

ANTITUMORAL DIHYDROPYRAN-2-ONE COMPOUNDS

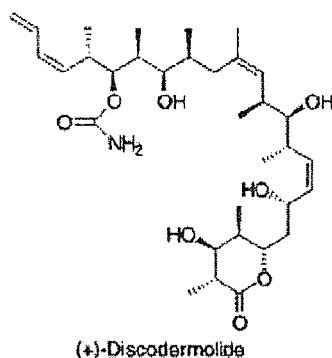
FIELD OF THE INVENTION

5 The present invention relates to new antitumoral compounds, pharmaceutical compositions containing them and their use as antitumoral agents.

BACKGROUND OF THE INVENTION

10

In 1990, Gunasekera SP et al. reported the isolation of a new polyhydroxylated lactone, (+)-discodermolide, from the deep-water Caribbean sponge *Discodermia dissoluta* (Gunasekera SP et al. J. Org. Chem. 1990, 55, 4912-4915 and J. Org. Chem. 1991, 56, 1346).

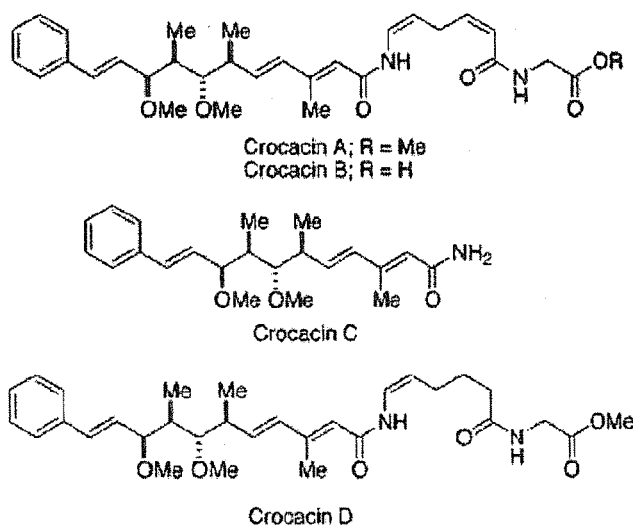


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This compound has been revealed to be a potent antimitotic agent (Hung DT et al. Chem. Biol. 1996, 3, 287-293 and ter Haar E et al. Biochemistry 1996, 35, 243-250), possessing a mode of action similar to
20 that of the clinically proven anticancer agent paclitaxel (Schiff PB et al. Nature 1979, 277, 665-667). Both natural products arrest the cell cycle at the M phase, promote microtubule formation, and have similar inhibitory effects against breast cancer carcinoma (IC₅₀ of 2.4 nM and 2.1 nM, respectively).

25

On the other hand, some unusual linear dipeptides containing a N-acyl enamide functionality have been isolated from a myxobacteria belonging to the *Chondromyces* genus (Kunze B et al. J. Antibiot. 1994, 47, 881-886 and Jansen R et al. J. Org. Chem. 1999, 1085-1089).
5 Specifically, these compounds are crocacin A, B, C and D and are a group of electron transport inhibitors.



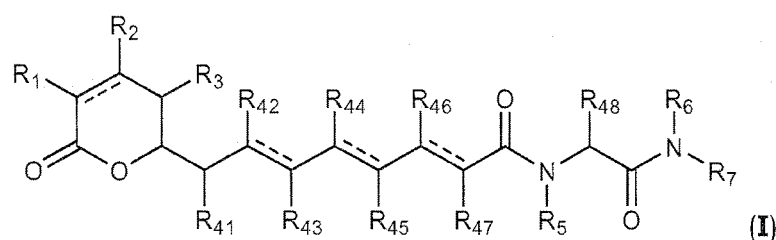
Crocacins A-D moderately inhibit the growth of a few Gram-
10 positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. The most active is crocacin D which showed a MIC of 1.4 ng/mL against the fungus *Saccharomyces cerevisiae* and strong toxicity (IC₅₀ of 0.06 mg/L) toward L929 mouse fibroblast cell culture.

15

Cancer is a leading cause of death in animals and humans. Huge efforts have been and are still being undertaken in order to obtain an antitumor agent active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to
20 provide compounds that are useful in the treatment of cancer.

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to compounds of general formula **I** or pharmaceutically acceptable salts, derivatives, tautomers, prodrugs or stereoisomers thereof



wherein

- 10 R₁ is selected from hydrogen, OR_a, OCOR_a, OCOOR_a, NR_aR_b, NR_aCOR_b, and NR_aC(NR_a)NR_aR_b;

- each R₂ and R₃ are independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl;

- each R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₆, R₄₇ and R₄₈ are independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl;

- each R₅, R₆, and R₇ are independently selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₅ and R₄₈ together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

each R_a and R_b are independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic group;

5 and

each dotted line represent an optional additional bond.

In another aspect, the present invention is directed to compounds
10 of formula **I** or pharmaceutically acceptable salts, derivatives, tautomers, prodrugs or stereoisomers thereof for use as a medicament, in particular as a medicament for treating cancer.

In a further aspect, the present invention is also directed to the
15 use of compounds of formula **I** or pharmaceutically acceptable salts, derivatives, tautomers, prodrugs or stereoisomers thereof in the treatment of cancer, or in the preparation of a medicament, preferably for the treatment of cancer. Other aspects of the invention are methods of treatment, and compounds for use in these methods. Therefore, the
20 present invention further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a compound as defined above.

25 In another aspect, the present invention is directed to pharmaceutical compositions comprising a compound of formula **I** or pharmaceutically acceptable salts, derivatives, tautomers, prodrugs or stereoisomers thereof together with a pharmaceutically acceptable carrier or diluent.

30

The present invention also relates to the isolation of the compounds of formula I from a porifera of the family Raspailiidae, genus *Lithoplocamia*, species *lithistoides*, the process for obtaining them and the formation of derivatives from these compounds.

5

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to compounds of general formula I
10 as defined above.

In these compounds the substituents can be selected in accordance with the following guidance:

15 Alkyl groups may be branched or unbranched, and preferably have from 1 to about 12 carbon atoms. One more preferred class of alkyl groups has from 1 to about 6 carbon atoms. Even more preferred are alkyl groups having 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl, sec-butyl and isobutyl are
20 particularly preferred alkyl groups in the compounds of the present invention. Another preferred class of alkyl groups has from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups of this class.

25 Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more unsaturated linkages and from 2 to about 12 carbon atoms. One more preferred class of alkenyl and alkynyl groups has from 2 to about 6 carbon atoms. Even more preferred are alkenyl and alkynyl groups
30 having 2, 3 or 4 carbon atoms. Another preferred class of alkenyl and alkynyl groups has from 4 to about 10 carbon atoms, still more

preferably 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms.

Suitable aryl groups in the compounds of the present invention
5 include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Preferably aryl groups contain from 6 to about 10 carbon ring atoms. Specially preferred aryl groups include substituted
10 or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted phenanthryl and substituted or unsubstituted anthryl.

Suitable heterocyclic groups include heteroaromatic and
15 heteroalicyclic groups containing from 1 to 3 separated or fused rings and from 5 to about 18 ring atoms. Preferably heteroaromatic and heteroalicyclic groups contain from 5 to about 10 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms
20 and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indoliziny, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl,
25 furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from
30 N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl,

morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridyl, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, 5 pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinoliziny.

10 The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR', SOR', SO₂R', NO₂, NHR', N(R')₂, =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', 15 OCON(R')₂, protected OH, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, CO₂H, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or 20 unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

 Suitable halogen substituents in the compounds of the present 25 invention include F, Cl, Br and I.

 Suitable protecting groups for OH are well known for the skill person in the art. A general review of protecting groups in organic chemistry is provided by Wuts, PGM and Greene TW in Protecting 30 Groups in Organic Synthesis, 4th Ed. Wiley-Interscience, and by Kocienski PJ in Protecting Groups, 3rd Ed. Georg Thieme Verlag. These

references provide sections on protecting groups for OH. All these references are incorporated by reference in their entirety. Examples of such protected OH include ethers, silyl ethers, esters, sulfonates, sulfenates and sulfinates, carbonates and carbamates. In the case of

5 ethers the protecting group for the OH can be selected from methyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, [(3,4-dimethoxybenzyl)oxy]methyl, *p*-nitrobenzyloxymethyl, *o*-nitrobenzyloxymethyl, [(*R*)-1-(2-nitrophenyl)ethoxy]methyl, (4-methoxyphenoxy)methyl,

10 guaiacolmethyl, [(*p*-phenylphenyl)oxy]methyl, *t*-butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *o*-bis(2-acetoxyethoxy)methyl, tetrahydropyranyl, fluororous tetrahydropyranyl, 3-bromotetrahydropyranyl,

15 tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1-(4-chlorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3 α ,4,5,6,7,7 α -

20 octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-hydroxyethyl, 2-bromoethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1,1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-

25 phenylisopropyl, 1-(2-cyanoethoxy)ethyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-phenylselenyl)ethyl, *t*-butyl, cyclohexyl, 1-methyl-1'-cyclopropylmethyl, allyl, prenyl, cinnamyl, 2-phenallyl, propargyl, *p*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-

30 dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, pentadienylnitrobenzyl, pentadienylnitropiperonyl, halobenzyl, 2,6-

dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluorous benzyl, 4-fluorousalkoxybenzyl, trimethylsilylxylyl, *p*-phenylbenzyl, 2-phenyl-2-propyl, *p*-acylaminobenzyl, *p*-azidobenzyl, 4-azido-3-chlorobenzyl, 2-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, *p*-(methylsulfinyl)benzyl, *p*-siletanylbenzyl, 4-acetoxybenzyl, 4-(2-trimethylsilyl)ethoxymethoxybenzyl, 2-naphthylmethyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, 2-quinolinylmethyl, 6-methoxy-2-(4-methylphenyl-4-quinolinemethyl, 1-pyrenylmethyl, diphenylmethyl, 4-methoxydiphenylmethyl, 4-phenyldiphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, tris(4-*t*-butylphenyl)methyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 4,4'-dimethoxy-3''-[*N*-(imidazolylmethyl)]trityl, 4,4'-dimethoxy-3''-[*N*-(imidazolethyl)carbamoyl]trityl, bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[*a,c,g,i*]fluorenylmethyl)-4,4''-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-phenylthioxanthyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and 4,5-bis(ethoxycarbonyl)-[1,3]-dioxolan-2-yl, benzoisothiazolyl *S,S*-dioxido. In the case of silyl ethers the protecting group for the OH can be selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl. In the case of esters the protecting group for the OH can be selected from formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate,

