 1363, 1149, 1101, 1060, 908; $[\alpha]_D^{20}$ = +6.1 (c = 0.56, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{41}H_{62}NaO_4Si$: 669.4315 $[M+Na]^+$; found: 669.4299.

Example 24

2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanoxy)-7-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 23 (33 mg, 0.05 mmol) was dissolved in degassed CH_2Cl_2 (5.1 mL). Grubbs-II (2 mg, 2.5 µmol) in degassed CH_2Cl_2 (0.5 mL) was slowly added. The reaction mixture stirred for 2 d at room temperature. Additional Grubbs-II (1 mg, 1.3 µmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 2 d at room temperature. Additional Grubbs-II (1 mg, 1.3 µmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 1 d at room

temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 8:2) to provide the title compound (23 mg, 73 %) as a colourless oil. R_f = 0.44 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.65 (m, 4H), 7.47–7.35 (m, 6H), 5.99 (dt, J = 11.5, 5.2 Hz, 1H), 5.58 (t, J = 10.5 Hz, 1H), 5.14 (br s, 1H), 5.05–4.96 (m, 1H), 4.77 (t, J = 9.9 Hz, 1H), 4.23–4.16 (m, 1H), 2.65–2.57 (m, 1H), 2.32–2.27 (m, 1H), 1.89–1.54 (m, 9H), 1.40–1.05 (m, 23H), 0.84 (d, J = 6.8 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 178.1, 137.1, 135.8 (4C), 135.4, 134.8, 134.5 (2C), 129.4 (2C), 127.4 (4C), 121.0, 117.2, 116.4, 74.4, 73.3, 72.2, 41.3, 39.2, 36.6, 34.6, 33.1, 27.7, 27.3 (3C), 26.9 (3C), 23.6, 22.6, 20.9 (2C), 20.0; IR (CCl_4): ν = 3630, 2958, 2925, 2852, 1730, 1425, 1367, 1155, 1112, 908; $[\alpha]_D^{20}$ = +17.5 (c = 0.60, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{39}H_{56}NaO_4Si$: 639.3846 $[M+Na]^+$; found: 639.3855.

Example 25

2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 24 (14 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.2 mL). 2,6-Di-*tert*-butyl-pyridine (44 mg, 0.23 mmol) and MeOTf (19 mg, 0.12 mmol) were added and the solution stirred for 18 h at 40 °C. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (14 mg, 96 %) as a colourless oil. R_f = 0.28 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74–7.60 (m, 4H), 7.54–7.27 (m, 6H), 6.08 (dt, J = 11.4, 5.3 Hz, 1H), 5.40 (t, J = 10.7 Hz, 1H), 5.16–5.01 (m, 2H), 4.29–4.08 (m, 2H), 3.18 (s, 3H), 2.68–2.49 (m, 1H), 2.35–2.17 (m, 1H), 2.09–0.84 (m, 31H), 0.80 (d, J = 6.8 Hz, 3H), 0.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 177.7, 138.6, 135.8 (4C), 134.3 (2C), 130.9, 129.6 (2C), 129.2, 127.6 (4C), 120.5, 78.8, 74.8, 72.2, 56.2, 37.6, 37.1, 36.4, 35.3, 32.6, 29.7, 27.2 (3C), 27.0 (3C), 26.9, 26.7, 24.3, 24.1, 21.0 (2C), 19.2; IR (CCl_4): ν = 2948, 2920, 2848, 1723, 1475, 1422, 1385, 1363, 1279, 1155, 1099, 1059; $[\alpha]_D^{20}$ = +7.8 (c = 0.77, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{40}H_{58}NaO_4Si$: 653.4002 $[M+Na]^+$; found: 653.3986.

Example 26

2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-hydroxy-4-isopropyl-7-methoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

The compound prepared in Example 25 (14 mg, 0.022 mmol) was dissolved in THF (0.50 mL) and TBAF (0.044 mL, 0.044 mmol, 1.0 M in THF) was added. The reaction mixture stirred 14 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield the title compound (8 mg, 89 %) as a colourless oil. R_f = 0.11 (hexanes/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (dt, J = 11.6, 5.4 Hz, 1H), 5.44 (t, J = 10.8 Hz, 1H), 5.32 (br s, 1H), 5.12–5.08 (m, 1H), 4.34–4.23 (m, 2H), 3.26 (s, 3H), 2.80–2.74 (m, 1H), 2.48–2.2.31 (m, 1H), 2.25–1.12 (m, 20H), 1.05–0.89 (m, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 177.6, 137.5, 130.0, 129.5, 121.0, 78.3, 74.7, 70.7, 56.2, 37.8, 37.3, 36.9, 36.6, 35.3, 32.4, 29.6, 27.2 (3C), 26.9, 26.7, 24.4, 21.0 (2C); IR (CCl_4): ν = 3620, 2954, 2923, 2864, 1728, 1478, 1451, 1395, 1386, 1367, 1280, 1160, 1099, 905; $[\alpha]_D^{20}$ = –8.4 (c = 0.37, EtOAc).

Example 27

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-methoxy-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 26 (6 mg, 0.0153 mmol) was dissolved in CH_2Cl_2 (1.8 mL) and added to Mixed Anhydride (76 mg, 0.325 mmol). NEt_3 (33 mg, 0.325 mmol) and DMAP (2 mg, 0.0153 mmol) were added and the solution stirred for 15 d at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:5) to yield the title compound (6 mg, 66 %) as a colourless oil. R_f = 0.22 (hexane/EtOAc 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 15.6 Hz, 1H), 7.48 (s, 1H), 7.10 (s, 1H), 6.53 (d, J = 15.6 Hz, 1H), 5.96–5.89 (m, 1H), 5.52–5.38 (m, 2H), 5.32 (br s, 1H), 5.12 (d, J = 7.3 Hz, 1H), 4.27 (t, J = 9.9 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 2.88–2.76 (m, 1H), 2.54–2.46 (m, 1H), 2.13–1.14 (m, 24H), 0.99–0.87 (m, 2H), 0.85 (d, J = 5.1 Hz, 3H), 0.65 (d, J = 5.1 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 177.7, 166.6, 139.2, 138.5, 136.1, 135.7, 130.3, 129.6, 122.3,

121.1, 116.3, 79.7, 74.7, 72.9, 56.7, 37.4 (2C), 35.3, 33.5, 33.2, 30.7, 29.6, 29.3, 27.2 (3C), 26.9, 26.6, 24.3, 24.4, 21.0 (2C); IR (CCl_4): ν = 2960, 2931, 2889, 2861, 1731, 1712, 1645, 1481, 1460, 1389, 1300, 1157, 1103; $[\alpha]_D^{20}$ = –17.0 (c = 0.33, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{32}H_{50}NaN_2O_5$: 565.3617 $[M+Na]^+$; found: 565.3611.

Example 28

2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-7-acetoxy-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 24 (16 mg, 0.026 mmol) was dissolved in pyridine (0.5 mL). Ac_2O (5 mg, 0.052 mmol) and DMAP (cat.) were added and the reaction mixture stirred for 24 h at room temperature. EtOAc (5 mL) was added and the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2x5 mL), the aqueous layer was back extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (12 mg, 71 %) as a colourless oil. R_f = 0.69 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69–7.61 (m, 4H), 7.46–7.30 (m, 6H), 6.11–5.87 (m, 2H), 5.45 (t, *J* = 10.7 Hz, 1H), 5.22–5.10 (m, 2H), 4.24–4.18 (m, 1H), 2.88–2.74 (m, 1H), 2.32–2.25 (m, 1H), 2.12–1.95 (m, 4H), 1.84–0.89 (m, 30H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.57 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 177.5, 170.0, 138.8, 135.7 (4C), 134.1 (2C), 132.1, 129.6, 129.5, 127.6 (2C), 127.5 (2C), 126.5, 120.3, 73.6, 72.0, 71.5, 37.7, 37.3, 36.4, 35.3, 32.9, 29.6, 27.04 (7C), 26.5, 24.3, 24.0 (2C), 21.0, 19.2, 14.5; IR (CCl_4): ν = 3078, 2959, 2938, 2860, 1739, 1732, 1482, 1460, 1430, 1371, 1155, 1112, 1070; $[\alpha]_D^{20}$ = +0.6 (c = 0.51, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{41}H_{58}NaO_5Si$: 681.3951 $[M+Na]^+$; found: 681.3967.

Example 29

2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-7-acetoxy-11-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

The compound prepared in Example 28 (11 mg, 0.0167 mmol) was dissolved in THF (0.30 mL) and TBAF (0.033 mL, 0.0334 mmol, 1.0 M in THF) was added. The reaction mixture stirred 20 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was

evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 8:2) to yield the title compound (7 mg, 92 %) as a colourless oil. R_f = 0.15 (hexanes/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.01 (t, J = 10.3 Hz, 1H), 5.91 (dt, J = 11.4, 5.4 Hz, 1H), 5.47 (t, J = 10.7 Hz, 1H), 5.29 (br s, 1H), 5.19 (dd, J = 10.1, 6.9 Hz, 1H), 4.46–4.24 (m, 1H), 3.08–2.91 (m, 1H), 2.44–2.33 (m, 1H), 2.18–1.22 (m, 17H), 1.18 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.61 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 177.4, 171.1, 138.8, 130.9, 127.3, 120.9, 73.5, 71.3, 70.5, 37.9, 37.4, 36.6, 35.3, 32.7, 29.7, 27.1 (3C), 26.9, 26.4, 24.4, 21.0 (2C), 14.5; IR (CCl_4): ν = 3622, 2957, 2935, 2870, 1745, 1730, 1479, 1452, 1395, 1388, 1369, 1280, 1155; $[\alpha]_D^{20}$ = –33.5 (c = 0.39, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{25}H_{40}NaO_5$: 443.2773 $[M+Na]^+$; found: 443.2761.

Example 30

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-10-acetoxy-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester

The compound prepared in Example 29 (6 mg, 0.014 mmol) was dissolved in CH_2Cl_2 (1.6 mL) and added to Mixed Anhydride (50 mg, 0.21 mmol). NEt_3 (21 mg, 0.21 mmol) and DMAP (2 mg, 0.014 mmol) were added and the solution stirred for 2 d at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield the title compound (6 mg, 80 %) as a colourless oil. R_f = 0.20 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1H), 7.54 (d, J = 15.7 Hz, 1H), 7.11 (s, 1H), 6.59 (d, J = 15.7 Hz, 1H), 6.04 (t, J 10.4 Hz, 1H), 5.89 (dt, J = 11.6, 5.6 Hz, 1H), 5.55–5.45 (m, 2H), 5.32 (s, 1H), 5.23 (dd, J = 10.1, 6.8 Hz, 1H), 3.75 (s, 3H), 3.13–3.03 (m, 1H), 2.54–2.48 (m, 1H), 2.22–1.17 (m, 25H), 0.85 (d, J = 6.9 Hz, 3H), 0.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 177.6, 170.1, 166.7, 138.6, 138.4, 136.1, 130.9, 127.5 (2C), 122.3, 120.9, 116.3, 73.4, 72.8, 71.1, 37.5, 36.5, 35.3, 33.7, 33.5, 30.0, 29.7, 27.2 (3C), 26.8, 26.3, 24.5, 21.0 (3C), 14.5; IR (CCl_4): ν = 2961, 2935, 1742, 1733, 1712, 1648, 1390, 1371, 1155; $[\alpha]_D^{20}$ = –39.6 (c = 0.24, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{32}H_{47}N_2O_6$: 555.3434 $[M+H]^+$; found: 555.3425.

Example 31

2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-4-isopropyl-1-methyl-7-[(2'*)-tetrahydro-pyran-2'-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester.

The compound prepared in Example 24 (29 mg, 0.047 mmol) was dissolved in CH_2Cl_2 (0.4 mL). Dihydropyran (6 mg, 0.071 mmol) and PPTS (1 mg, 0.005 mmol) were added and the solution stirred for 11 h at room temperature. *i*-Pr_2O (5 mL) was added, the organic layer was washed with a semisaturated NaCl solution (2x5 mL) and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 14:1) to yield the title compound (25 mg, 77 %) as a colourless oil. R_f = 0.33 (hexane/EtOAc 14:1); ^{1}H NMR (250 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 7.68–7.61 (m, 4H), 7.38–7.28 (m, 6H), 6.08+5.93 (dt, J = 11.6, 5.5 Hz, 1H), 5.59+5.32 (t, J = 10.4 Hz, 1H), 5.18–5.01 (m, 2H), 4.88–4.61 (m, 2H), 4.23–4.10 (m, 1H), 3.94–3.72 (m, 1H), 3.51–3.33 (m, 1H), 2.76–2.57 (m, 1H), 2.35–2.17 (m, 1H), 2.13–1.95 (m, 1H), 1.91–0.95 (m, 36H), 0.80 (d, J = 5.8 Hz, 3H), 0.61–0.55 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 177.6+177.4, 138.9+138.8, 135.7 (4C), 134.4+134.2 (2C), 132.0, 130.0+129.5 (2C), 128.4, 127.9+127.5+127.4 (4C), 120.2, 99.2+93.0, 76.5, 74.9+74.6, 72.1+70.5, 61.5+60.4, 37.7, 37.3, 36.5, 35.4, 32.6, 30.4+30.1, 29.6, 27.3 (3C), 27.0+26.6 (3C), 26.3, 25.4, 24.3, 23.9, 21.0 (2C), 19.2, 16.7+16.3, 14.6; IR (CCl_4): ν = 3062, 2945, 2918, 2844, 1722, 1474, 1465, 1448, 1422, 1381, 1362, 1151, 1107, 1059, 902; $[\alpha]_D^{20}$ = –7.2 (c = 1.16, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{44}H_{64}NaO_5Si$: 723.4421 $[M+Na]^+$; found: 723.4416.

Example 32

2,2-Dimethyl-propionic acid {(4*R*,4a*R*,6*S*,7*S*,11*R*,12a*R*)-11-hydroxy-4-isopropyl-1-methyl-[(2'*)-7-(tetrahydro-pyran-2'-yloxy)]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester.

The compound prepared in Example 31 (23 mg, 0.033 mmol) was dissolved in THF (2.0 mL) and TBAF (165 µL, 0.165 mmol, 1.0 M in THF) was added. The reaction mixture stirred 20 h at room temperature. An aqueous phosphate buffer solution (1.0 mL, pH = 7) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was

evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 4:1) to yield the title compund (15 mg, quant.) as a colourless oil. R_f = 0.10 (hexanes/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 5.97+5.78 (dt, J = 9.3, 5.8 Hz, 1H), 5.60+5.35 (t, J = 10.3 Hz, 1H), 5.29–5.01 (m, 2H), 4.93–4.65 (m, 2H), 4.39–4.15 (m, 1H), 4.02–3.73 (m, 1H), 3.55–3.33 (m, 1H), 2.93–2.71 (m, 1H), 2.40–2.22 (m, 1H), 2.17–1.09 (m, 29H), 0.82 (d, J = 6.7 Hz, 3H), 0.62+0.59 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 177.5, 133.8, 129.2, 126.6, 120.9+120.8, 99.3+93.1, 76.5, 74.9+74.7, 70.7+70.4, 61.5+60.6, 37.9+37.8, 37.4, 36.6, 35.5, 32.4, 30.4+30.2, 27.4, 27.3 (3C), 27.2, 26.9, 26.7+26.3, 25.5+25.4, 24.5, 21.1 (2C), 18.7+18.4; IR (CCl_4): ν = 3620, 3440, 2950, 2865, 1723, 1477, 1451, 1392, 1385, 1365, 1279, 1155, 1110, 1072, 1050, 905; $[\alpha]_D^{20}$ = – 36.1 (c = 0.75, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{28}H_{46}NaO_5$: 485.3243 $[M+Na]^+$; found: 485.3238.

Example 33

3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid {(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-4-methyl-10-[(2'*)-(tetrahydro-pyran-2-yloxy)]-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl} ester.

The compound prepared in Example 32 (15 mg, 0.032 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and added to Mixed Anhydride (118 mg, 0.494 mmol). NEt_3 (50 mg, 0.494 mmol) and DMAP (4 mg, 0.032 mmol) were added and the solution stirred for 3 d at room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 1:4) to yield the title compound (12 mg, 61 %) as a colourless oil. R_f = 0.15 (hexane/EtOAc 1:4); ^{1}H NMR (400 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 7.62 (s, 1H), 7.57+7.53 (d, J = 15.7 Hz, 1H), 7.10 (s, 1H), 6.56 (d, J = 15.7 Hz, 1H), 5.94+5.75 (dt, J = 9.1, 6.2 Hz, 1H), 5.65 (t, J = 10.4 Hz, 1H), 5.45–5.37 (m, 2H), 5.30 (s, 1H), 5.23–5.08 (m, 1H), 4.92+4.78 (t, J = 10.2 Hz, 1H), 4.90–4.85+4.68–4.65 (m, 1H), 3.99–3.92+3.84–3.77 (m, 1H), 3.74 (s, 3H), 3.57–3.47+3.45–3.38 (m, 1H), 2.97–2.83 (m, 1H), 2.48–2.41 (m, 1H), 2.17–1.38 (m, 15H), 1.33–1.18 (m, 12H), 0.84 (d, J = 6.8 Hz, 3H), 0.67–0.61 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, signal doubling due to diastereomers): δ = 177.2, 166.5, 137.9, 135.2, 130.9+130.8, 129.4, 126.7, 122.1, 120.8, 117.0, 99.3+93.3, 74.7+74.5, 73.1, 70.2, 61.5+60.8, 37.4, 36.6, 35.4, 33.7, 30.3, 29.6, 27.3 (3C), 27.0, 26.8, 26.5, 26.2, 25.4, 24.5,

24.3, 21.0 (2C), 19.0+18.7, 14.6; IR (CCl_4): ν = 2959, 2877, 1725, 1709, 1645, 1481, 1452, 1385, 1398, 1156, 1113, 909; $[\alpha]_D^{20}$ = –44.4 (c = 0.59, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{32}H_{53}N_2O_6$: 597.3904 $[M+H]^+$; found: 597.3900.

Example 34

3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10*S*,11*S*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-10-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

The compound prepared in Example 33 (13 mg, 0.022 mmol) was dissolved in EtOH (2.0 mL, 80 %). PTSA (0.8 mg, 0.0044 mmol) were added and the solution stirred for 72 h at room temperature. EtOAc (5 mL) was added, the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2x5 mL), with a saturated aqueous NaCl solution (5 mL) and then the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (EtOAc) to yield the title compound (7 mg, 82 %) as a colourless oil. R_f = 0.16 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.09 (s, 1H), 6.58 (d, J = 5.2 Hz, 1H), 5.77 (dt, J = 11.5, 5.3 Hz, 1H), 5.60 (t, J = 10.5 Hz, 1H), 5.43–5.37 (m, 1H), 5.29 (s, 1H), 5.11–5.00 (m, 1H), 4.84 (t, J = 9.8 Hz, 1H), 3.74 (s, 3H), 2.87–2.78 (m, 1H), 2.51–1.71 (m, 11H), 1.62–1.36 (m, 3H), 1.35–1.15 (m, 10H), 0.84 (d, J = 6.8 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 178.5, 166.5, 138.9, 137.7, 135.1, 131.4, 128.2, 122.4, 121.1, 117.2, 77.7, 73.1, 70.4, 69.5, 37.4, 33.9, 33.1, 30.1, 29.7, 27.3 (3C), 27.2, 26.9, 26.8, 24.4, 24.3, 21.0 (2C), 19.1; IR (CCl_4): ν = 3620, 3240, 2957, 2922, 2865, 1709, 1643, 1478, 1455, 1385, 1367, 1322, 1297, 1155, 1109, 1043, 908; $[\alpha]_D^{20}$ = –45.0 (c = 0.28, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{30}H_{45}N_2O_5$: 513.3329 $[M+H]^+$; found: 513.3321.

Example 35

2,2-Dimethyl-propionic acid {(1*R*,2*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-methoxymethoxy-but-3-enyl} ester.

The compound prepared in Example 21 (26 mg, 0.043 mmol) was dissolved in pyridine (1.0 mL). DMAP (1 mg, 0.004 mmol) and PivCl (26 mg, 0.215 mmol) were added. The mixture stirred at room temperature for 72 h. EtOAc (5 mL) were added, the organic layer was washed with a saturated aqueous $KHSO_4$ solution (2x5 mL), the combined aqueous

layers were back extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4 The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (27 mg, 91 %) as a colourless oil. R_f = 0.71 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67–7.59 (m, 4H), 7.42–7.28 (m, 6H), 6.03–5.91 (m, 1H), 5.87–5.76 (m, 1H), 5.31–4.95 (m, 6H), 4.63 (d, J = 6.7 Hz, 1H), 4.55 (d, J = 6.7 Hz, 1H), 4.04–3.89 (m, 2H), 3.35 (s, 3H), 2.23–2.15 (m, 3H), 1.96–1.91 (m, 2H), 1.87–0.80 (m, 28H), 0.75 (d, J = 6.7 Hz, 3H), 0.62 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.7, 137.4, 135.9 (4C), 135.1, 134.9, 134.6, 134.3, 129.4, 129.3, 127.4 (2C), 127.3 (2C), 121.8, 119.2, 117.2, 94.3, 78.5, 71.8, 71.5, 55.7, 40.3, 37.2, 37.0, 35.8, 35.6, 29.7, 28.8, 27.3 (3C), 27.1 (4C), 24.3, 23.8, 21.0 (2C), 19.3; IR (CCl_4): ν = 2935, 2905, 2867, 2830, 1728, 1431, 1372, 1159, 1107, 910; $[\alpha]_D^{20}$ = +52.7 (c = 0.77, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{43}H_{64}NaO_5Si$: 711.4421 $[M+Na]^+$; found: 711.4406.

Example 36

2,2-Dimethyl-propionic acid {(1*R*,2*R*)-1-{(1*R*,2*R*,6*R*)-2-[(2*R*)-2-(*tert*-butyl-diphenyl-silanoxy)-pent-4-enyl]-6-isopropyl-3-methyl-cyclohex-3-enylmethyl}-2-hydroxy-but-3-enyl} ester.

The compound prepared in Example 35 (32 mg, 0.046 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to –78 °C. PhSH (10 mg, 0.093 mmol) and BF_3*Et_2O (13 mg, 0.093 mmol) were added and the solution was allowed to warm to –10 °C over 3 h and stirred at –10 °C for 2 h. PhSH (5 mg, 0.046 mmol) and BF_3*Et_2O (7 mg, 0.046 mmol) were added again and the solution stirred at –10 °C for another 1 h. Then a saturated aqueous $NaHCO_3$ solution (1 mL) was added and the solution was warmed up to room temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3x5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide the title compound (19 mg, 63 %) as a colourless oil. R_f = 0.40 (hexane/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74–7.63 (m, 4H), 7.48–7.28 (m, 6H), 6.05–5.68 (m, 2H), 5.36–4.88 (m, 6H), 4.08–3.89 (m, 2H), 2.41–2.18 (m, 2H), 2.09–1.95 (m, 1H), 1.84–0.82 (m, 31H), 0.78 (d, J = 6.7 Hz, 3H), 0.66 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 178.3, 137.3, 137.1, 135.9 (4C), 135.1, 134.6 (2C), 129.5 (2C), 127.4 (4C), 121.7, 117.3, 116.3, 74.3, 73.1, 71.6, 40.5, 37.4, 36.7, 35.6, 35.3,

29.7, 28.7, 27.2 (3C), 27.1 (4C), 24.0, 23.7, 21.0 (2C), 19.3; IR (CCl_4): ν = 3580, 3066, 2951, 2922, 2850, 1724, 1425, 1384, 1365, 1152, 1107, 905; $[\alpha]_D^{20}$ = +70.7 (c = 0.81, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{41}H_{60}NaO_4Si$: 667.4159 $[M+Na]^+$; found: 667.4128.

Example 37

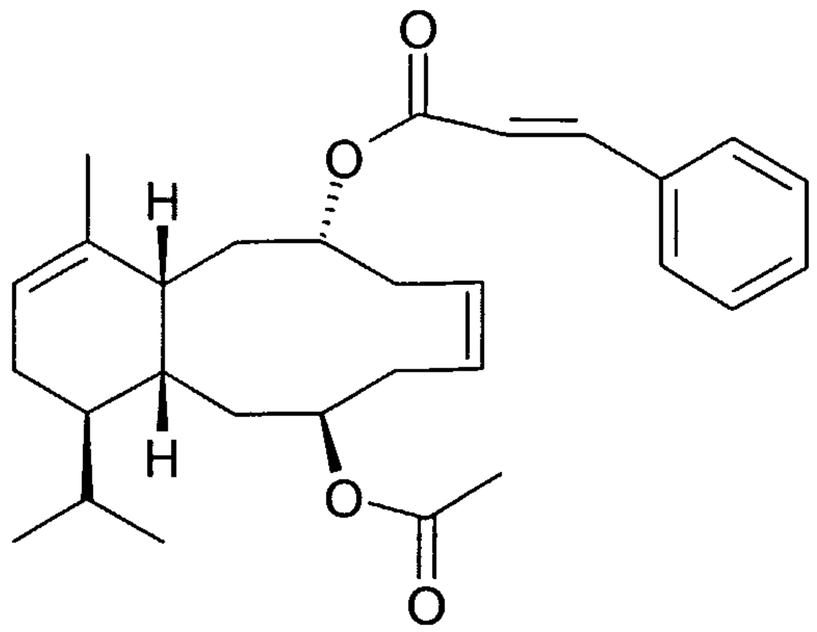
2,2-Dimethyl-propionic acid [(4*R*,4a*R*,6*R*,7*R*,11*R*,12a*R*)-11-(*tert*-butyl-diphenyl-silanoxy)-7-hydroxy-4-isopropyl-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

The compound prepared in Example 36 (18 mg, 0.028 mmol) was dissolved in degassed CH_2Cl_2 (2.3 mL). Grubbs-II (1 mg, 1.4 µmol) in degassed CH_2Cl_2 (0.5 mL) was slowly added. The reaction mixture stirred for 2 d at room temperature. Additional Grubbs-II (1 mg, 1.4 µmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 3 d at room temperature. Additional Grubbs-II (1 mg, 1.3 µmol) in degassed CH_2Cl_2 (0.2 mL) was slowly added and the mixture stirred for further 1 d at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 9:1) to provide unreacted starting compound (4 mg) and the title compound (10 mg, 55 %, 66 % after recovered starting material) as a colourless oils. R_f = 0.20 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 4H), 7.44–7.32 (m, 6H), 6.10–5.91 (m, 2H), 5.75–5.70 (m, 1H), 5.55–5.49 (m, 1H), 5.14–5.05 (m, 2H), 4.40–4.36 (m, 1H), 4.30–3.80 (m, 4H), 2.81–2.73 (m, 1H), 2.38–2.25 (m, 2H), 2.15–2.10 (m, 1H), 1.82–1.10 (m, 16H), 1.06 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$): δ = 173.9, 136.3, 135.9 (2C), 135.8 (2C), 133.9 (2C), 130.3, 129.8, 129.7, 127.7, 127.6 (2C), 127.5 (2C), 119.3, 75.3, 73.1, 72.3, 37.2, 36.5, 35.1, 34.7, 30.5, 27.7, 27.2 (3C), 27.0 (3C), 26.4, 24.4, 22.7, 21.0 (2C), 20.8, 19.2; IR (CCl_4): ν = 3618, 3070, 2955, 2923, 2850, 1725, 1477, 1459, 1425, 1384, 1365, 1155, 1100, 1080; $[\alpha]_D^{20}$ = +4.0 (c = 0.35, EtOAc); HRMS (ESI): *m/z*: calcd for $C_{39}H_{56}NaO_4Si$: 639.3846 $[M+Na]^+$; found: 639.3860.