trichloroacetamidate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, phenylacetate, diphenylacetate, 3-phenylpropionate, bisfluorous chain type propanoyl, 4-pentenoate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, 5 [3-bis(4-methoxyphenyl)hydroxymethylphenoxy]levulinate, pivaloate, 1-adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate, 4-bromobenzoate, 2,5-difluorobenzoate, *p*-nitrobenzoate, picolinate, nicotinate, 2-(azidomethyl)benzoate, 4-azidobutyrate, (2-azidomethyl)phenylacetate, 2-[[tritylthio]oxy]methyl]benzoate, 2-[[4-methoxytritylthio]oxy]methyl]benzoate, 2-[[methyl(tritylthio)amino]methyl]benzoate, 2-[[[4-methoxytrityl]thio]methylamino]-methyl]benzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxymethyl)benzoate, 6-(levulinyloxymethyl)-3-methoxy-2-nitrobenzoate, 6-(levulinyloxymethyl)-3-methoxy-4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsilyloxybutyrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2-(chloroacetoxymethyl)benzoate, 2-[(2-chloroacetoxy)ethyl]benzoate, 2-[2-(benzyloxy)ethyl]benzoate, 2-[2-(4-methoxybenzyloxy)ethyl]benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenolate, *o*-(methoxycarbonyl)benzoate, α -naphthoate, nitrate, alkyl 25 *N,N,N,N*-tetramethylphosphorodiamidate, and 2-chlorobenzoate. In the case of sulfonates, sulfenates and sulfinates the protecting group for the OH can be selected from sulfate, allylsulfonate, methanesulfonate, benzylsulfonate, tosylate, 2-[(4-nitrophenyl)ethyl]sulfonate, 2-trifluoromethylbenzenesulfonate, 4-monomethoxytritylsulfenate, alkyl 2,4-dinitrophenylsulfenate, 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate, 30 borate, and dimethylphosphinothiolyl. In the case of carbonates the

protecting group for the OH can be selected from methyl carbonate, methoxymethyl carbonate, 9-fluorenylmethyl carbonate, ethyl carbonate, bromoethyl carbonate, 2-(methylthiomethoxy)ethyl carbonate, 2,2,2-trichloroethyl carbonate, 1,1-dimethyl-2,2,2-trichloroethyl carbonate, 2-
 5 (trimethylsilyl)ethyl carbonate, 2-[dimethyl(2-naphthylmethyl)silyl]ethyl carbonate, 2-(phenylsulfonyl) ethyl carbonate, 2-(triphenylphosphonio)ethyl carbonate, *cis*-[4-[[[(methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-yl]oxy carbonate, isobutyl carbonate, *t*-butyl carbonate, vinyl carbonate, allyl carbonate, cinnamyl carbonate, propargyl carbonate, *p*-chlorophenyl
 10 carbonate, *p*-nitrophenyl carbonate, 4-ethoxy-1-naphthyl carbonate, 6-bromo-7-hydroxycoumarin-4-ylmethyl carbonate, benzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, anthraquinon-2-ylmethyl carbonate, 2-dansylethyl carbonate, 2-(4-nitrophenyl)ethyl carbonate, 2-(2,4-
 15 dinitrophenyl)ethyl carbonate, 2-(2-nitrophenyl)propyl carbonate, alkyl 2-(3,4-methylenedioxy-6-nitrophenyl)propyl carbonate, 2-cyano-1-phenylethyl carbonate, 2-(2-pyridyl)amino-1-phenylethyl carbonate, 2-[*N*-methyl-*N*-(2-pyridyl)]amino-1-phenylethyl carbonate, phenacyl carbonate, 3',5'-dimethoxybenzoin carbonate, methyl dithiocarbonate, and *S*-benzyl
 20 thiocarbonate. And in the case of carbamates the protecting group for the OH can be selected from dimethylthiocarbamate, *N*-phenylcarbamate, *N*-methyl-*N*-(*o*-nitrophenyl)carbamate. The mention of these groups should be not interpreted as a limitation of the scope of the invention, since they have been mentioned as a mere illustration of protecting groups for OH, but further
 25 groups having said function may be known by the skill person in the art, and they are to be understood to be also encompassed by the present invention.

The term "pharmaceutically acceptable salts, derivatives, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate,
 30 hydrate or any other compound which, upon administration to the patient is capable of providing (directly or indirectly) a compound as

described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs
5 and derivatives can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods.
10 Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of
15 the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-
20 toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkyl ethanolamine, triethanolamine and basic aminoacids salts.

25

The compounds of the invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

30

Any compound that is a prodrug of a compound of formula **I** is within the scope and spirit of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives
5 would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative.

Any compound referred to herein is intended to represent such
10 specific compound as well as certain variations or forms. In particular, compounds referred to herein may have asymmetric centres and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention. Thus
15 any given compound referred to herein is intended to represent any one of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Particularly, the compounds of the present invention represented by the above described formula **I** may include enantiomers
20 depending on their asymmetry or diastereoisomers. Stereoisomerism about the double bond is also possible, therefore in some cases the molecule could exist as (E)-isomer or (Z)-isomer. If the molecule contains several double bonds, each double bond will have its own stereoisomerism, that could be the same or different than the
25 stereoisomerism of the other double bonds of the molecule. The single isomers and mixtures of isomers fall within the scope of the present invention.

Furthermore, compounds referred to herein may exist as
30 geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Specifically, the term tautomer refers to one of two or

more structural isomers of a compound, that exist in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are amine-imine, amide-imide, keto-enol, lactam-lactim, etc. Additionally, any compound referred to herein is intended to
5 represent hydrates, solvates, and polymorphs, and mixtures thereof when such forms exist in the medium. In addition, compounds referred to herein may exist in isotopically-labelled forms. All geometric isomers, tautomers, atropisomers, hydrates, solvates, polymorphs, and isotopically labelled forms of the compounds referred to herein, and
10 mixtures thereof, are considered within the scope of the present invention.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is
15 understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental
20 and/or measurement conditions for such given value.

In compounds of general formula **I**, particularly preferred R_1 is hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is
25 hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R_1 groups.

30 Particularly preferred R_2 and R_3 are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_2 and R_3 are hydrogen and

substituted or unsubstituted C₁-C₆ alkyl, and even more preferred are hydrogen.

Particularly preferred R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₆, R₄₇ and R₄₈ are
5 hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred
R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₆, R₄₇ and R₄₈ are hydrogen and substituted or
unsubstituted C₁-C₆ alkyl, and even more preferred is hydrogen,
substituted or unsubstituted methyl, substituted or unsubstituted
ethyl, substituted or unsubstituted propyl, substituted or
10 unsubstituted isopropyl and substituted or unsubstituted butyl,
including substituted or unsubstituted tert-butyl, substituted or
unsubstituted isobutyl and substituted or unsubstituted sec-butyl.
Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R',
NO₂, NHR', N(R')₂, =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R',
15 CN, halogen, COR', COOR', OCOR', OCONHR', OCON(R')₂, protected
OH, substituted or unsubstituted aryl, and substituted or
unsubstituted heterocyclic group, wherein each of the R' groups is
independently selected from the group consisting of hydrogen, OH, NO₂,
NH₂, SH, CN, halogen, COH, COalkyl, COOH, substituted or
20 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂
alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or
unsubstituted aryl, and substituted or unsubstituted heterocyclic
group. Where such groups are themselves substituted, the substituents
may be chosen from the foregoing list. Even more preferred substituents
25 of the above mentioned groups are OH, SCH₃, SH, NH₂, NHC(=NH)NH₂,
CONH₂, COOH, phenyl, *p*-, *m*- or *o*-hydroxyphenyl, indolyl, including 1-,
2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl.
Hydrogen, methyl, isopropyl, tert-butyl and benzyl are the most
preferred R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₆, R₄₇ and R₄₈ groups. Specifically,
30 particularly preferred R₄₂, R₄₄, R₄₅, R₄₆, and R₄₇ are hydrogen.

Particularly preferred R_{41} and R_{43} are methyl. And particularly preferred R_{48} is isopropyl, tert-butyl, or benzyl.

Particularly preferred R_5 and R_6 are hydrogen and substituted or
5 unsubstituted C_1 - C_{12} alkyl. More preferred R_5 and R_6 are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen is the most preferred.

10 In another embodiment of the invention, it is also preferred that R_5 and R_{48} together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted heterocyclic group. Preferred heterocyclic group is pyrrolidinyl, including 1-, 2- and 3-pyrrolidinyl.

15

Particularly preferred R_7 is hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl and substituted or unsubstituted C_2 - C_{12} alkenyl, and more preferably is hydrogen, substituted C_1 - C_{12} alkyl and substituted C_2 - C_{12} alkenyl. The preferred substituted alkyl and
20 substituted alkenyl may present not only one but two or more substituents. More preferred alkyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are those having from 6
25 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-dienyl, octa-1,4-dienyl, octa-1,3-dienyl, nona-1,7-dienyl, nona-1,6-dienyl, nona-1,5-dienyl, nona-1,4-dienyl, nona-1,3-dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-dienyl are the most preferred alkenyl groups. Preferred substituents for
30 said alkyl and alkenyl groups are OR' , $=O$, SR' , SOR' , SO_2R' , NO_2 , NHR' , $N(R')_2$, $=N-R'$, $NHCOR'$, $N(COR')_2$, $NHSO_2R'$, $NR'C(=NR')NR'R'$, CN ,

halogen, COR', COOR', OCOR', OCONHR', OCON(R')₂, protected OH, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN,

5 halogen, COH, COalkyl, COOH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the

10 foregoing list. More preferred substituents for the above mentioned alkyl and alkenyl groups are halogen, OR', =O, OCOR', OCONHR', OCON(R')₂, and protected OH, wherein each of the R' groups is preferably selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂

15 alkynyl, and substituted or unsubstituted aryl. Even more preferred substituents for these alkyl and alkenyl groups are halogen, OR', =O, OCONHR', OCON(R')₂, and protected OH wherein the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl,

20 dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-

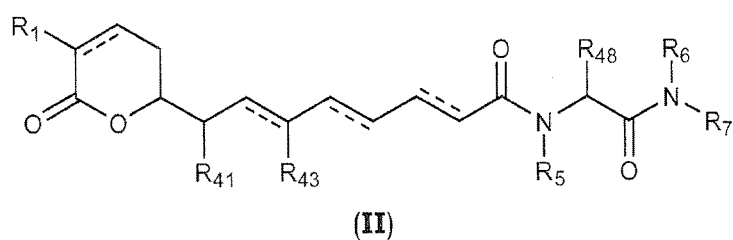
25 butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and wherein each of the R' groups is more preferably selected from hydrogen, unsubstituted C₁-C₆ alkyl, and substituted or unsubstituted aryl. Cl, OH, =O, OCONH₂, OCONHPhenyl, and protected OH wherein

30 the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl,

diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorosilyl, are the most preferred substituents for these alkyl and alkenyl groups.

Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. More preferred is the presence of an additional bond in all the places indicated with a dotted line. In addition, the stereochemistry of each double bond may exist as (E) or (Z). The single isomers and mixtures of the isomers fall within the scope of the present invention.

More particularly, the invention provides compounds of general formula **II** or pharmaceutically acceptable salts, derivatives, tautomers, prodrugs or stereoisomers thereof



wherein

R_1 is selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, NR_aR_b , NR_aCOR_b , and $NR_aC(NR_a)NR_aR_b$;

each R_{41} , R_{43} and R_{48} are independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl;

- 5 each R_5 , R_6 , and R_7 are independently selected from hydrogen, COR_a , $COOR_a$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, or R_5 and R_{48} together with the corresponding N atom and C atom to which they are attached may form a substituted or
10 unsubstituted heterocyclic group;

each R_a and R_b are independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or
15 unsubstituted aryl and substituted or unsubstituted heterocyclic group; and

each dotted line represent an optional additional bond.

- 20 In compounds of general formula **II**, particularly preferred R_1 is hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl,
25 including tert-butyl. Hydrogen, OH and methoxy are the most preferred R_1 groups.