Example 38

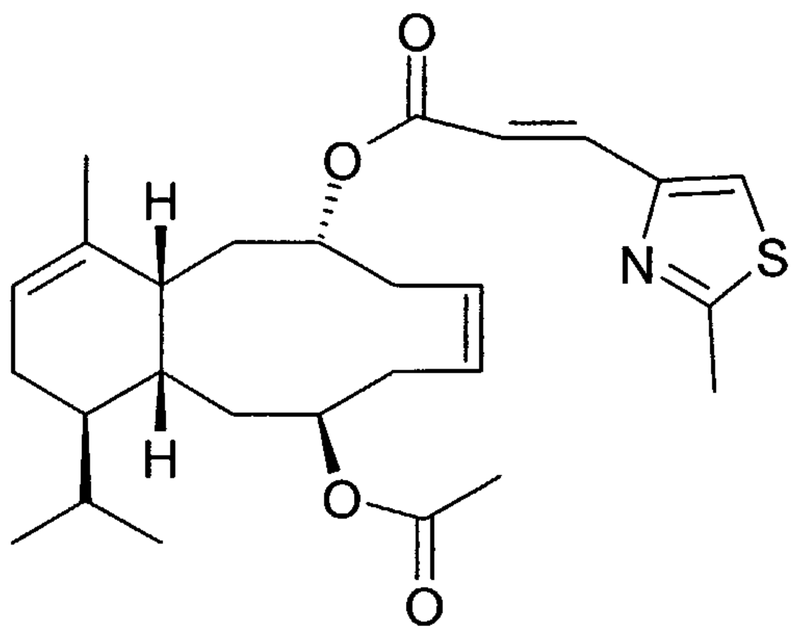
Operating as described in the previous examples, the following compounds are prepared:

AA 3-Phenyl-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



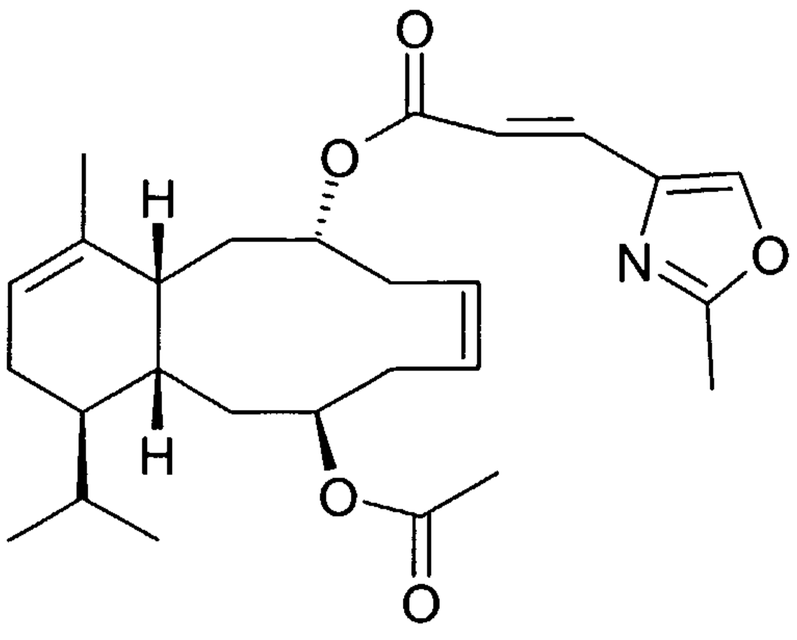
$C_{29}H_{38}O_4$
Exact Mass: 450,2770
Mol. Wt.: 450,6096
C, 77,30; H, 8,50; O, 14,20

AB 3-(2-Methyl-thiazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



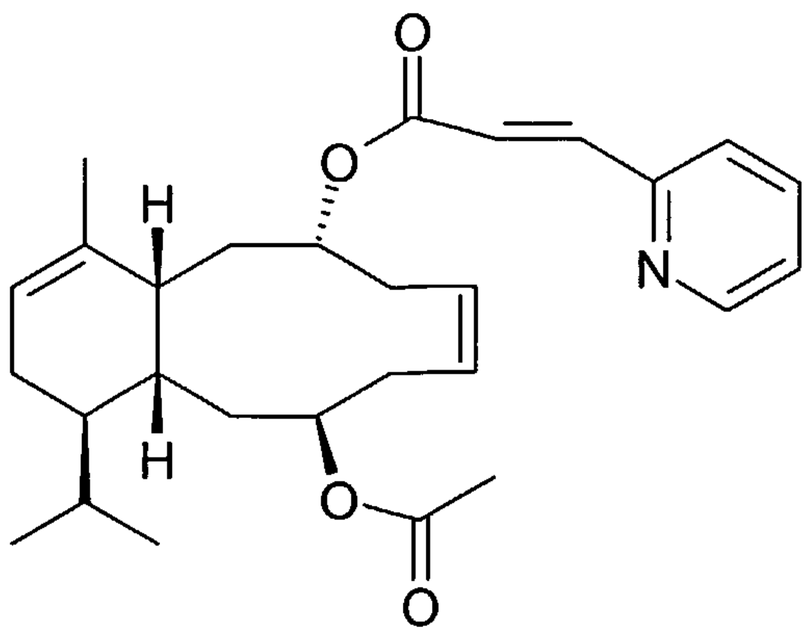
$C_{27}H_{37}NO_4S$
Exact Mass: 471,2443
Mol. Wt.: 471,6530
C, 68,76; H, 7,91; N, 2,97; O, 13,57; S, 6,80

AC 3-(2-Methyl-oxazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



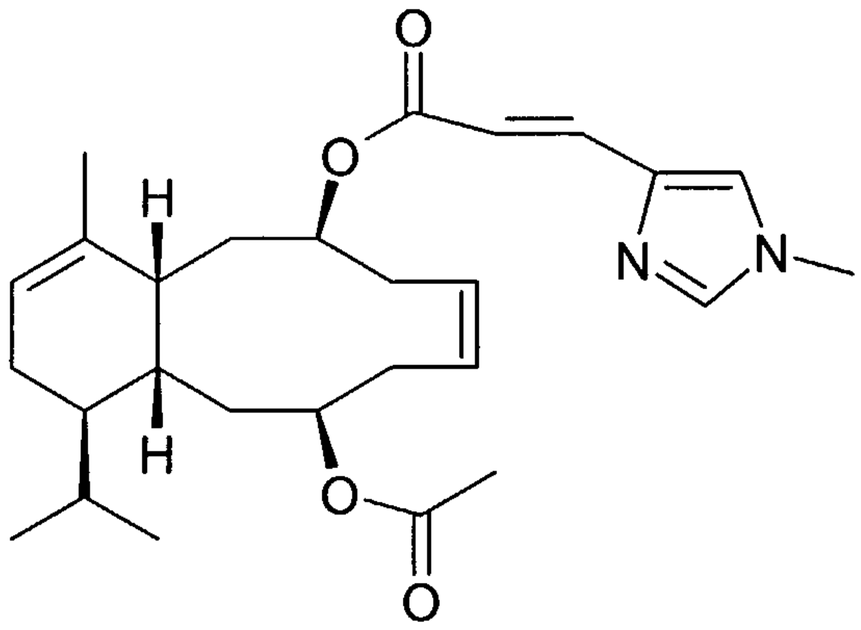
$C_{27}H_{37}NO_5$
Exact Mass: 455,2672
Mol. Wt.: 455,5864
C, 71,18; H, 8,19; N, 3,07; O, 17,56

AD 3-Pyridin-2-yl-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



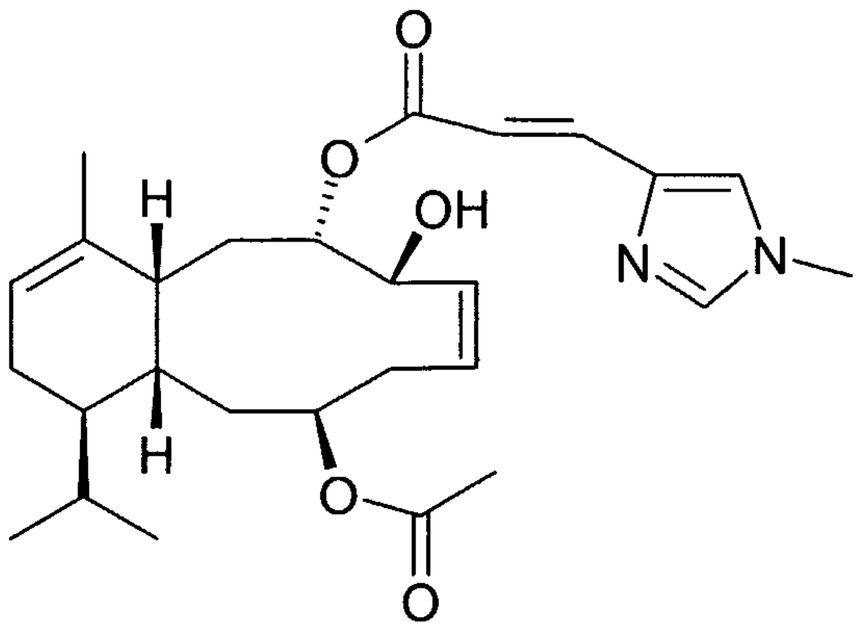
$C_{28}H_{37}NO_4$
Exact Mass: 451,2723
Mol. Wt.: 451,5977
C, 74,47; H, 8,26; N, 3,10; O, 14,17

AE 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



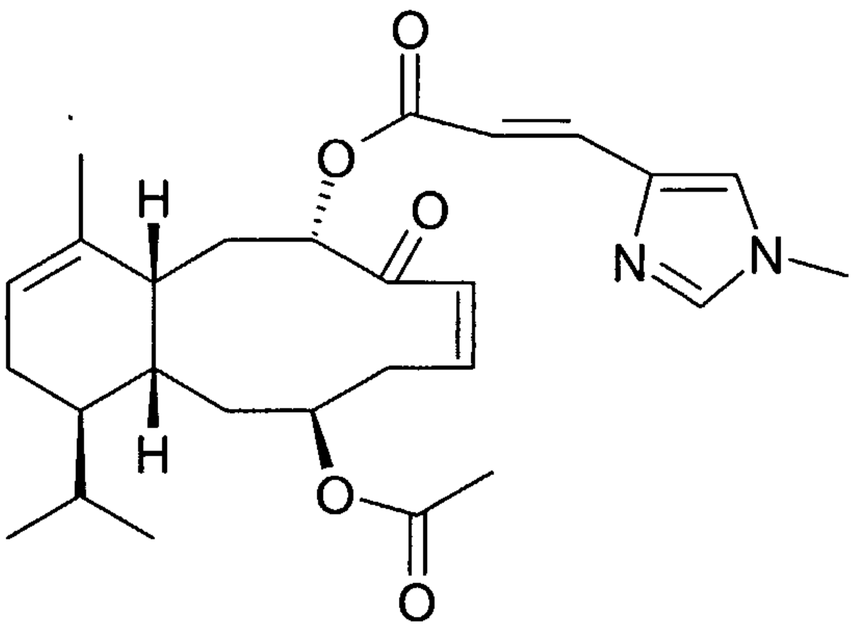
$C_{27}H_{38}N_2O_4$
Exact Mass: 454,2832
Mol. Wt.: 454,6017
C, 71,33; H, 8,43; N, 6,16; O, 14,08

AF 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-7-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



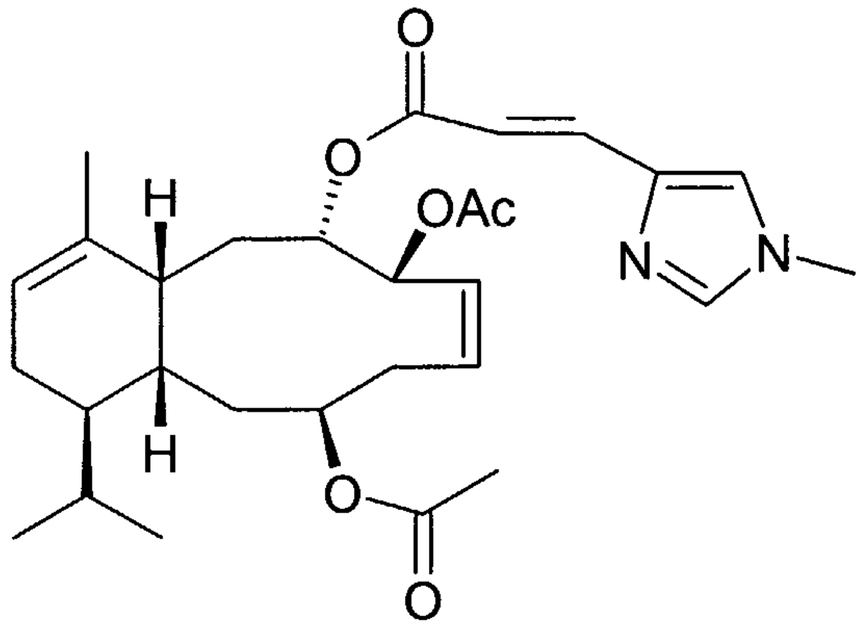
$C_{27}H_{38}N_2O_5$
Exact Mass: 470,2781
Mol. Wt.: 470,6011
C, 68,91; H, 8,14; N, 5,95; O, 17,00

AG 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-7-oxo-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



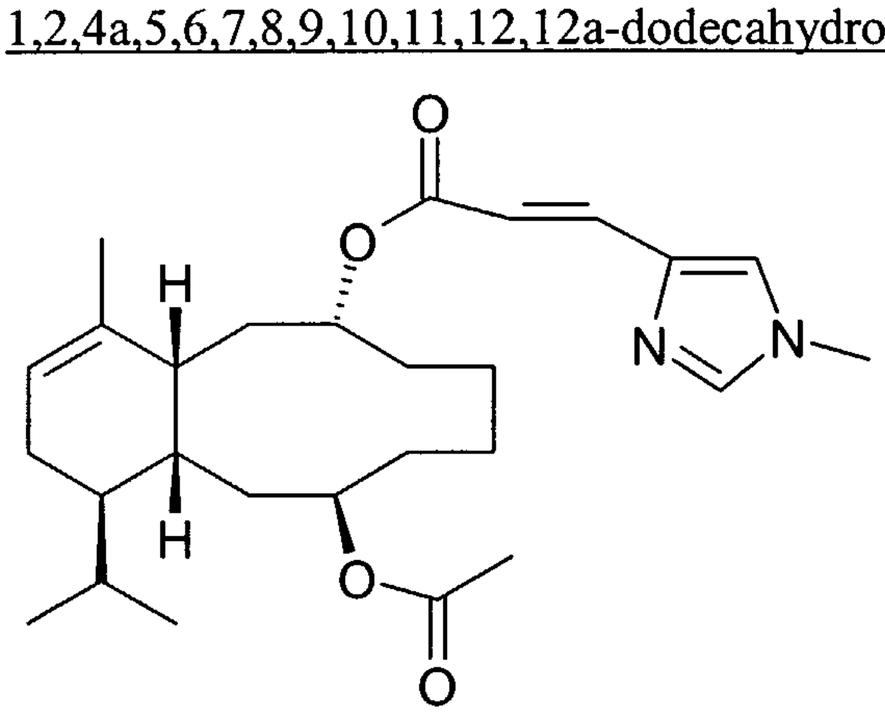
$C_{27}H_{36}N_2O_5$
Exact Mass: 468,2624
Mol. Wt.: 468,5852
C, 69,21; H, 7,74; N, 5,98; O, 17,07

AH 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 7,11-diacetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



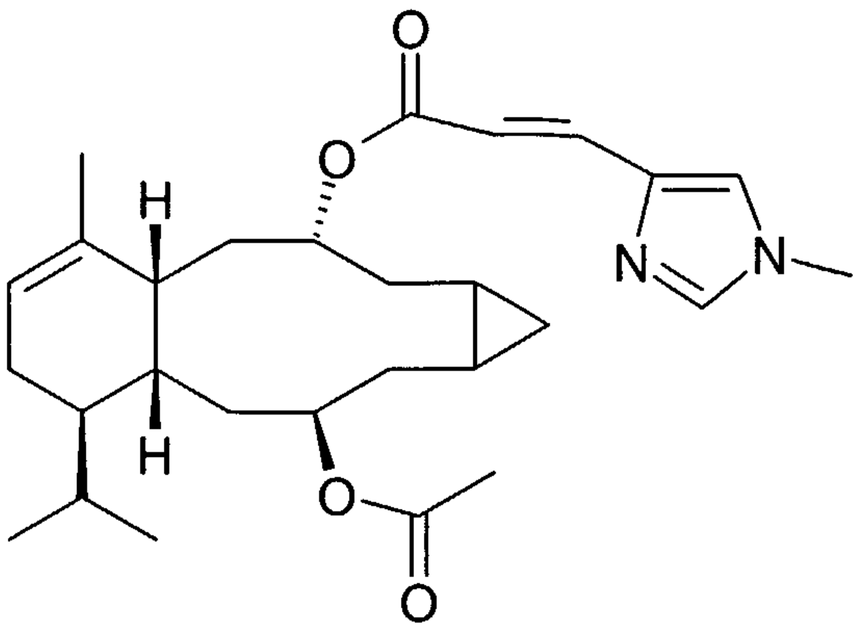
$C_{29}H_{40}N_2O_6$
Exact Mass: 512,2886
Mol. Wt.: 512,6378
C, 67,94; H, 7,86; N, 5,46; O, 18,73

AI 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,8,9,10,11,12,12a-dodecahydro-benzocyclodecen-6-yl ester.



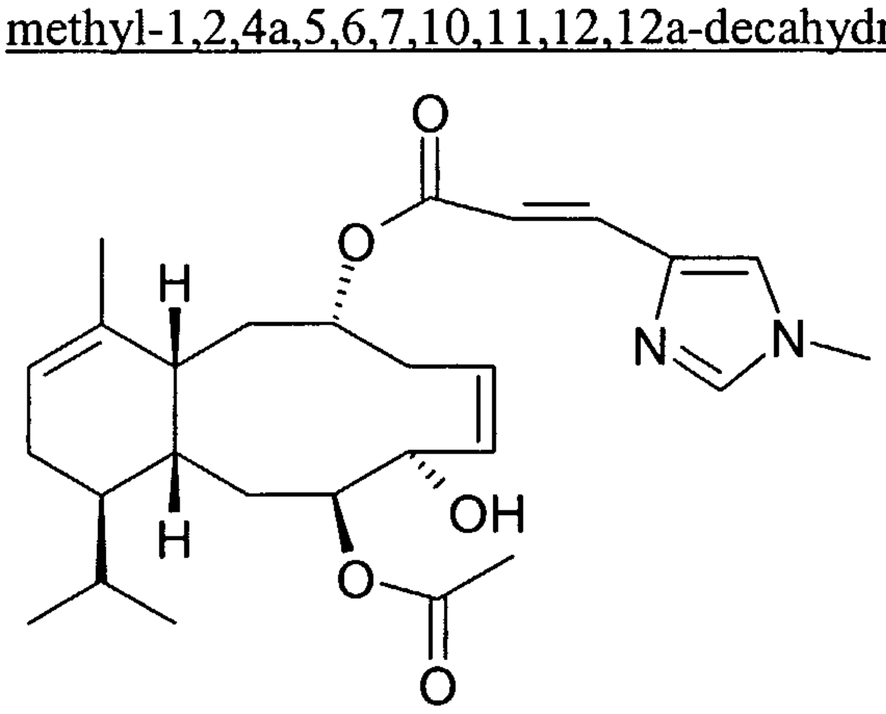
$C_{27}H_{40}N_2O_4$
Exact Mass: 456,2988
Mol. Wt.: 456,6176
C, 71,02; H, 8,83; N, 6,13; O, 14,02

AL 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 9-acetoxy-12-isopropyl-15-methyl-tricyclo[9.4.0.0^{5,7}]pentadec-14-en-3-yl ester.



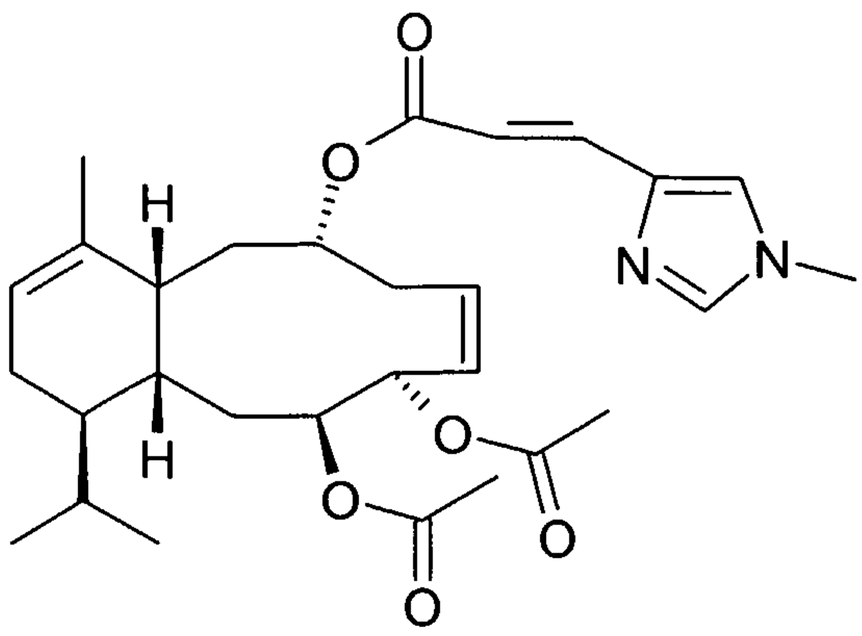
$C_{28}H_{40}N_2O_4$
Exact Mass: 468,2988
Mol. Wt.: 468,6283
C, 71,76; H, 8,60; N, 5,98; O, 13,66

AM 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-10-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



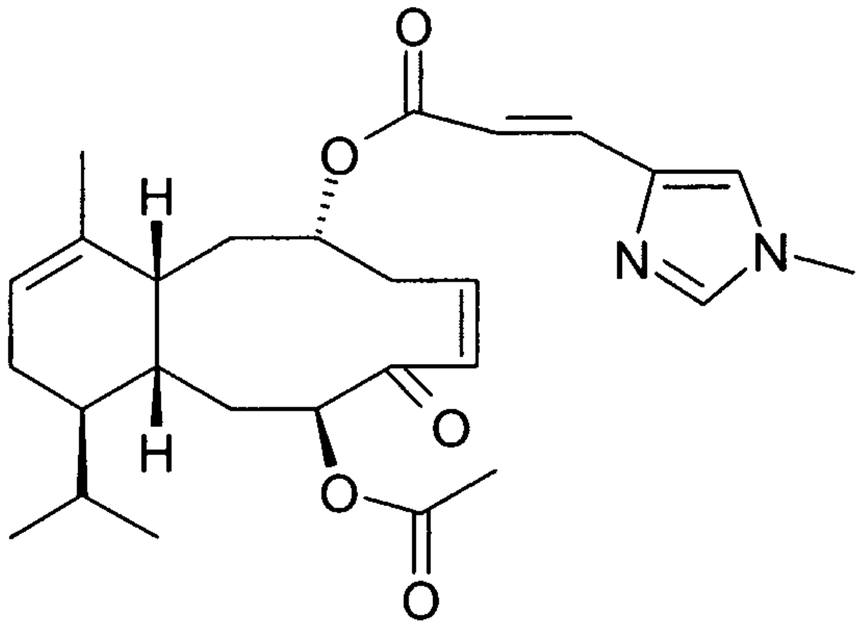
$C_{27}H_{38}N_2O_5$
Exact Mass: 470,2781
Mol. Wt.: 470,6011
C, 68,91; H, 8,14; N, 5,95; O, 17,00

AN 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 10,11-diacetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