Particularly preferred R_{41} , R_{43} and R_{48} are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_{41} , R_{43} and
30 R_{48} are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, and even more preferred is hydrogen, substituted or unsubstituted methyl,

substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl and substituted or unsubstituted butyl, including substituted or unsubstituted tert-butyl, substituted or unsubstituted isobutyl and substituted or unsubstituted sec-butyl. Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', N(R')₂, =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCON(R')₂, protected OH, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, COOH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. Even more preferred substituents of the above mentioned groups are OH, SCH₃, SH, NH₂, NHC(=NH)NH₂, CONH₂, COOH, phenyl, *p*-, *m*- or *o*-hydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen, methyl, isopropyl, tert-butyl and benzyl are the most preferred R₄₁, R₄₃ and R₄₈ groups. Specifically, particularly preferred R₄₁ and R₄₃ are methyl, and particularly preferred R₄₈ is isopropyl, tert-butyl, or benzyl.

Particularly preferred R₅ and R₆ are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₅ and R₆ are hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen is the most preferred.

In another embodiment of the invention, it is also preferred that R_5 and R_{48} together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted heterocyclic group. Preferred heterocyclic group is pyrrolidinyl, including 1-, 2- and 3-pyrrolidinyl.

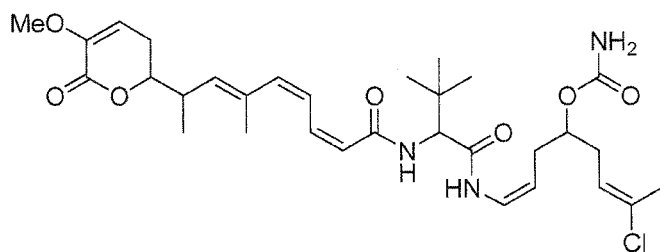
Particularly preferred R_7 is hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl and substituted or unsubstituted C_2 - C_{12} alkenyl, and more preferably is hydrogen, substituted C_1 - C_{12} alkyl and substituted C_2 - C_{12} alkenyl. More preferred alkyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-dienyl, octa-1,4-dienyl, octa-1,3-dienyl, nona-1,7-dienyl, nona-1,6-dienyl, nona-1,5-dienyl, nona-1,4-dienyl, nona-1,3-dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-dienyl are the most preferred alkenyl groups. Preferred substituents for said alkyl and alkenyl groups are OR' , $=O$, SR' , SOR' , SO_2R' , NO_2 , NHR' , $N(R')_2$, $=N-R'$, $NHCOR'$, $N(COR')_2$, $NHSO_2R'$, $NR'C(=NR')NR'R'$, CN , halogen, COR' , $COOR'$, $OCOR'$, $OCONHR'$, $OCON(R')_2$, protected OH, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO_2 , NH_2 , SH, CN, halogen, COH, COalkyl, COOH, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. More preferred substituents for the above mentioned alkyl and alkenyl groups are halogen, OR' , $=O$,

OCOR', OCONHR', OCON(R')₂, and protected OH, wherein each of the R' groups is preferably selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted aryl. Even more preferred substituents for these alkyl and alkenyl groups are halogen, OR', =O, OCONHR', OCON(R')₂, and protected OH wherein the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and wherein each of the R' groups is more preferably selected from hydrogen, unsubstituted C₁-C₆ alkyl, and substituted or unsubstituted aryl. Cl, OH, =O, OCONH₂, OCONHPhenyl, and protected OH wherein the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are the most preferred substituents for these alkyl and alkenyl groups.

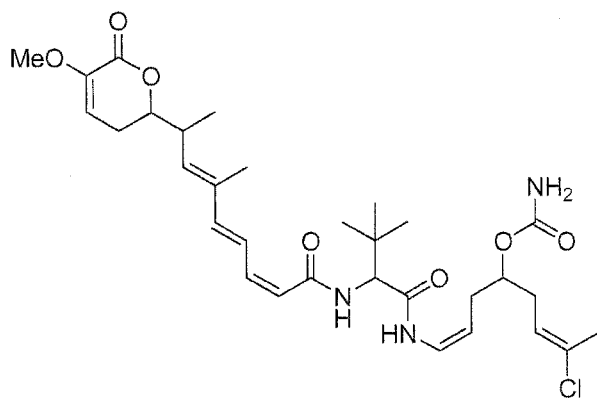
Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. More preferred is the presence of an additional bond in all the places indicated with a dotted line. In addition, the stereochemistry of each double bond may exist as (E) or (Z). The single isomers and mixtures of the isomers fall within the scope of the present invention.

Particularly preferred compounds of the invention are the following:

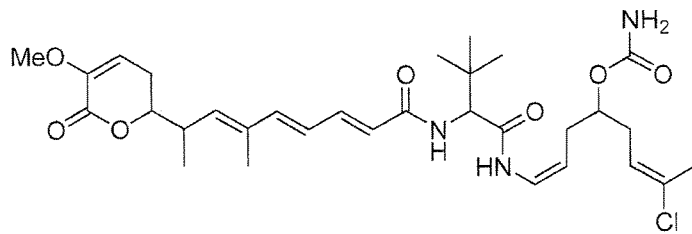
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Compound 1

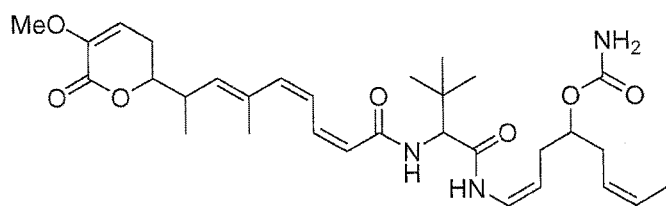


Compound 2

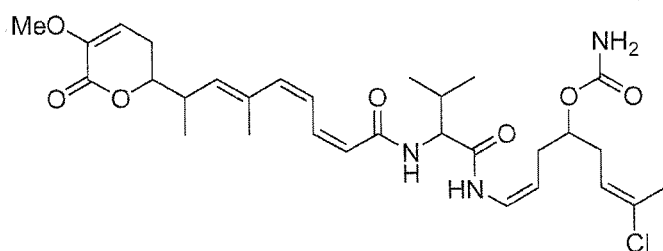


Compound 3

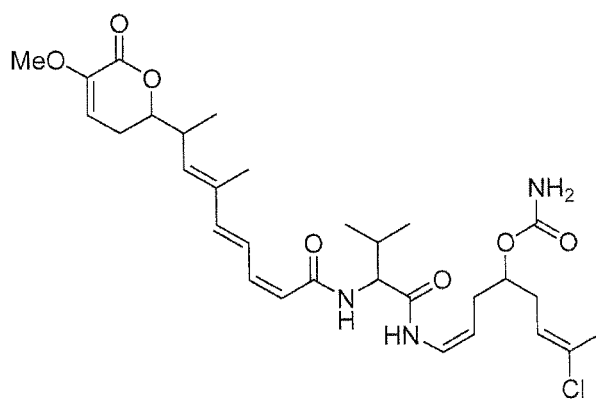
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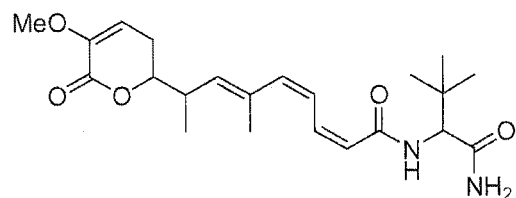
Compound 4



Compound 5

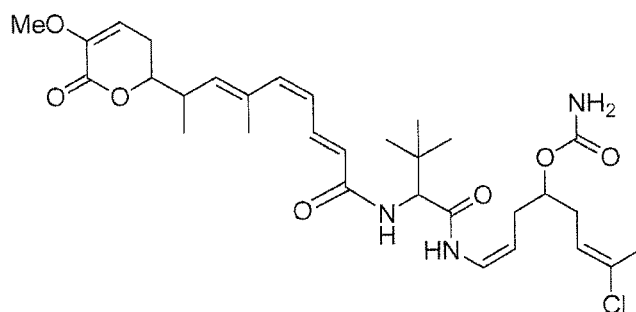


Compound 6



Compound 7

5



Compound 8

Compounds 1-8 were isolated from a porifera, of the family Raspailiidae, genus *Lithoplocamia*, species *lithistoides*.

A sample of *Lithoplocamia lithistoides* was deposited in the "Instituto de Ciencias del Mar y Limnología" of the Universidad Nacional Autónoma de México in Mazatlan, in Mexico, with the reference code
5 LEB-ICML-UNAM-11-2004. This sponge was collected by hand using SCUBA diving in Madagascar (S 17° 06.071' / E 49° 51.385') at a depth ranging between 6 and 20 m, and its description is the following:

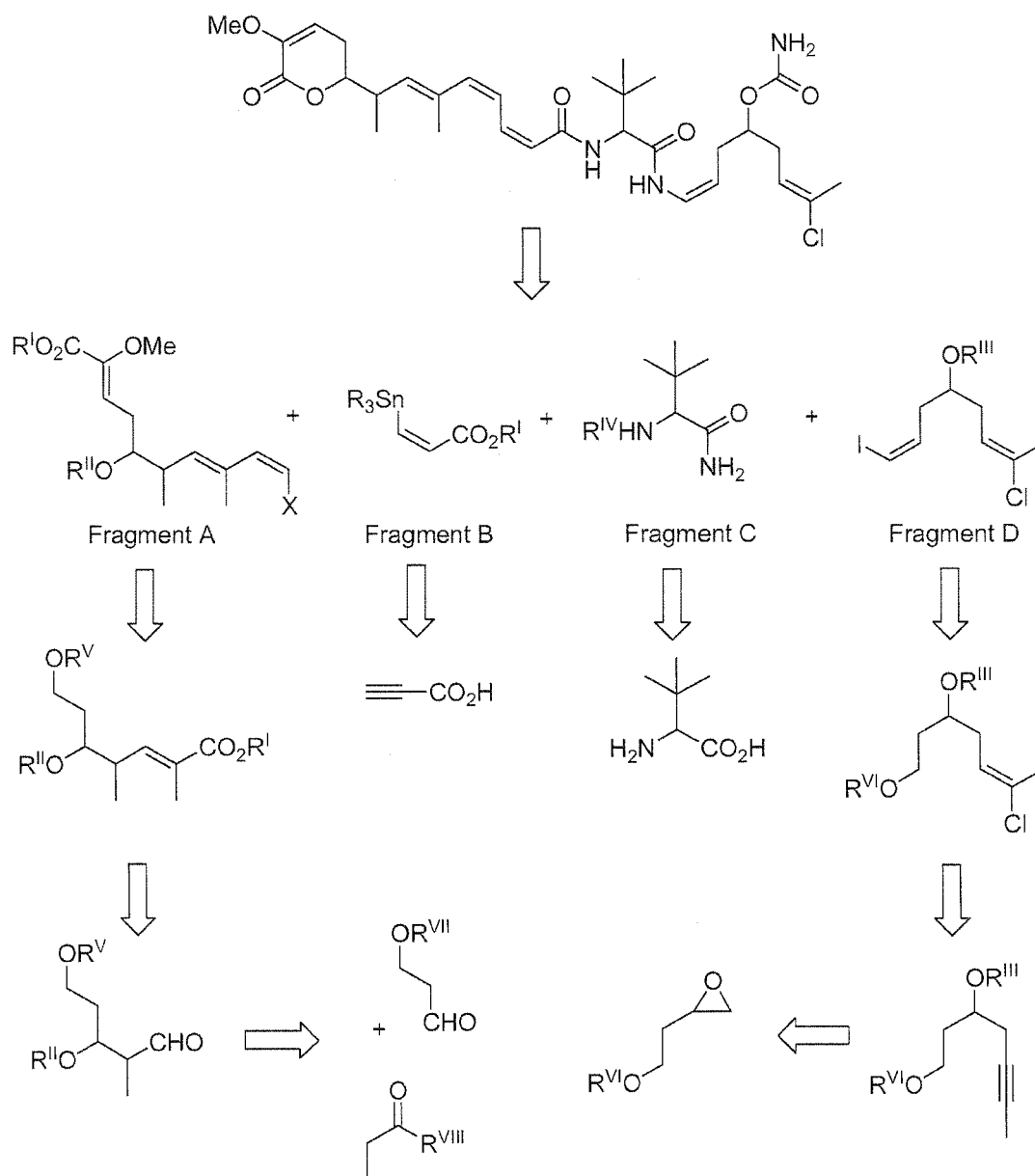
Family Raspailiidae: Raspailiidae Hentschel, 1923 are sponges
10 with encrusting, massive, lobate, fan-shaped or branching growth forms, usually with a very hispid surface. A specialised ectosomal skeleton is typically present, consisting of brushes of small thin styles (Hooper & Wiedenmayer 1994: fig. 17) or oxeas (Hooper & Wiedenmayer 1994: fig. 5), surrounding individual long thick styles or oxeas. The
15 choanosomal skeleton varies from a compressed axial skeleton, to plumo-reticulate or exclusively reticulate structures. Spongin fibres usually completely enclose coring spicules (choanosomal styles, oxeas or both). A special category of spined styles (Hooper & Wiedenmayer 1994: fig. 22), or modifications to styles (*e.g.* Figs 22-25, 28), echinate
20 fibres, protrude at right angles from fibres. Microscleres are usually absent, although single raphides (Hooper & Wiedenmayer 1994: fig. 109) or bundles (trichodragmata; Hooper & Wiedenmayer 1994: fig. 110) may occur in some genera. Raspailiids are widely distributed, ranging from shallow waters to at least 2460 m in depth (Hartman
25 1982).