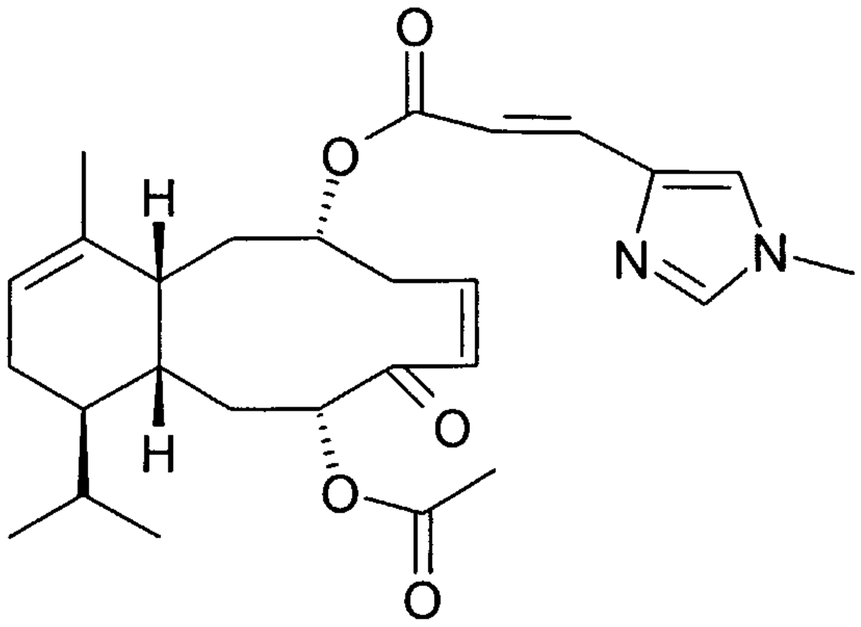
$C_{29}H_{40}N_2O_6$
Exact Mass: 512,2886
Mol. Wt.: 512,6378
C, 67,94; H, 7,86; N, 5,46; O, 18,73

AO 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-10-oxo-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



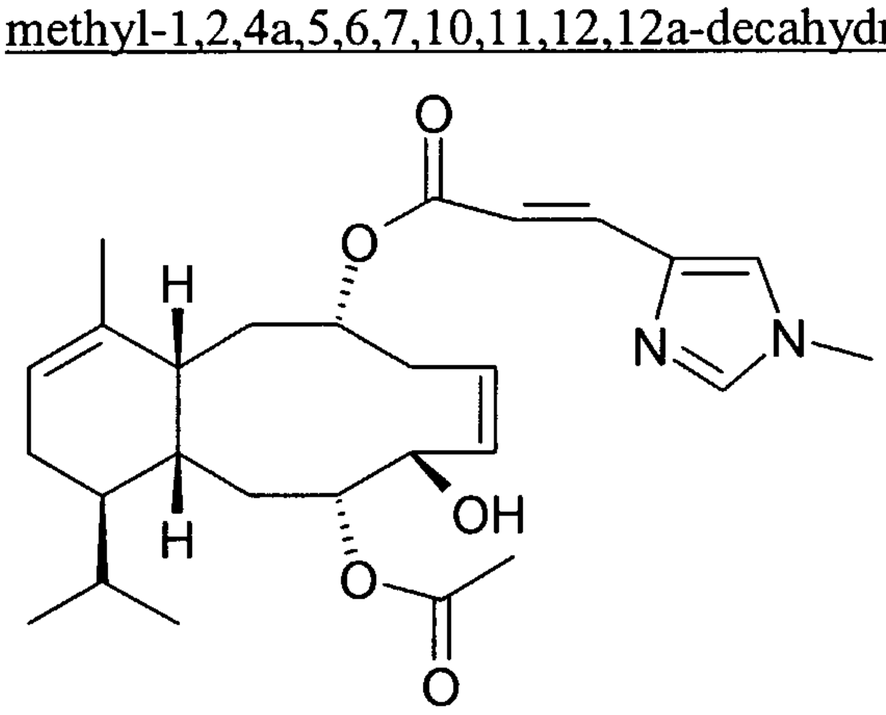
$C_{27}H_{36}N_2O_5$
Exact Mass: 468,2624
Mol. Wt.: 468,5852
C, 69,21; H, 7,74; N, 5,98; O, 17,07

AP 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-10-oxo-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



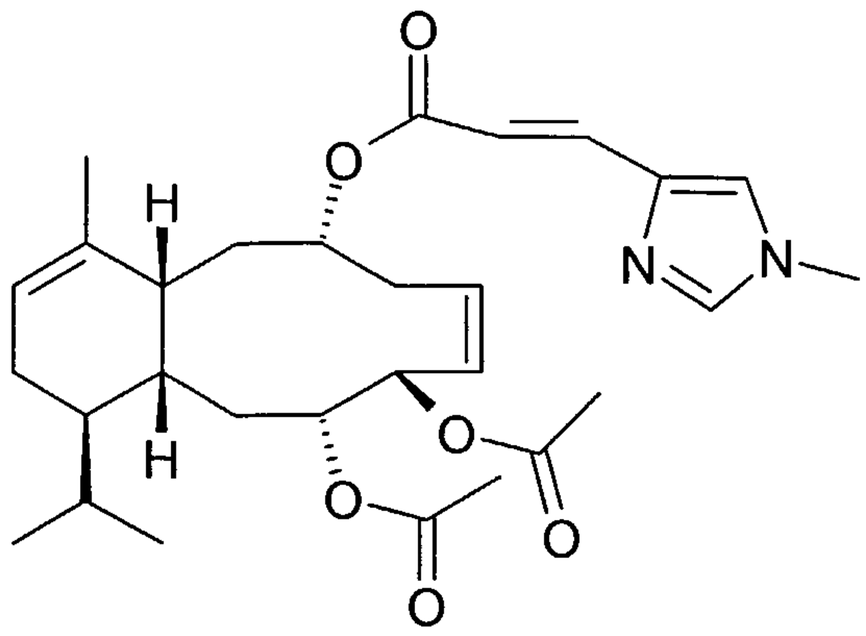
$C_{27}H_{36}N_2O_5$
Exact Mass: 468,2624
Mol. Wt.: 468,5852
C, 69,21; H, 7,74; N, 5,98; O, 17,07

AQ 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-10-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester



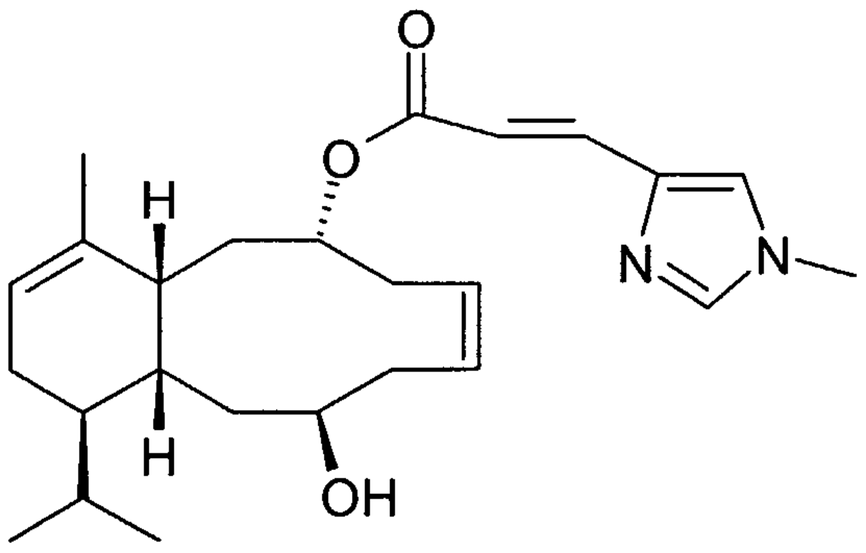
$C_{27}H_{38}N_2O_5$
Exact Mass: 470,2781
Mol. Wt.: 470,6011
C, 68,91; H, 8,14; N, 5,95; O, 17,00

AR 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 10,11-diacetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



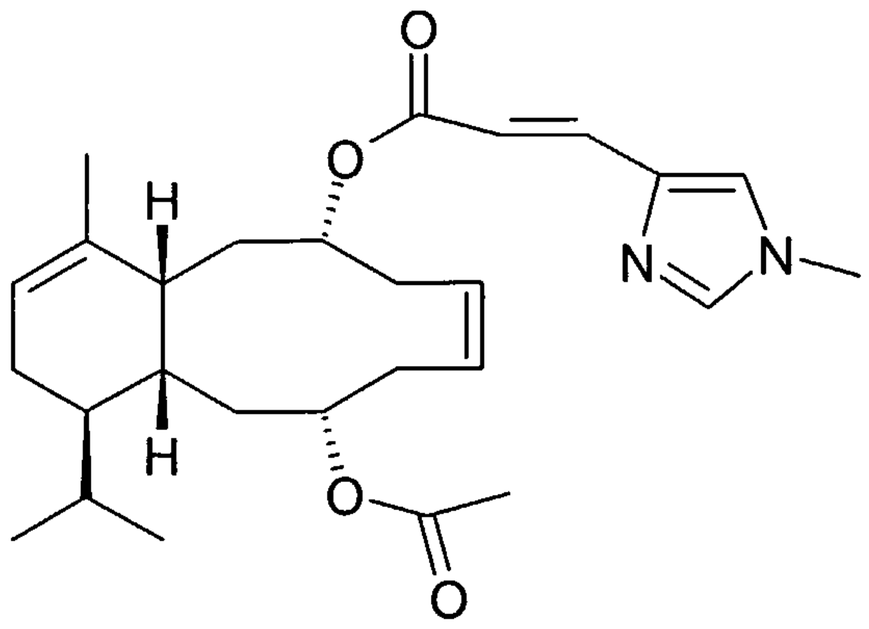
$C_{29}H_{40}N_2O_6$
Exact Mass: 512,2886
Mol. Wt.: 512,6378
C, 67,94; H, 7,86; N, 5,46; O, 18,73

AS 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



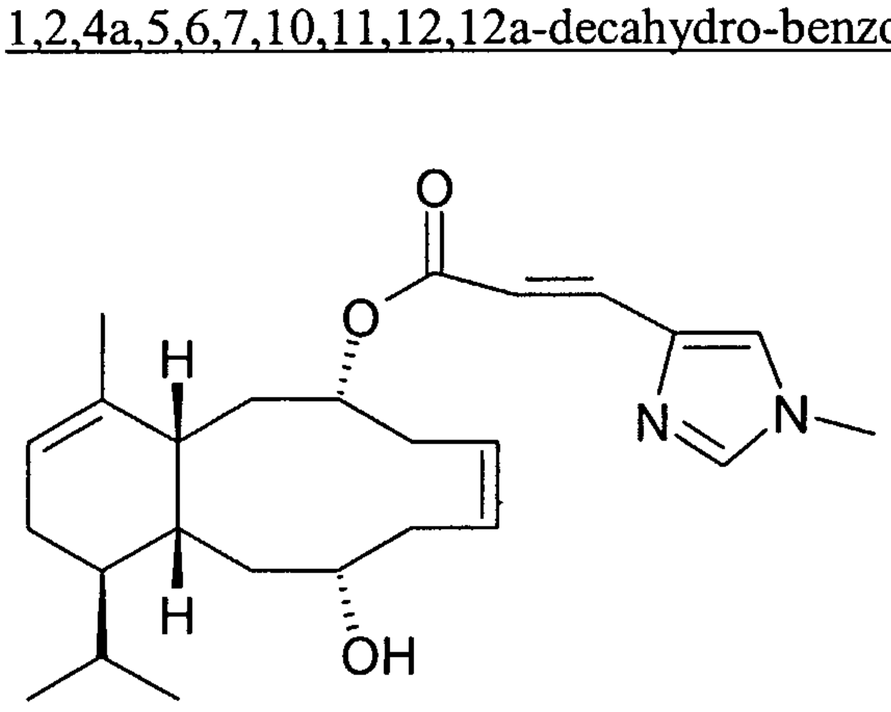
$C_{25}H_{36}N_2O_3$
Exact Mass: 412,2726
Mol. Wt.: 412,5650
C, 72,78; H, 8,80; N, 6,79; O, 11,63

AT 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-acetoxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester



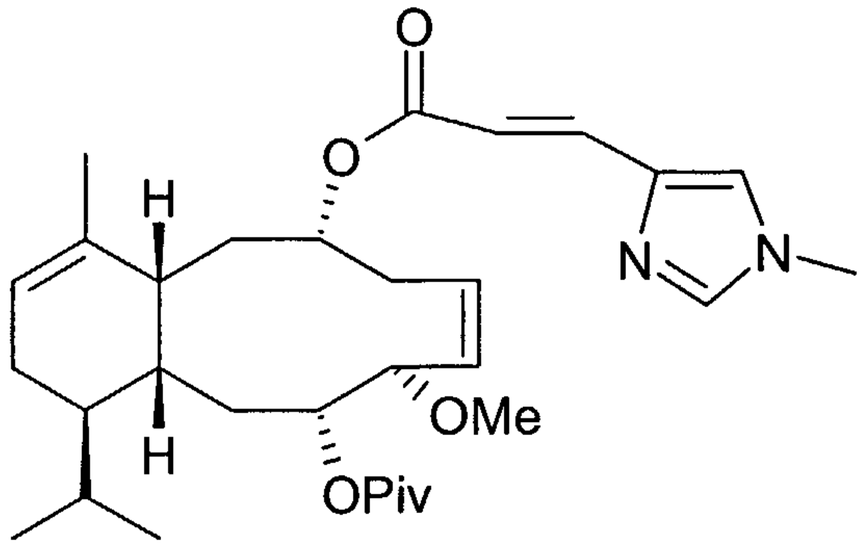
$C_{27}H_{38}N_2O_4$
Exact Mass: 454,2832
Mol. Wt.: 454,6017
C, 71,33; H, 8,43; N, 6,16; O, 14,08