Genus *Lithoplocamia*, species *lithistoides* are encrusting and massive growth forms, choanosomal skeleton is a dense isodictyal or irregularly subisodictyal reticulation of acanthostrongyles, in 1 or 2 size
30 categories, without axial condensation, without echinating acanthostyles, with extra-axial radial tracts of smooth styles, and

typically without a specialized raspailiid ectosomal skeleton (although when present ectosomal spicules are long slender oxeas); microscleres absent.

5 Samples of *Lithoplocamia lithistoides* were also collected in Kenya (S 04° 40' 5.5" / E 39° 26' 4.3", and S 03° 38' 36.5" / E 39° 53' 53.8") and Tanzania (S 08° 55' 31.7" / E 39° 34' 53.5", and S 05° 24.200' / E 39° 47.730') at a depth ranging between 30 and 40 m.

10 Additionally, the compounds of the invention can be obtained by synthesis. For example, compound 1 can be made by joining different fragments as indicated in the Scheme 1.



Scheme 1

where R, R^I , R^{II} , R^{III} , R^{IV} , R^V , R^{VI} , R^{VII} and R^{VIII} are the desired group or
 5 an appropriate protecting group as needed.

This process can comprise the following key steps:

- Amidation of the iodoalkenyl derivative (Fragment D) with
 10 Fragment C following standard literature procedures (Kozawa Y et al.

Tetrahedron Lett. 2002, 43, 111) to afford the corresponding enamide (fragment CD).

b) Stille coupling reaction between Fragment A and Fragment B following known procedures in organic synthesis (Scott WJ et al. J. Am. Chem. Soc. 1984, 106, 4630; Labadie J W et al. J. Org. Chem. 1983, 48, 4634-4642; Farina V et al. Organic Reactions 1998, Wiley) to obtain the linear polyene (fragment AB).

c) Fragments AB and CD can be coupled following standard procedures (Bodanszky M and Bodanszky A, The Practice of Peptide Synthesis, Springer-Verlag, 1993) to obtain the carbon skeleton of compound 1.

d) Deprotection of the alcohol OR^{II} followed by lactonization can be achieved according to known procedures in organic synthesis (Greene and Wuts, Protective Groups in Organic Synthesis, 3rd ed., Wiley-Interscience; Burke and Danheiser, Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents, Wiley; Pla D et al. J. Org. Chem. 2005, 70, 8231).

e) Finally, deprotection of alcohol OR^{III} followed by formation of the carbamate can be achieved by means of standard literature procedures (Love B et al. Organic Syntheses, Coll. Vol. 5, p. 162; Vol. 48, p. 32; Müller E et al. Methoden der Organischen Chemie (Houben-Weyl), 4th ed., Vol. 8, G. Thieme, Stuttgart, 1952, p. 137) to obtain compound 1.

The sequence of steps can be interchanged to obtain the final compound. For example, fragment BC can be prepared at first stage and then the sequential coupling with fragments A and D afford the

carbon skeleton of compound 1. Likewise, compound 1 can be prepared by the sequential coupling of fragments A, B, C, and D in any order. Another option is to perform the formation of the lactone moiety on fragment A previous to its coupling with any other fragment.

5

Analogues of compound 1 can be synthesized by an equivalent process as those described for compound 1, by choosing the appropriate substituents of the intermediate compounds in each case.

10

When necessary, appropriate protecting groups can be used on the substituents to ensure that reactive groups are not affected. The synthesis can be designed to employ precursor substituents which can be converted at the appropriate stage to a desired substituent. Saturation or unsaturation in the ring-structure can be introduced or

15 removed as part of the synthesis. Starting materials and reagents can be modified as desired to ensure synthesis of the intended compound. In addition, analogues can also be synthesized from compound 1 by usual procedures in synthetic organic chemistry which are known by a person skilled in the art.

20

The synthetic routes above mentioned can be modified as desired to give stereospecific compounds as well as mixtures of stereoisomers. It is possible to synthesize specific stereoisomers or specific mixtures by various methods including the use of stereospecific reagents or by

25 introducing chiral centers into the compounds during the synthesis. It is possible to introduce one or more stereocenters during synthesis and also invert existing stereocenters. In addition, it is possible to separate stereoisomers once the compound has been synthesized by standard resolution techniques known to the skilled reader.

30

An important feature of the above described compounds of formula **I** and **II** is their bioactivity and in particular their cytotoxic and antimitotic activity.

5 With this invention we provide novel pharmaceutical compositions of compounds of general formula **I** and **II** that possess cytotoxic and antimitotic activities and their use as antitumor agents. Thus the present invention further provides pharmaceutical compositions comprising a compound of this invention, a pharmaceutically
10 acceptable salt, derivative, tautomer, prodrug or stereoisomer thereof with a pharmaceutically acceptable carrier.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions
15 or emulsions) compositions for oral, topical or parenteral administration.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion,
20 oral preparations, and intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 1-12 hours, with 1-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24
25 hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of
5 the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of this invention may be used
10 with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

Antitumoral activities of these compounds include, but are not
15 limited, lung cancer, colon cancer, breast cancer and cervix cancer.

EXAMPLES

EXAMPLE 1: DESCRIPTION OF THE MARINE ORGANISM AND 20 COLLECTION SIDE

Lithoplocamia lithistoides was collected by hand using SCUBA diving in Madagascar (S 17° 06.071' / E 49° 51.385') at a depth ranging between 6 and 20 m. The animal material was identified by José Luis
25 Carballo (Universidad Autónoma de México). A sample of the specimen was deposited in the "Instituto de Ciencias del Mar y Limnología" of the Universidad Nacional Autónoma de México in Mazatlan, in Mexico, with the reference code LEB-ICML-UNAM-11-2004.

30

EXAMPLE 2: ISOLATION OF COMPOUND 1

The frozen specimen of Example 1 (61 g) was diced and extracted with H₂O (3 x 200 mL) and then with a mixture of MeOH:Dichloromethane (1:1, 3 x 200 mL) at room temperature. The combined organic extracts were concentrated to yield a crude of 1.11 g.

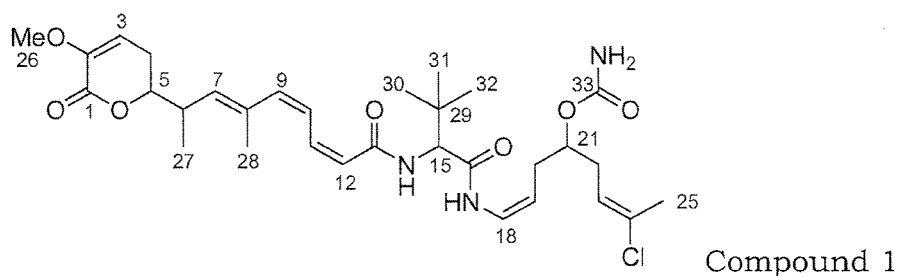
- 5 This material was subjected to VLC on Lichroprep RP-18 with a stepped gradient from H₂O to MeOH.

Compound **1** (1.6 mg) was isolated from fractions eluting with MeOH by semipreparative reversed phase HPLC (SymmetryPrep C18 7
10 μ m, 7.8 x 150 mm, gradient H₂O:MeCN from 35 to 100% MeCN in 30 min, UV detection, flow 2.5 mL/min, rt 14.4 min.).

Compound 1: amorphous white solid. (+)HRESIMS m/z 606.2940
[M+H]⁺ (Calcd. for C₃₁H₄₅³⁵ClN₃O₇ 606.2946); ¹H (500 MHz) and ¹³C
15 NMR (125 MHz) see Table 1.

Table 1. ^1H and ^{13}C NMR data of Compound 1 (CDCl_3)

N°	^1H (Multiplicity, J)	^{13}C	N°	^1H (Multiplicity, J)	^{13}C
1	-	161.6	18	6.84 (br dd, 10.8, 9.7)	124.5
2	-	145.2	19	4.80 (m)	105.0
3	5.63 (dd, 6.5, 2.6)	108.2	20	2.46 (m) 2.09 (ddd, 14.1, 8.4, 8.1)	30.7
4	2.45 (ddd, 17.3, 11.5, 2.6) 2.37 (ddd, 17.3, 6.5, 4.1)	26.1	21	4.41 (m)	74.9
5	4.24 (ddd, 11.5, 7.1, 4.1)	81.9	22	2.33 (m), 2H	33.0
6	2.85 (ddq, 9.8, 7.1, 6.7)	37.1	23	5.61 (br t, 6.8)	122.4
7	5.29 (d, 9.8)	134.1	24	-	132.0
8	-	133.7	25	2.06 (s), 3H	21.0
9	6.17 (d, 11.6)	140.2	26	3.66 (s), 3H	55.4
10	7.30 (dd, 11.6, 11.6)	124.6	27	1.15 (d, 6.7), 3H	16.3
11	6.91 (dd, 11.6, 11.6)	137.6	28	1.82 (s), 3H	17.1
12	5.70 (d, 11.6)	120.7	29	-	34.7
13	-	166.3	30	1.04 (s), 3H	26.7
14	6.51 (d, 9.5)	-	31	1.04 (s), 3H	26.7
15	4.41 (d, 9.5)	60.8	32	1.04 (s), 3H	26.7
16	-	168.2	33	-	157.2
17	8.78 (d, 10.8)	-			



EXAMPLE 3: ISOLATION OF COMPOUNDS 2, 3, 4, 5, 6 AND 7

A second group of samples of *Lithoplocamia lithistoides* (7.66 kg) was triturated and exhaustively extracted with a mixture of MeOH:Dichloromethane (1:1, 14 L, 2 × 5 L, 4 L). The solvent was removed *in vacuo* and the remaining aqueous solution was extracted with EtOAc (12 L, 3 × 8 L). The organic layer was evaporated to yield a crude of 21.71 g.

This material was subjected to RP-18 column chromatography with a stepped gradient from H₂O:MeOH (4:6) to MeOH. Fractions eluted with H₂O:MeOH (2:8, 430 mg) were pooled and subjected to preparative HPLC (Atlantis dC₁₈, OBD, 5 μm, 19 × 150 mm, isocratic H₂O:MeOH (39:61), flow: 20 mL/min, UV detection) to yield pure compounds **1** (160.8 mg), **2** (13.2 mg), and **7** (1.8 mg), and mixtures of **3** and **4** (11.4 mg) and **5** and **6** (10.0 mg). Pure compounds **3** (5.1 mg) and **4** (2.6 mg) were obtained after a final purification of the mixture by semipreparative HPLC (X-Terra Prep RP-18, 10 μm, 10 × 150 mm, gradient H₂O:MeOH for 50 to 70 % MeOH in 70 min, flow: 2.5 mL/min, UV detection). Compounds **5** (3.6 mg) and **6** (1.0 mg) were separated in a similar manner by semipreparative HPLC (X-Terra Prep RP-18, 10 μm, 10 × 150 mm, isocratic H₂O:MeOH (45:55), flow: 2.5 mL/min, UV detection).

Compound 2: amorphous white solid. MS (ES) *m/z* 606.3 [M+H]⁺, 628.3 [M+Na]⁺; ¹H (500 MHz) and ¹³C NMR (125 MHz) see Table 2.

Compound 3: amorphous white solid. (+)HRESIMS *m/z* 628.2774 [M+Na]⁺ (Calcd. for C₃₁H₄₄³⁵ClN₃O₇Na 628.2760); ¹H (500 MHz) and ¹³C NMR (125 MHz) see Table 3.

Compound 4: amorphous white solid. (+)HRESIMS m/z 594.3152 $[M+Na]^+$ (Calcd. for $C_{31}H_{45}N_3O_7Na$ 594.3150); 1H (500 MHz) and ^{13}C NMR (125 MHz) see Table 4.

- 5 Compound 5: amorphous white solid. MS (ES) m/z 592.3 $[M+H]^+$, 614.3 $[M+Na]^+$; 1H (500 MHz) and ^{13}C NMR (125 MHz) see Table 5.

Compound 6: amorphous white solid. MS (ES) m/z 592.3 $[M+H]^+$, 614.3 $[M+Na]^+$; 1H (500 MHz) and ^{13}C NMR (125 MHz) see Table 6.

10

Compound 7: amorphous white solid. (+)HRESIMS m/z 427.2207 $[M+Na]^+$ (Calcd. for $C_{22}H_{32}N_2O_5Na$ 427.2203); 1H (500 MHz) and ^{13}C NMR (125 MHz) see Table 7.

15

Table 2. ^1H and ^{13}C NMR data of Compound 2 (CDCl_3)

N°	^1H (Multiplicity, J)	^{13}C	N°	^1H (Multiplicity, J)	^{13}C
1	-	161.5	18	6.83 (ddd, 10.8, 8.9, 1.2)	124.4
2	-	145.2	19	4.80 (m)	105.5
3	5.61 (dd, 6.4, 3.1)	108.1	20	2.43 (m) 2.12 (m)	30.6
4	2.41 (ddd, 17.1, 11.3, 3.0) 2.34 m	26.6	21	4.50 (m)	74.9
5	4.18 (ddd, 11.3, 7.8, 4.3)	81.6	22	2.36 (m), 2H	33.2
6	2.88 (ddq, 10.0, 7.8, 6.7)	37.4	23	5.61 (br t, 6.5)	122.2
7	5.46 (br d, 10.0)	136.5	24	-	132.1
8	-	135.6	25	2.07 (d, 1.0), 3H	21.0
9	6.41 (d, 15.5)	145.0	26	3.65 (s), 3H	55.4
10	7.60 (dd, 15.5, 11.4)	124.2	27	1.16 (d, 6.7), 3H	16.5
11	6.49 (dd, 11.4, 11.3)	142.5	28	1.86 (d, 1.0), 3H	13.1
12	5.63 (d, 11.3)	119.0	29	-	34.6
13	-	166.5	30	1.05 (s), 3H	26.6
14	6.39 (d, 9.4)	-	31	1.05 (s), 3H	26.6
15	4.44 (d, 9.4)	60.7	32	1.05 (s), 3H	26.6
16	-	168.3	33	-	157.0
17	8.50 (br d, 10.8)	-			

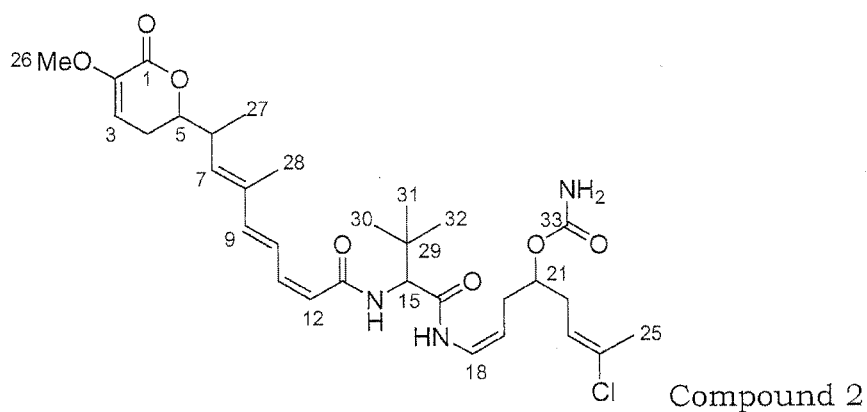


Table 3. ^1H and ^{13}C NMR data of Compound 3 (CDCl_3)

N°	^1H (Multiplicity, J)	^{13}C	N°	^1H (Multiplicity, J)	^{13}C
1	-	161.5	18	6.83 (br dd, 10.7, 9.6)	124.4
2	-	145.3	19	4.81 (m)	105.4
3	5.61 (dd, 6.3, 3.0)	108.1	20	2.47 (m) 2.10 (m)	30.8
4	2.39 (m) 2.37 (m)	26.3	21	4.43 (m)	75.0
5	4.21 (ddd, 10.9, 7.6, 4.7)	81.7	22	2.34 (m), 2H	33.0
6	2.90 (ddq, 10.0, 7.6, 6.6)	37.4	23	5.62 (br t, 6.5)	122.4
7	5.46 (br d, 10.0)	136.4	24	-	132.0
8	-	135.1	25	2.07 (s), 3H	21.0
9	6.51 (d, 15.3)	144.1	26	3.65 (s), 3H	55.4
10	6.27 (dd, 15.3, 11.1)	125.2	27	1.15 (d, 6.6), 3H	16.6
11	7.25 (dd, 14.8, 11.1)	141.9	28	1.83 (d, 1.0), 3H	12.9
12	5.96 (d, 14.8)	122.9	29	-	35.1
13	-	166.0	30	1.03 (s), 3H	26.6
14	6.39 (d, 9.3)	-	31	1.03 (s), 3H	26.6
15	4.43 (d, 9.3)	60.8	32	1.03 (s), 3H	26.6
16	-	168.3	33	-	157.9
17	8.82 (d, 10.7)	-			

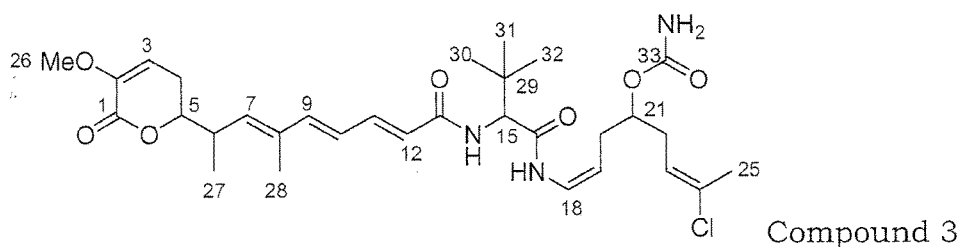
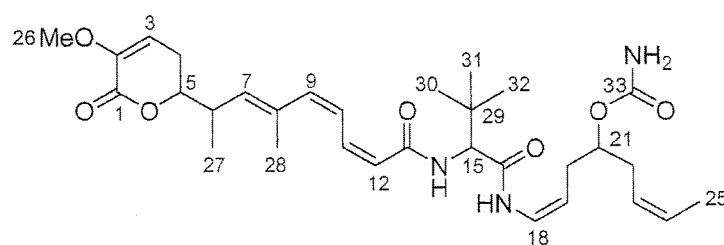


Table 4. ^1H and ^{13}C NMR data of Compound 4 (CDCl_3)

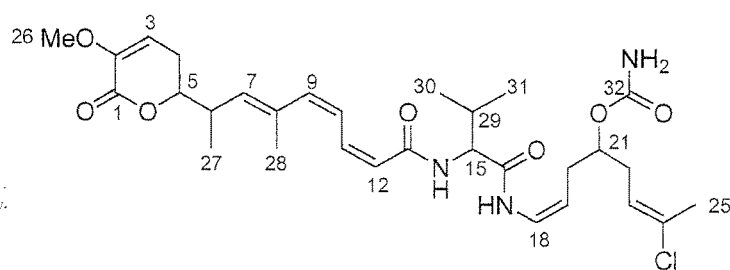
Nº	¹ H (Multiplicity, J)	¹³ C	Nº	¹ H (Multiplicity, J)	¹³ C
1	-	161.6	18	6.82 (ddd, 10.4, 9.1, 0.9)	124.2
2	-	145.2	19	4.82 (m)	105.8
3	5.63 (dd, 6.6, 2.7)	108.2	20	2.46 (m) 2.12 (ddd, 14.1, 8.0, 8.0)	30.9
4	2.44 (m) 2.39 (m)	26.1	21	4.45 (m)	75.6
5	4.25 (ddd, 11.3, 7.0, 4.0)	81.9	22	2.35 (m), 2H	31.4
6	2.85 (ddq, 9.9, 7.0, 6.7)	37.1	23	5.40 (m)	124.9
7	5.29 (d, 9.9)	134.1	24	5.60 (m)	127.1
8	-	133.8	25	1.63 (dd, 6.8, 1.0), 3H	13.0
9	6.15 (d, 11.6)	140.2	26	3.66 (s), 3H	55.4
10	7.31 (dd, 11.6, 11.6)	124.4	27	1.15 (d, 6.7), 3H	16.4
11	6.90 (dd, 11.6, 11.6)	137.5	28	1.82 (s), 3H	17.1
12	5.72 (br d, 11.6)	120.8	29	-	34.8
13	-	166.3	30	1.04 (s), 3H	26.7
14	6.53 (d, 9.6)	-	31	1.04 (s), 3H	26.7
15	4.44 (d, 9.6)	60.7	32	1.04 (s), 3H	26.7
16	-	168.2	33	-	157.6
17	8.69 (d, 10.4)	-			