AU 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



$C_{25}H_{36}N_2O_3$
Exact Mass: 412,2726
Mol. Wt.: 412,5650
C, 72,78; H, 8,80; N, 6,79; O, 11,63

AV (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10R,11*R*,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-methoxy-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

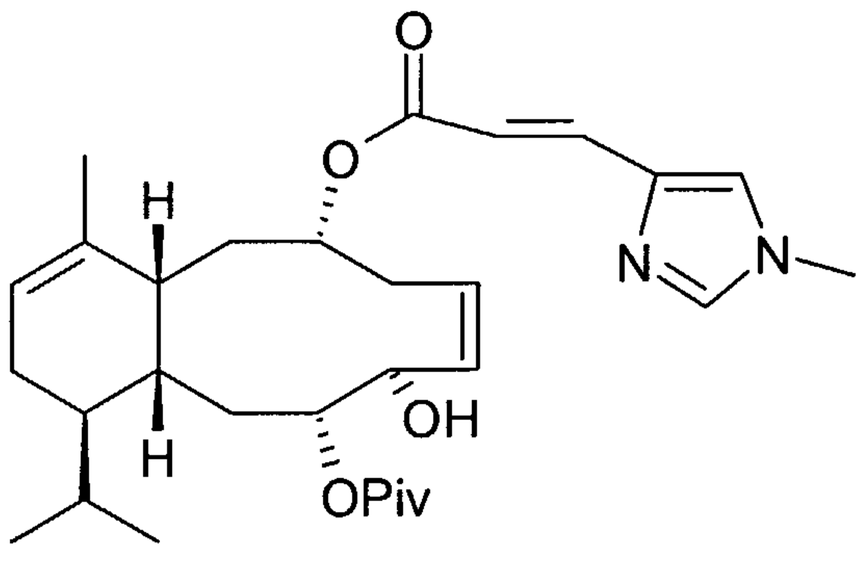


$C_{31}H_{46}N_2O_5$

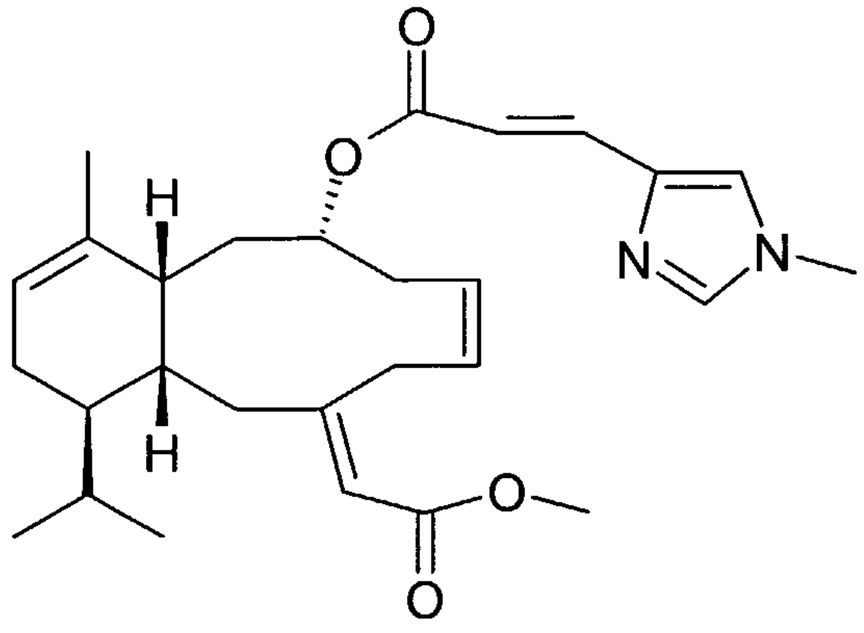
Exact Mass: 527.3499

Mol. Wt: 527.3485

AX (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,10R,11R,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-hydroxy-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

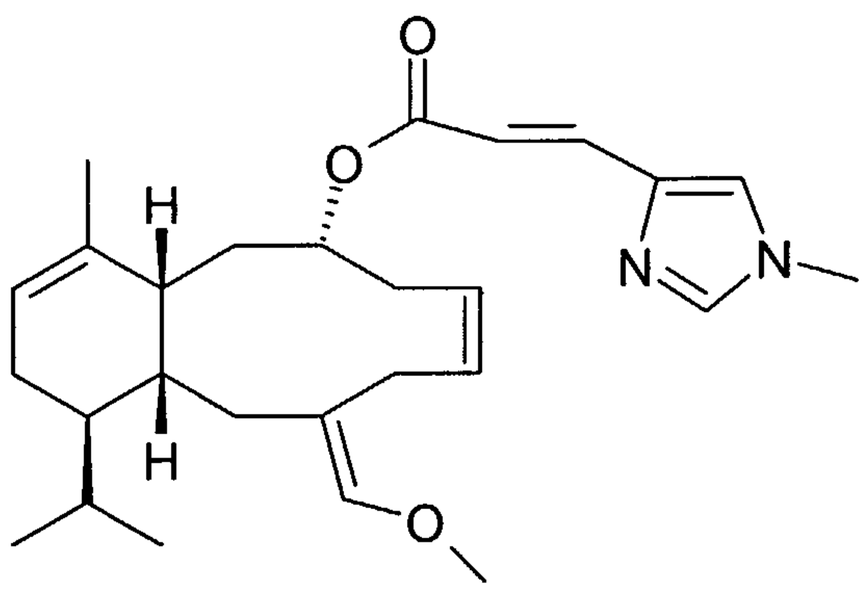


AY 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 1-isopropyl-11-methoxycarbonylmethylene-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



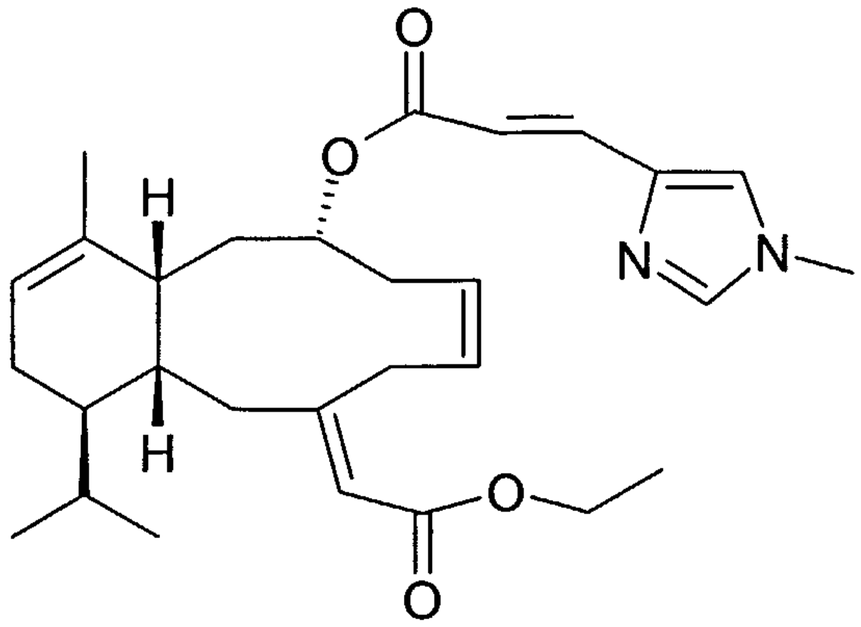
$C_{28}H_{38}N_2O_4$
Exact Mass: 466,2832
Mol. Wt.: 466,6124
C, 72,07; H, 8,21; N, 6,00; O, 13,72

AW 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 1-isopropyl-11-methoxymethylene-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



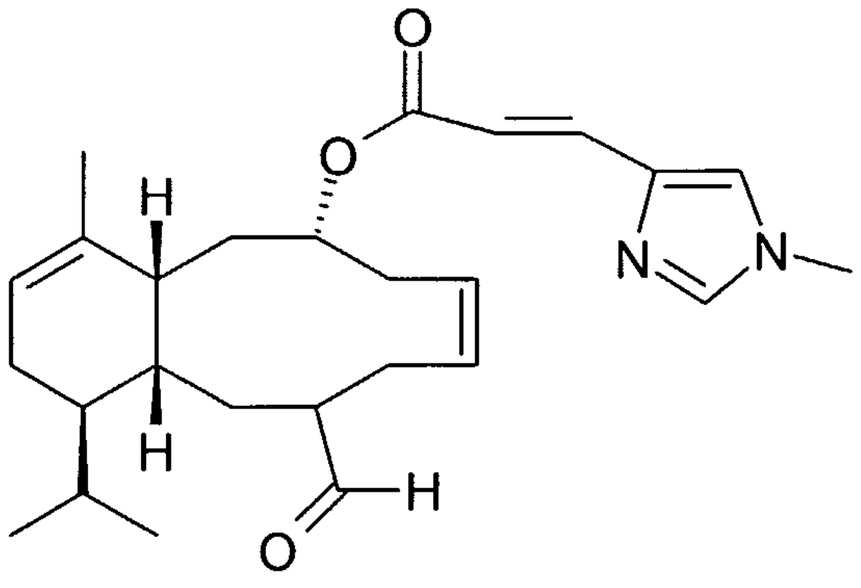
$C_{27}H_{38}N_2O_3$
Exact Mass: 438,2882
Mol. Wt.: 438,6023
C, 73,94; H, 8,73; N, 6,39; O, 10,94

AZ 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-ethoxycarbonylmethylene-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



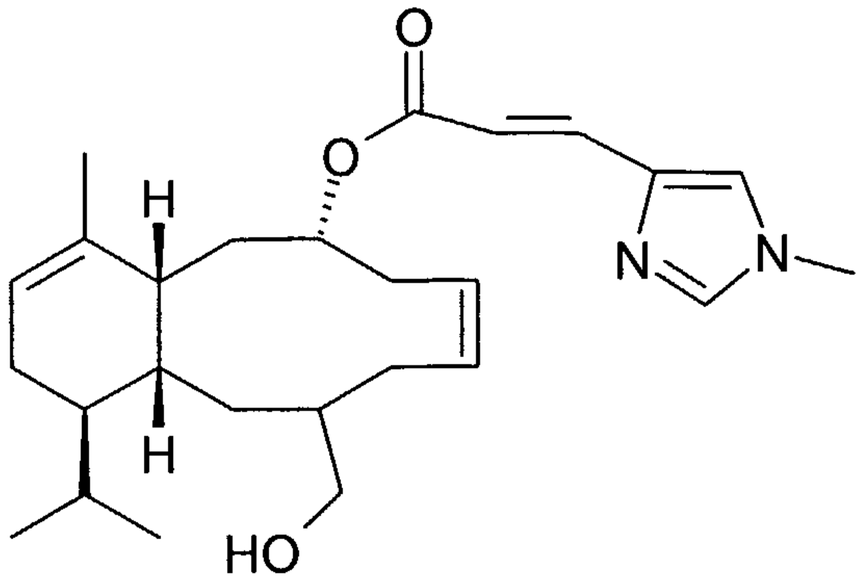
$C_{29}H_{40}N_2O_4$
Exact Mass: 480,2988
Mol. Wt.: 480,6390
C, 72,47; H, 8,39; N, 5,83; O, 13,32

BA 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-formyl-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



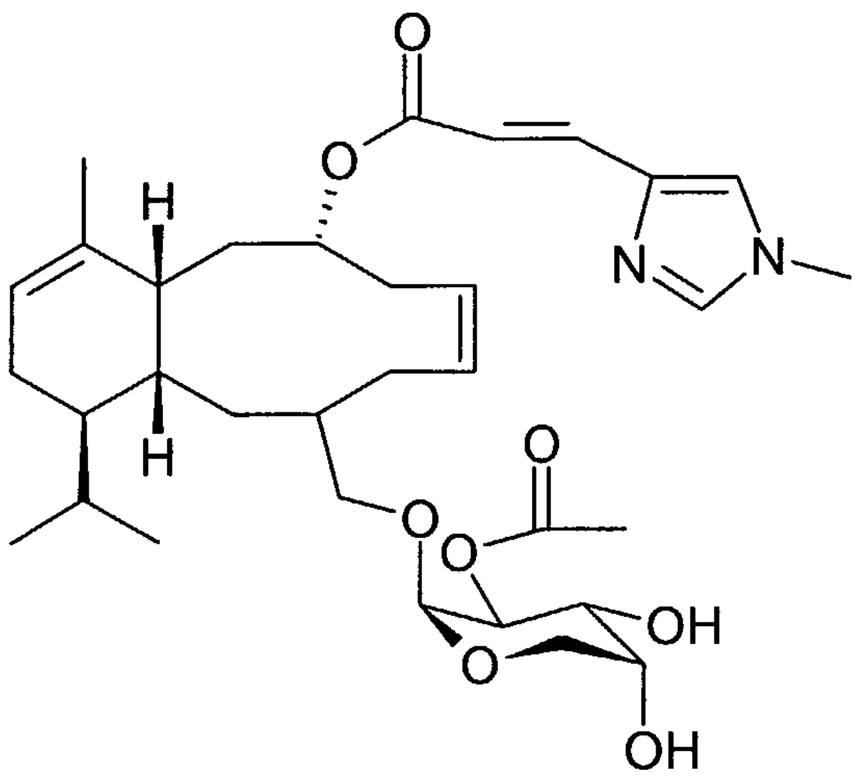
$C_{26}H_{36}N_2O_3$
Exact Mass: 424,2726
Mol. Wt.: 424,5757
C, 73,55; H, 8,55; N, 6,60; O, 11,30