Compound 4

Table 5. ^1H and ^{13}C NMR data of Compound 5 (CDCl_3)

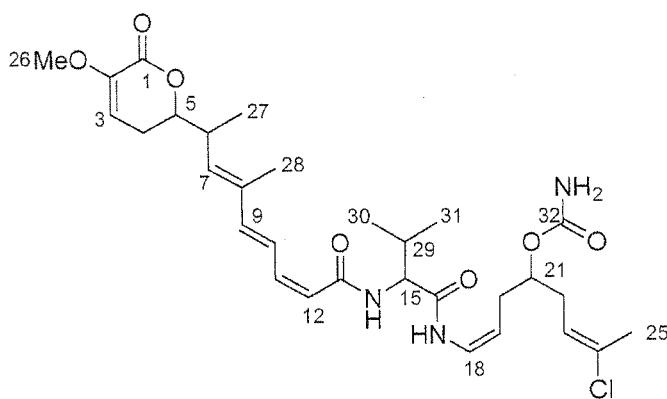
N°	^1H (Multiplicity, J)	^{13}C	N°	^1H (Multiplicity, J)	^{13}C
1	-	161.7	17	8.69 (d, 10.7)	-
2	-	145.1	18	6.84 (ddd, 10.7, 9.8, 0.9)	124.5
3	5.64 (dd, 6.6, 2.6)	108.3	19	4.80 (m)	105.2
4	2.48 (ddd, 17.4, 12.0, 2.6) 2.37 (ddd, 17.4, 6.6, 3.9)	26.0	20	2.45 (m) 2.10 (ddd, 15.0, 7.1, 6.2)	30.7
5	4.28 (ddd, 12.0, 6.6, 3.9)	81.9	21	4.44 (m)	74.8
6	2.85 (ddq, 9.7, 6.6, 6.7)	37.0	22	2.33 (m), 2H	33.0
7	5.31 (d, 9.7)	134.1	23	5.60 (br t, 7.1)	122.4
8	-	133.6	24	-	132.0
9	6.17 (d, 11.5)	140.3	25	2.06 (s), 3H	21.0
10	7.31 (dd, 11.5, 11.5)	124.5	26	3.66 (s), 3H	55.4
11	6.93 (dd, 11.5, 11.5)	137.6	27	1.15 (d, 6.7), 3H	16.2
12	5.73 (d, 11.5)	120.5	28	1.82 (br s), 3H	17.1
13	-	166.5	29	2.22 (m)	31.1
14	6.54 (d, 9.2)	-	30	1.00 (d, 6.8), 3H	19.3
15	4.46 (dd, 9.2, 6.4)	58.5	31	0.96 (d, 6.8), 3H	18.0
16	-	169.1	32	-	157.4



Compound 5

Table 6. ^1H and ^{13}C NMR data of Compound 6 (CDCl_3)

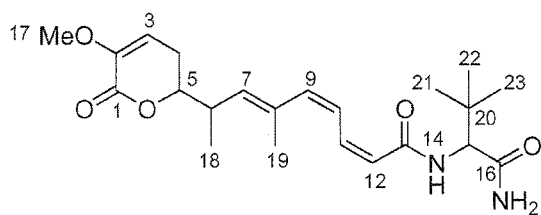
N°	^1H (Multiplicity, J)	^{13}C	N°	^1H (Multiplicity, J)	^{13}C
1	-	161.5	17	8.59 (d, 10.8)	-
2	-	145.2	18	6.84 (br dd, 10.8, 8.7)	124.5
3	5.61 (dd, 6.8, 2.8)	108.2	19	4.81 (m)	105.5
4	2.41 (m), 2H	26.6	20	2.42 (m) 2.13 (ddd, 14.1, 7.5, 7.2)	30.6
5	4.18 (ddd, 11.6, 7.7, 4.2)	81.6	21	4.49 (m)	74.7
6	2.88 (ddq, 10.0, 7.7, 6.6)	37.4	22	2.35 (m), 2H	33.1
7	5.47 (br d, 10.0)	136.5	23	5.61 (m)	122.3
8	-	135.5	24	-	132.1
9	6.41 (d, 15.4)	145.0	25	2.07 (s), 3H	21.0
10	7.61 (dd, 15.4, 11.3)	124.2	26	3.65 (s), 3H	55.4
11	6.49 (dd, 11.3, 11.3)	142.5	27	1.15 (d, 6.6), 3H	16.5
12	5.63 (d, 11.3)	118.9	28	1.86 (s), 3H	13.1
13	-	166.6	29	2.20 (m)	30.9
14	6.34 (d, 8.9)	-	30	1.01 (d, 6.7), 3H	19.3
15	4.42 (dd, 8.9, 7.1)	58.6	31	0.98 (d, 6.8), 3H	18.2
16	-	169.0	32	-	157.0



Compound 6

Table 7. ^1H and ^{13}C NMR data of Compound 7 (CDCl_3)

N°	^1H (Multiplicity, J)	^{13}C
1	-	161.5
2	-	145.3
3	5.62 (dd, 6.1, 3.2)	108.1
4	2.43 (m) 2.38 (m)	26.3
5	4.21 (ddd, 12.0, 7.0, 4.8)	81.8
6	2.86 (ddq, 9.9, 7.0, 6.6)	37.4
7	5.29 (d, 9.9)	134.2
8	-	134.1
9	6.17 (d, 11.6)	140.2
10	7.26 (dd, 11.6, 11.5)	124.1
11	6.90 (dd, 11.5, 11.5)	137.4
12	5.67 (d, 11.5)	120.8
13	-	166.2
14	6.22 (d, 9.2)	-
15	4.34 (d, 9.2)	59.8
16	-	172.5
17	3.66 (s), 3H	55.4
18	1.17 (d, 6.6), 3H	16.7
19	1.85 (s), 3H	17.2
20	-	34.5
21	1.05 (s), 3H	26.6
22	1.05 (s), 3H	26.6
23	1.05 (s), 3H	26.6



Compound 7

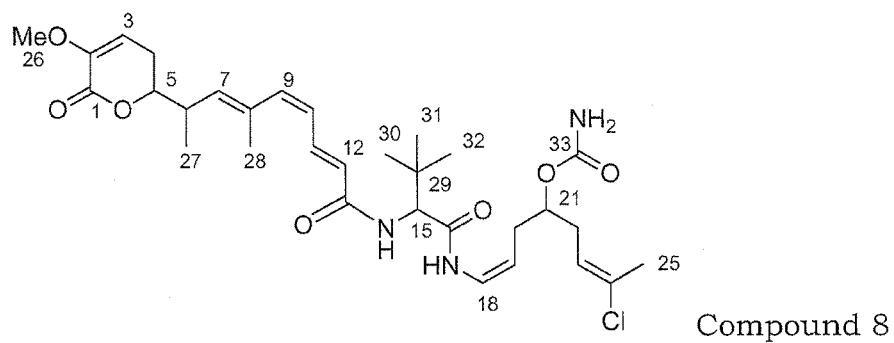
EXAMPLE 4: ISOLATION OF COMPOUND 8

A fraction containing compound 1 (61.6 mg) coming from the extraction procedure disclosed in Example 3 was further purified by semipreparative HPLC (Symmetryprep C-18, 7 μ m, 7.8 $\times$ 150 mm, isocratic H₂O:CH₃CN (55:45), flow: 2.3 mL/min, UV detection) and 0.9 mg of compound **8** were obtained in a pure form.

Compound 8: amorphous white solid. MS (ES) m/z 606.2 [M+H]⁺, 628.3 [M+Na]⁺; ¹H (500 MHz) and ¹³C NMR (125 MHz) see Table 8.

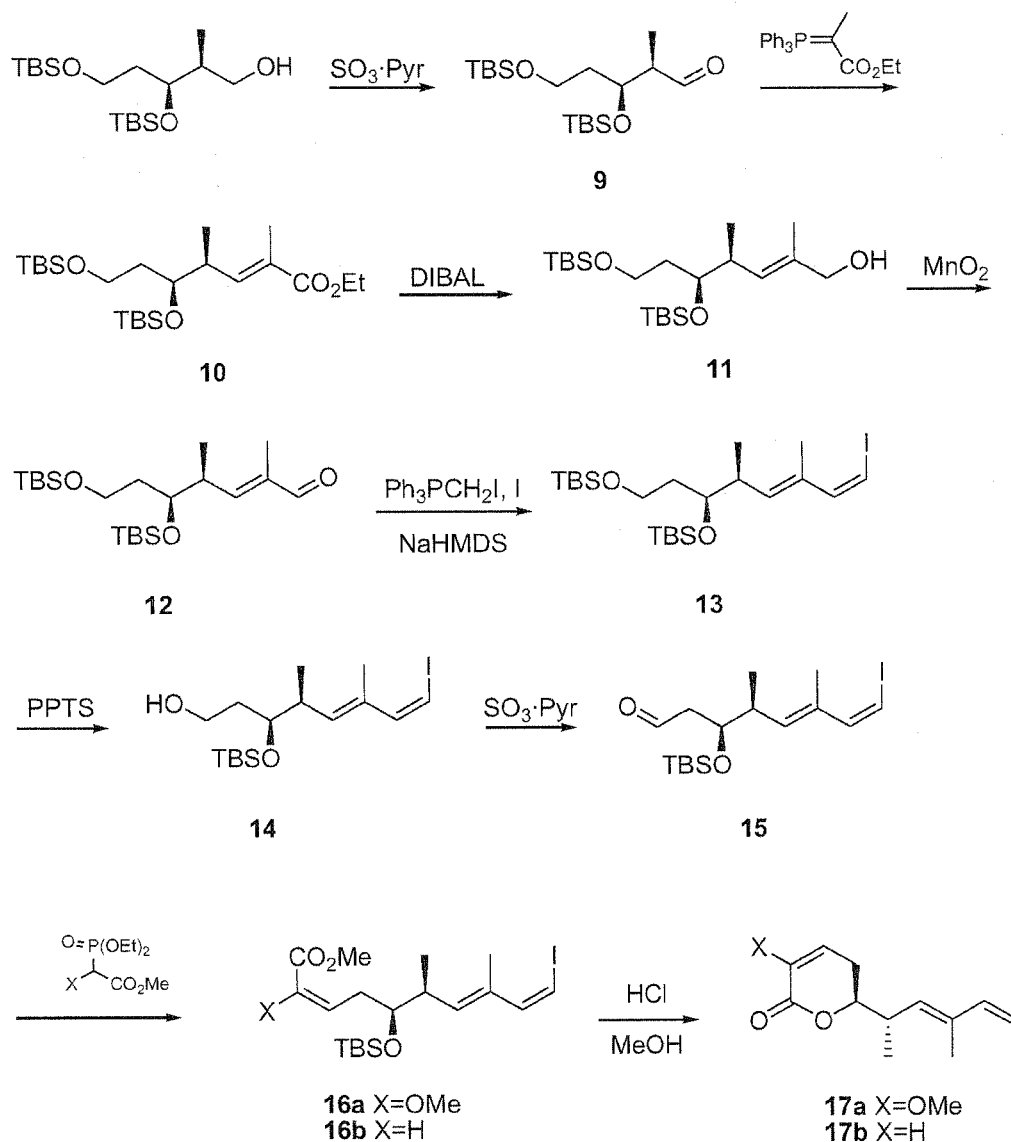
Table 8. ¹H and ¹³C NMR data of Compound 8 (CDCl₃)