BB 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-hydroxymethyl-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



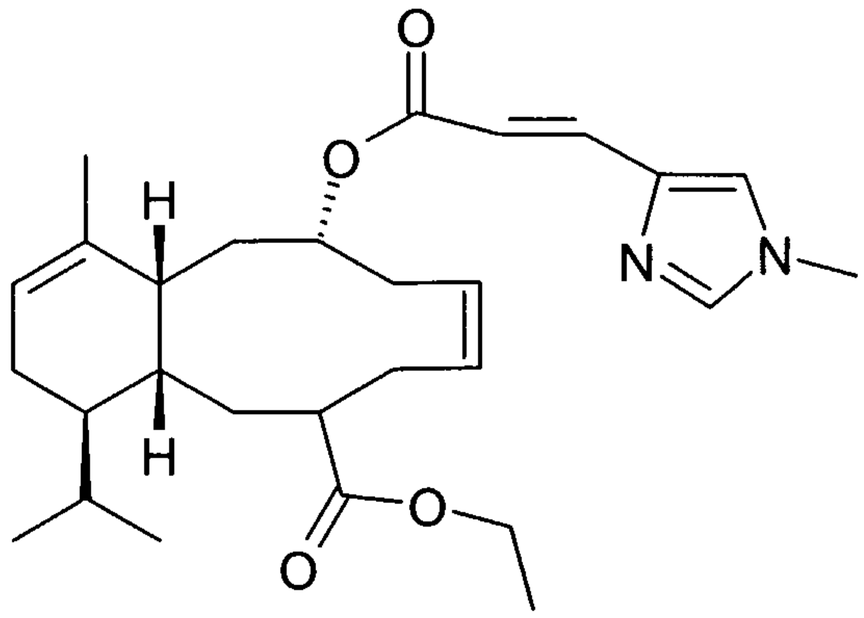
$C_{26}H_{38}N_2O_3$
Exact Mass: 426,2882
Mol. Wt.: 426,5916
C, 73,20; H, 8,98; N, 6,57; O, 11,25

BC 3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid 11-(3-acetoxy-4,5-dihydroxy-tetrahydro-pyran-2-yloxymethyl)-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester.



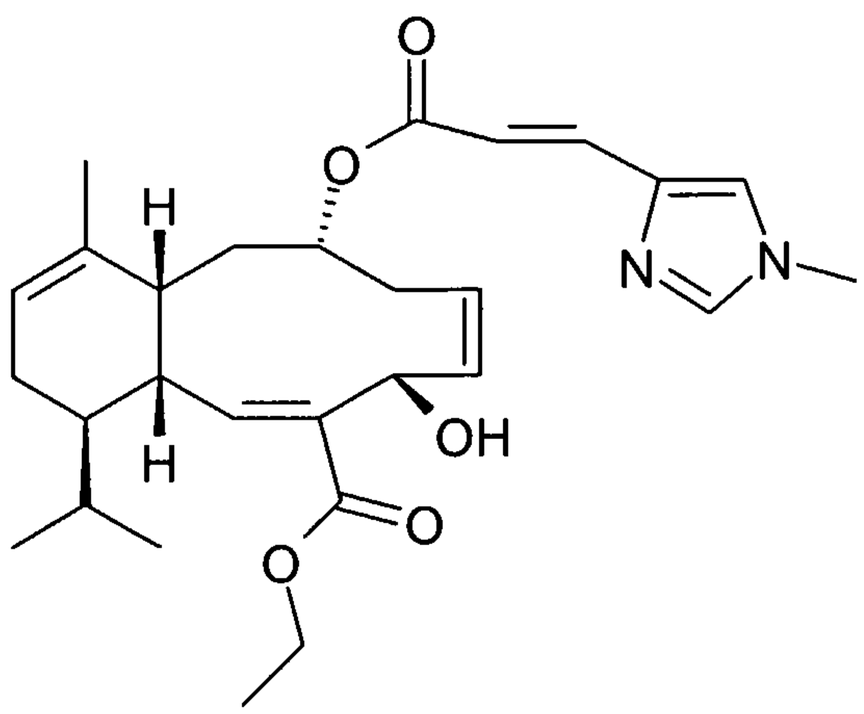
$C_{33}H_{48}N_2O_8$
Exact Mass: 600,3411
Mol. Wt.: 600,7429
C, 65,98; H, 8,05; N, 4,66; O, 21,31

BD 4-Isopropyl-1-methyl-11-[3-(1-methyl-1*H*-imidazol-4-yl)-acryloyloxy]-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecene-6-carboxylic acid ethyl ester.



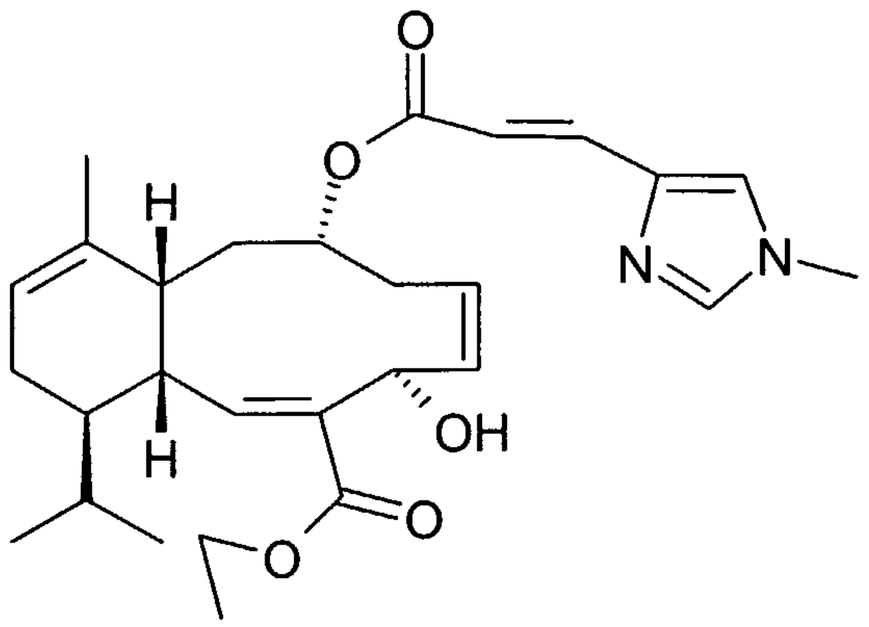
$C_{28}H_{40}N_2O_4$
Exact Mass: 468,2988
Mol. Wt.: 468,6283
C, 71,76; H, 8,60; N, 5,98; O, 13,66

BE 7-Hydroxy-4-isopropyl-1-methyl-11-[3-(1-methyl-1*H*-imidazol-4-yl)-acryloyloxy]-3,4,4a,7,10,11,12,12a-octahydro-benzocyclodecene-6-carboxylic acid ethyl ester.



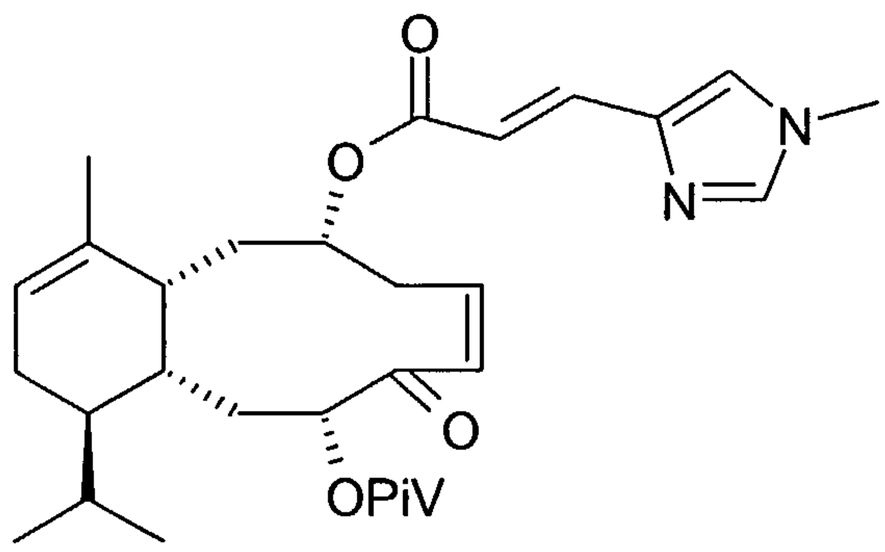
$C_{28}H_{38}N_2O_5$
Exact Mass: 482,2781
Mol. Wt.: 482,6118
C, 69,68; H, 7,94; N, 5,80; O, 16,58

BF 7-Hydroxy-4-isopropyl-1-methyl-11-[3-(1-methyl-1*H*-imidazol-4-yl)-acryloyloxy]-3,4,4a,7,10,11,12,12a-octahydro-benzocyclodecene-6-carboxylic acid ethyl ester.

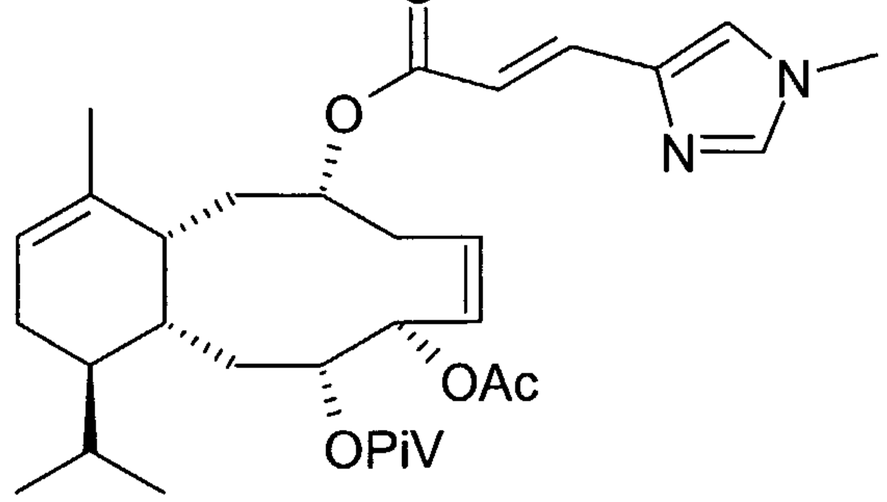


$C_{28}H_{38}N_2O_5$
Exact Mass: 482,2781
Mol. Wt.: 482,6118
C, 69,68; H, 7,94; N, 5,80; O, 16,58

BG (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*,11R,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-oxo-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.

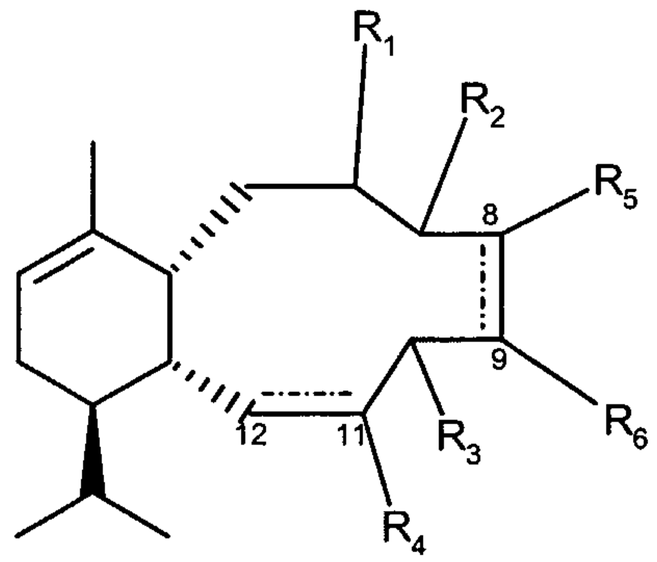


BH (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid [(1*R*,4a*R*,6*R*, 10 R, 11R,12a*R*)-11-(2,2-dimethyl-propionyloxy)-1-isopropyl-10-acetoxy-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester.