N°	¹ H (Multiplicity, J)	¹³ C	N°	¹ H (Multiplicity, J)	¹³ C
1	-	161.6	18	6.83 (ddd, 10.8, 8.7, 1.0))	124.4
2	-	145.2	19	4.80 (m)	105.2
3	5.66 (br t, 4.6)	108.4	20	2.11 (ddd, 14.2, 8.1, 7.8) 2.45 (m)	30.7
4	2.45 (m), 2H	26.6	21	4.46 (m)	75.0
5	4.21 (ddd, 7.7, 7.7, 7.7)	81.7	22	2.34 (t, 6.7), 2H	33.0
6	2.85 (ddq, 10.0, 7.7, 6.7)	37.4	23	5.60 (td, 7.8, 1.2)	122.3
7	5.35 (d, 10.0)	135.1	24	-	132.0
8	-	134.6	25	2.06 (s), 3H	21.0
9	6.16 (d, 11.7)	140.6	26	3.66 (s), 3H	55.4
10	6.06 (dd, 11.7, 11.7)	125.6	27	1.17 (d, 6.7), 3H	16.6
11	7.71 (dd, 14.7, 11.7)	137.9	28	1.91 (d, 0.7), 3H	17.0
12	5.95 (d, 14.7)	124.5	29	-	34.8
13	-	166.0	30	1.04 (s), 3H	26.6
14	6.35 (d, 9.5)	-	31	1.04 (s), 3H	26.6
15	4.47 (d, 9.5)	61.0	32	1.04 (s), 3H	26.6
16	-	168.3	33	-	157.1
17	8.65 (d, 10.8)	-			

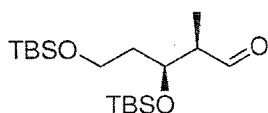


EXAMPLE 5: SYNTHESIS OF FRAGMENT A

Scheme 2 provides several examples of synthesis of fragment A, in
5 accordance with the nomenclature provided in Scheme 1.



Scheme 2

5 Synthesis of intermediate 9

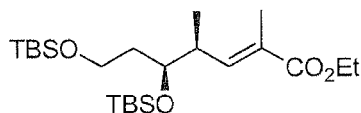
To a 0 °C solution of (2*S*,3*S*)-3,5-Bis[[(*tert*-butyl)dimethylsilyl]oxy]-4-methylpentan-1-ol (P. Phukan, S. Sasmal and M.E. Maier *Eur. J. Org. Chem.* 2003, 1733-1740) (50 g, 0.14 mol) in a mixture of

Dichloromethane/DMSO (331mL/149 mL), Et₃N (96.1 mL, 0.69 mol) was added via addition funnel. After 10 min, SO₃·Pyr (54.8 g, 0.34 mol) was added portionwise and the solution was stirred for another 2h at 0 °C. Then, it was diluted with dichloromethane (800 ml) and quenched
5 with HCl (0.5N, 800 mL). The organic layer was decanted, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 100:0 to 10:1) afforded 45 g (yield: 90%) of aldehyde **9**.

¹H-RMN (CDCl₃, 300 MHz) δ: 9.79 (s, 1H), 4.30 (m, 1H), 3.65 (m, 2H),
10 2.51 (m, 1H), 1.69 (m, 2H), 1.04 (d, 3H, *J* = 6.9Hz), 0.85-0.88 (m, 18H), 0.03-0.07 (m, 12H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 205.4, 69.4, 59.6, 51.7, 37.5, 26.1, 26.0, 18.4, 18.2, 8.0, -4.3, -4.5, -5.2.

15 Synthesis of intermediate 10

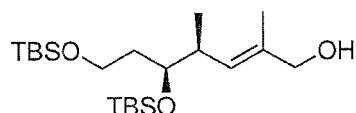


Over a solution of aldehyde **9** (45 g, 0.12 mol) in toluene (625 mL)
20 Carboethoxyethylidene-triphenylphosphorane (113 g, 0.31 mol) was added and the mixture was heated at 60°C over 17 h. Then, the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 100:0 to 10:1) affording 53.3 g (yield: 96%) of ester compound **10**.

25 ¹H-RMN (CDCl₃, 300 MHz) δ: 6.71 (dd, 1H, *J* = 1.5, 10.2 Hz), 4.19 (m, 2H), 3.77 (m, 1H), 3.66 (m, 2H), 2.61 (m, 1H), 1.85 (d, 3H, *J* = 1.5 Hz), 1.68 (m, 2H), 1.30 (t, 3H, *J* = 7.2 Hz), 0.98 (d, 3H, 6.9 Hz), 0.90 (m, 18H), 0.05 (m, 12H).

30 ¹³C-RMN (CDCl₃, 75 MHz) δ: 168.3, 145.4, 126.7, 72.2, 60.4, 59.7, 38.4, 38.0, 25.9, 18.2, 18.1, 14.3, 14.3, 12.6, -4.4, -4.6, -5.4.

Synthesis of intermediate 11

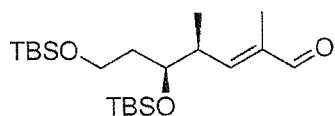


Over a -78°C cooled solution of ester **10** (46.7 g, 0.105 mol) in anhydrous THF (525 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (231 mL, 0.231 mol) was added over a
10 period of 10 min and the mixture was stirred at -78°C. After 4 hours the reaction was quenched with MeOH (10 mL) and a saturated solution of sodium potassium tartrate was added (800 mL) and diluted with EtOAc (1000 mL). This mixture was stirred for 2 h and then the organic layer was decanted. The aqueous residue was extracted with additional
15 EtOAc (2 x 400 mL) and the combined organic layers were dried (Na₂SO₄) and the solvent was evaporated. The resulting oil was purified by column chromatography (hexane/EtOAc 20:1 to 10:1) affording 32.5 g (yield: 77%) of alcohol **11**.

¹H-RMN (CDCl₃, 300 MHz) δ: 5.31 (d, 1H, *J* = 9.6 Hz), 3.98 (m, 2H), 3.66 (m, 3H), 2.49 (m, 1H), 1.67 (s, 3H), 1.70-1.62 (m, 2H), 0.91 (d, 3H, *J* = 6.9 Hz), 0.88 (m, 18H), 0.03 (m, 12H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 133.9, 129.8, 73.1, 69.1, 59.9, 37.8, 37.5, 25.9, 18.3, 18.1, 15.9, 13.9, -4.4, -4.4, -5.3.

25 Synthesis of intermediate 12



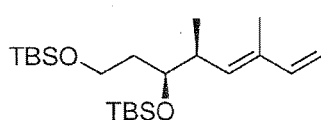
Over a solution of alcohol **11** (31.2 g, 77.5 mmol) in ethyl ether (387 mL) under argon atmosphere, MnO₂ (101 g, 1.16 mol) were added and the mixture was stirred at room temperature for 2 hours. This mixture was filtrated over a silica gel column eluting with EtOAc (3L) and the
5 resulting solution was dried under reduced pressure to afford 29.1 g (yield: 94 %) of aldehyde **12**.

¹H-RMN (CDCl₃, 300 MHz) δ : 9.37 (s, 1H), 6.44 (d, 1H, J = 9.6 Hz), 3.82 (dd, 1H, J = 6.3, 10.8 Hz), 3.65 (m, 2H), 2.82 (m, 1H), 1.74 (s, 3H), 1.67 (m, 2H), 1.02 (d, 3H, J = 6.9 Hz), 0.86 (s, 18H), 0.04-0.01 (m, 12H).

10 ¹³C-RMN (CDCl₃, 75 MHz) δ : 195.4, 157.8, 138.3, 134.5, 72.0, 59.5, 36.7, 37.5, 25.8, 18.2, 18.1, 14.3, 9.4, -4.4, -4.5, -5.4.

Synthesis of intermediate 13

15



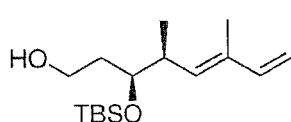
To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (96.3 g, 181.7 mmol) in THF (727 mL) at 0°C, a 1M solution of sodium hexamethyldisilazane
20 (NaHMDS) (181.7 mL, 181.7 mmol) was slowly added, via addition funnel, over a period of 10 min. After stirring for an additional 5 min, the solution was cooled to -78°C and 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (43.9 mL, 363.4 mmol) was then added via cannula, followed by the addition of aldehyde **12** (29.1 g, 72.7 mmol)
25 dissolved in THF (727 mL). The temperature was kept at -78°C while the reaction mixture was stirred for 2 hours. Hexane (1L) was added and the resulting slurry was filtrated over celite and washed with additional hexane (3L). The filtrate was evaporated under reduced pressure and the resulting oil was purified by column chromatography
30 (hexane/EtOAc 100:0 to 20:1) affording 32 g (yield: 84%) of iodide **13**.

^1H -RMN (CDCl_3 , 300 MHz) δ : 6.73 (d, 1H, $J = 8.4$ Hz), 6.09 (dd, 1H, $J = 8.4$, 1.2 Hz), 5.57 (dd, 1H, $J = 9.6$, 1.2 Hz), 3.63-3.71 (m, 3H), 2.58 (m, 1H), 1.90 (s, 3H), 1.70 (m, 2H), 0.96 (dd, 3H, $J = 6.6$, 1.2 Hz), 0.88 (s, 18H), 0.04 (m, 12H).

5 ^{13}C -RMN (CDCl_3 , 75 MHz) δ : 142.3, 138.1, 131.8, 74.6, 72.9, 59.8, 38.1, 37.9, 26.0, 18.3, 18.2, 15.7, 15.7, -4.4, -5.2, -5.2.

Synthesis of intermediate 14

10



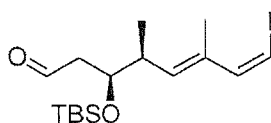
To a solution of iodide **13** (12 g, 22.9 mmol) in EtOH (114 mL) pyridinium *p*-toluenesulfonate (PPTS) (2.01 g, 8.0 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours.

15 Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 10:1) affording 8.7 g (yield: 93%) of alcohol **14**.

^1H -RMN (CDCl_3 , 300 MHz) δ : 6.69 (d, 1H, $J = 8.4$ Hz), 6.12 (d, 1H, $J = 8.4$ Hz), 5.47 (d, 1H, $J = 9.9$ Hz), 3.67-3.87 (m, 4H), 2.71 (m, 1H), 1.89
20 (s, 3H), 1.73-1.86 (m, 2H), 1.01 (d, 3H, $J = 6.9$ Hz), 0.91 (s, 9H), 0.087-0.115 (m, 6H).

^{13}C -RMN (CDCl_3 , 75 MHz) δ : 142.4, 136.4, 132.6, 75.8, 75.2, 60.0, 38.1, 36.4, 26.1, 18.2, 17.1, 16.0, -4.1, -4.2.

25 Synthesis of intermediate 15

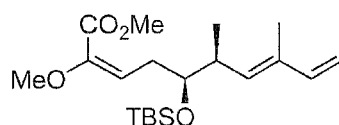


To a 0 °C solution of alcohol **14** (8.7 g, 21.2 mmol) in a mixture of Dichloromethane/DMSO (50.9 mL/22.9mL), Et₃N (14.8 mL, 106 mmol) was added via addition funnel. After 10 min, SO₃·Pyr (8.43 g, 53.0 mol) was added portionwise and the solution was stirred for another 2h at 0 °C. Then, it was diluted with Dichloromethane (800 mL) and quenched with HCl (0.5N, 50 mL). The organic layer was decanted, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 10:1) afforded 6.9 g (yield: 80%) of aldehyde **15**.