CLAIMS

1. A compound which is a sarcodictyin derivative having the formula I:

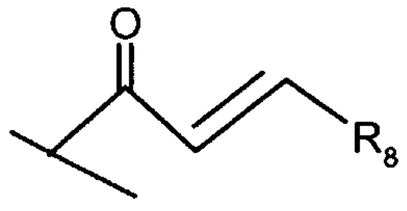


(I)

wherein:

----- at positions 8-9 and 11-12 independently represents a single or double bond,

$-R_1$ represents oxygen (=O), or a residue $-OR_7$, wherein R_7 represents hydrogen, linear or branched C_1-C_7 alkanoyl, benzoyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or a residue of the formula



wherein R_8 is an optionally substituted aryl or heterocyclyl;

one of $-R_2$ and $-R_3$ represents hydrogen and the other one is chosen from the group consisting of hydrogen, oxygen (=O) and a residue $-OR_9$, wherein R_9 represents hydrogen, C_1-C_6 alkanoyl or benzoyl;

when ----- at position 11-12 represents a single bond, then $-R_4$ represents oxygen (=O), methylene ($=CH_2$), $=CHCOOR_{10}$, wherein R_{10} represents C_1-C_{10} alkyl or optionally substituted aryl; $=CH(OCH_3)$, or a residue of formula

$-OR_9$, wherein R_9 is as defined above;

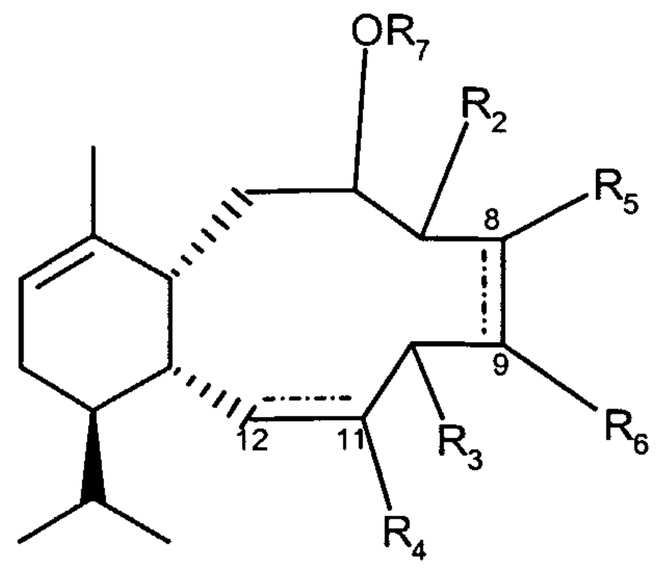
$-CH_2OR_{11}$ wherein R_{11} represents hydrogen or a sugar residue, or

$-COR_{12}$ wherein R_{12} represents hydrogen, -OH or $-OR_{10}$, wherein R_{10} is as defined above;

or

when ----- at position 11-12 represents a double bond, then $-R_4$ represents a residue of formula $-CH_2OR_{11}$ or $-COR_{12}$ as defined above; - R_5 and $-R_6$ are both hydrogen or, when ---- at position 8-9 represents a single bond, taken together with the carbon atoms to which they are attached form a cyclopropane ring; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim I wherein the sarcodictyin derivative is of formula Ia

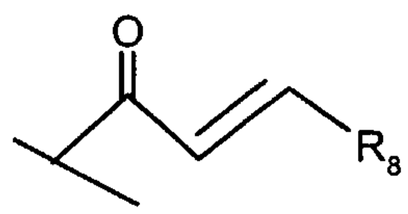


(Ia)

wherein:

----- at positions 8-9 and 11-12 independently represents a single or double bond,

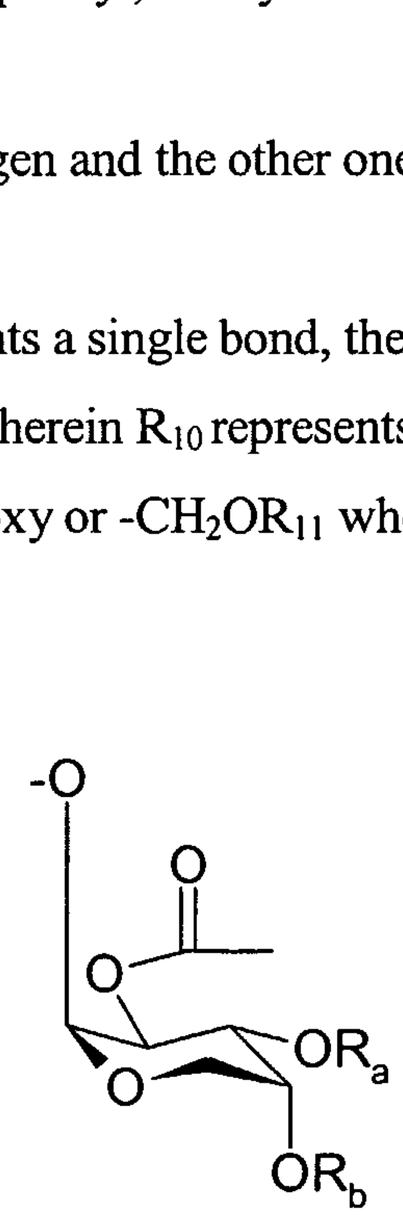
R_7 represents a residue of the formula



wherein R_8 is N-methyl imidazolyl, phenyl, methyl-thiazolyl, methyl-oxazolyl or pyridyl group;

one of -R_2 and -R_3 represents hydrogen and the other one is hydrogen or oxygen (=O), hydroxy or acetoxy;

when ----- at position 11-12 represents a single bond, then -R_4 represents oxygen (=O), methylene (=CH_2), =$CHCOOR_{10}$, wherein R_{10} represents methyl or ethyl, =$CH(OCH_3)$, –CHO; hydroxy, acetoxy, pivaloyloxy or -CH_2OR_{11} wherein R_{11} represents hydrogen or a sugar residue having the formula:



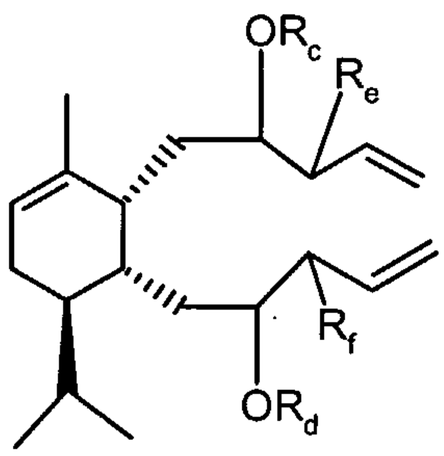
wherein R_a and R_b independently represent hydrogen, a hydroxy protecting group, or C_1-C_6 alkanoyl,

or , when ----- at position 11-12 represents a double bond, then -R_4 represents a residue of formula $-CO_2C_2H_5$; and

- R_5 and -R_6 are both hydrogen or, when ----- at position 8-9 represents a single bond, taken together with the carbon atoms to which they are attached form a cyclopropane ring.

3. A compound as claimed in claim 2 wherein the substituent OR_7 in formula Ia is under the plane and the substituent R_4 is above the plane; R_2 and R_3 are hydrogen and R_8 is N-methyl imidazolyl.

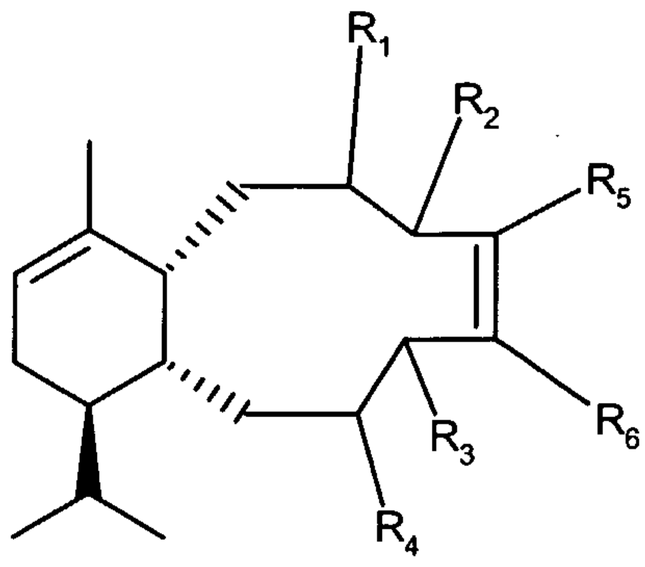
4. A process for producing a compound as defined in claim 1, which process comprises cyclizing a compound of formula II



II

wherein R_c represents hydrogen, a silyl protecting group, C_1-C_6 alkanoyl or benzoyl or , taken together with R_e, forms an acetonide ring; R_d represents hydrogen, C_1-C_6 alkanoyl, or benzoyl, or , taken together with R_f, forms an acetonide ring; either R_e represents H and R_f either represents OH or is linked to the adjacent OR_d substituent as defined above, or R_f represents H and R_e either represents OH or is linked to the adjacent OR_c substituent as defined above;

and, if desired, converting one resulting sarcodictyin derivative of formula I',



I'

wherein R_1 is OR_c, R_2 is R_e, R_3 is R_f, R_4 is OR_d, in which R_c, R_d, R_e and R_f are as defined above and R_5 and R_6 are hydrogen, into another sarcodictyin derivative of formula I as defined in claim 1 and/or, if desired, converting a sarcodictyin derivative of formula I' or

I into a pharmaceutically acceptable salt thereof; and/or, if desired converting a pharmaceutically acceptable salt of a sarcodictyin derivative of formula I or I' into the corresponding free compound.

5. A process according to claim 4 wherein the cyclization is carried out through the Ring Closing Metathesis (RCM) reaction.

6. A process according to claim 5 in which the RCM reaction is carried out in the presence of a Nolan and Grubb's catalyst

7. A pharmaceutical composition which comprises a pharmaceutically acceptable diluent or carrier and, as an active ingredient, a compound as defined in any of claims 1 to 3.

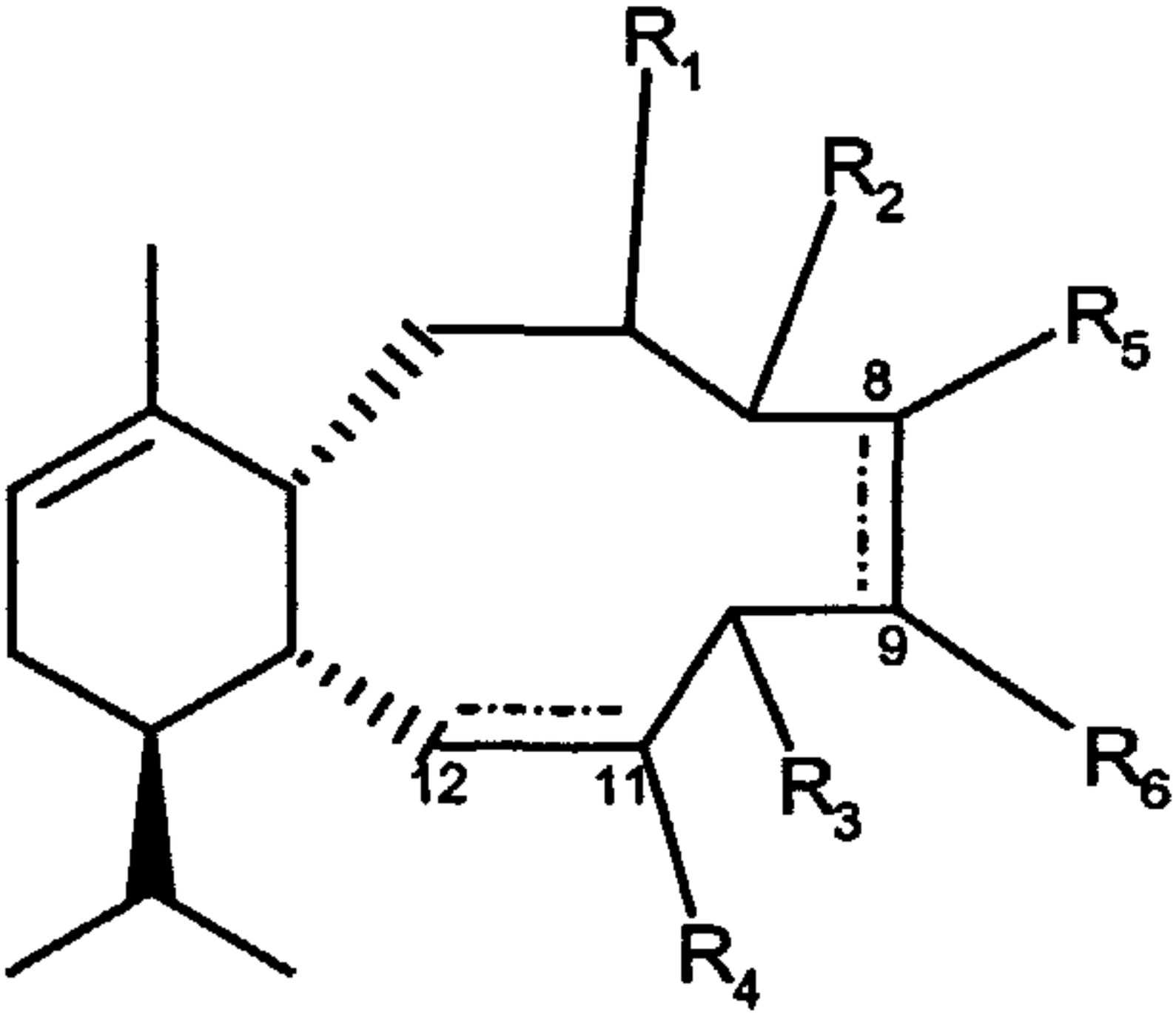
8. A compound as defined in any one of claims 1 to 3 for use in a method of treatment of the human or animal body by therapy or prophylaxis.

9. A compound as claimed in claim 8 for use as an antitumour agent.

10. Use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use as an antitumour agent.

11. A method of treating a patient in need of an antitumour agent, which method comprises the administration thereto of a compound as defined in any one of claims 1 to 3.

12. A method according to claim 11 wherein the patient is suffering from leukemia or a solid tumour.



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