¹H-RMN (CDCl₃, 300 MHz) δ: 9.89 (t, 1H, *J* = 1.5 Hz), 6.67 (d, 1H, *J* = 8.4 Hz), 6.13 (d, 1H, *J* = 8.4 Hz), 5.43 (d, 1H, *J* = 10.2 Hz), 3.98 (m, 1H), 2.59-2.69 (m, 3H), 1.85 (s, 3H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 201.8, 141.9, 135.2, 133.3, 76.3, 71.9, 49.3, 39.3, 25.8, 18.0, 16.7, 15.9, -4.4, -4.5.

Synthesis of intermediate 16a



20

To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (5.51 g, 14.45 mmol) and 18-crown-6 (11.5 g, 43.34 mmol) in dry THF (390 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide solution (KHMDs) (43.34 mL, 21.67 mmol) was added dropwise. After 15 min aldehyde **15** (5.9 g, 14.45 mmol) in dry THF was added dropwise over a period of 30 min and stirred at -78°C for 90 min. Then, the reaction was quenched with a saturated NH₄Cl solution (200 mL), warmed to room temperature and diluted with Dichloromethane (1000 mL). The organic phase was dried (Na₂SO₄) and evaporated at reduced pressure. Purification by column

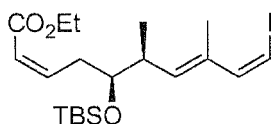
30

chromatography (hexane/Et₂O 20:1) afforded pure 4.2 g (59%) of (**E**)-**16a**.

¹H-RMN (CDCl₃, 300 MHz) δ: 6.70 (d, 1H, *J* = 8.4 Hz), 6.08 (d, 1H, *J* = 8.4 Hz), 5.47 (d, 1H, *J* = 9.9 Hz), 5.37 (t, 1H, *J* = 7.2 Hz), 3.78 (s, 3H),
 5 3.60 (s, 3H), 3.60 (m, 1H), 2.79 (m, 1H), 2.52-2.67 (m, 2H), 1.83 (s, 3H),
 0.99 (d, 3H, *J* = 6.6 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 163.7, 145.9, 142.1, 137.3, 132.1, 110.4, 75.4, 74.8, 55.4, 51.9, 38.1, 32.3, 25.9, 18.1, 16.5, 15.7, -4.3, -4.5.

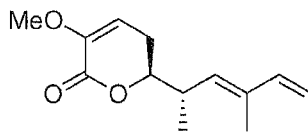
10 Synthesis of intermediate 16b



To a solution of Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (0.16
 15 mL, 0.66 mmol) and 18-crown-6 (350 mg, 1.32 mmol) in dry THF (2.4
 mL) stirred under argon atmosphere at 0°C, KHMDS (1.23 mL, 0.62
 mmol) was added dropwise. After 30 min aldehyde **15** (180 mg, 0.44
 mmol) in dry THF was added dropwise and stirred at -78°C for 60 min.
 Then, the reaction was quenched with saturated NH₄Cl solution,
 20 warmed to room temperature and diluted with EtOAc. The organic
 phase was dried (Na₂SO₄) and evaporated at reduced pressure.
 Purification by column chromatography (hexane/EtOAc 100:1 to 15:1)
 afforded 172 mg (yield: 82 %) of (**Z**)-**16b**.

¹H-RMN (CDCl₃, 300 MHz) δ: 6.70 (d, 1H, *J* = 8.7 Hz), 6.44-6.36 (m, 1H),
 25 6.09 (d, 1H, *J* = 8.7 Hz), 5.86-5.81 (m, 1H), 5.47 (d, 1H, *J* = 9.9 Hz),
 4.14 (q, 2H, *J* = 7.2 Hz), 3.69-3.64 (m, 1H), 3.06-3.00 (m, 1H), 2.85-2.75
 (m, 1H), 2.59-2.51 (m, 1H), 1.84 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.00 (d,
 3H, *J* = 6.6 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

MS (ES) *m/z* 501.0 [M+Na]⁺

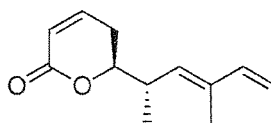
Synthesis of intermediate 17a

5 To a solution of ester **16a** (4.15 g, 8.39 mmol) in MeOH (125 mL) at room temperature, HCl 37% (1.04 mL) was added and the reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was
10 extracted with Dichloromethane (3 x 200 mL), dried and evaporated. Filtration by column chromatography (hexane/EtOAc 10:1 to 2:1) afforded 2.76 g (yield: 94%) of lactone **17a**.

¹H-RMN (500 MHz, CDCl₃) δ: 6.68 (d, 1H, *J* = 9.0 Hz), 6.20 (d, 1H, *J* = 8.5 Hz), 5.63 (dd, 1H, *J* = 2.5, 6.5 Hz), 5.43 (d, 1H, *J* = 10.0 Hz), 4.19
15 (m, 1H), 3.65 (s, 3H), 2.84 (m, 1H), 2.55 (m, 1H), 2.43 (dc, *J* = 1H, 3.0, 12.0, 15.0, 18.0 Hz), 1.87 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz).

¹³C-RMN (125 MHz, CDCl₃) δ: 161.6, 145.2, 141.8, 134.4, 132.7, 108.3, 81.7, 77.4, 55.4, 37.1, 26.6, 16.5, 16.1.

20 Synthesis of intermediate 17b



To a solution of ester **16b** (172 mg, 0.36 mmol) in MeOH (4.5 mL) at
25 room temperature, HCl 37% (0.03 mL) was added and the reaction mixture was stirred for 3 hours. Then the mixture was neutralized with a saturated solution of NaHCO₃ (pH 7-8) and the organic solvent was

evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane, dried and evaporated. Filtration by column chromatography (hexane/EtOAc 10:1 to 5:1) afforded 70 mg (yield: 61%) of lactone **17b**.

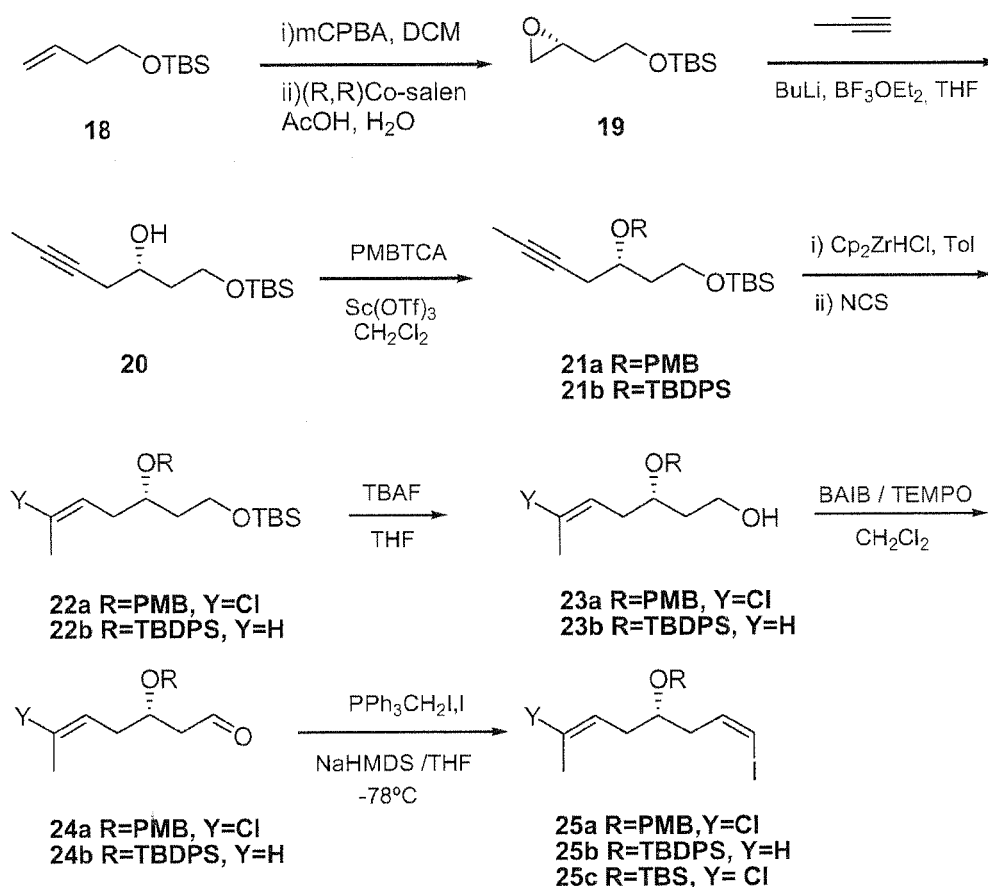
- 5 ^1H -RMN (CDCl_3 , 300 MHz) δ : 6.91-6.85 (m, 1H), 6.68 (d, 1H, $J = 8.4$ Hz), 6.62 (d, 1H, $J = 8.4$ Hz), 6.02 (dd, 1H, $J = 2.7, 9.6$ Hz), 5.45 (d, 1H, $J = 9.9$ Hz), 4.19 (m, 1H), 3.65 (s, 3H), 4.26-4.18 (m, 1H), 2.92-2.79 (m, 1H), 2.57-2.48 (m, 1H), 2.39-2.28 (m, 1H), 1.88 (s, 3H), 1.17 (d, 3H, $J = 6.6$ Hz).

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EXAMPLE 6: SYNTHESIS OF FRAGMENT D

Scheme 3 provides several examples of synthesis of fragment D, in accordance with the nomenclature provided in Scheme 1.

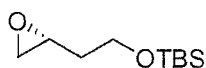
15



Scheme 3

Synthesis of intermediate 19

5



To a solution of intermediate **18** (72.3 g) in dichloromethane (DCM) (918 mL) at room temperature 3-Chloroperbenzoic acid (*m*-CPBA) (100 g, 0.58 mol) was added in portionwise, and the mixture was stirred at room temperature for 18 h. The white precipitate was quenched with saturated solution of NaHCO₃, extracted with DCM (3 x 250 mL) and washed again with saturated aqueous solution of NaHCO₃ (3 x 250 mL). The organic layers were combined, dried over Na₂SO₄ and concentrated in vacuo. The resulting oil was purified on silica gel (Hexane-AcOEt; 15:1) to provide epoxide as a colourless oil (64.5 g, 82%). To a solution of racemic epoxide (30 g) in anhydrous THF (7.5 mL) (*R,R*)Co(II) complex (448 mg, 0.74 mmol) was added, followed by AcOH (0.14 mL). The solution was cooled to 0°C and water (1.2 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir 18 h. After that time the volatile materials were concentrated in vacuo and the crude was directly loaded on a silica gel column. Flash chromatography using Hexane/EtOAc (15:1 to 12:1) as eluant, provided chiral epoxide **(+)-19** (13.6 g, yield: 46%) as a colourless oil.

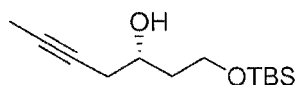
25 $[\alpha]_D = +14.1$ ($c = 1$, CHCl₃).

¹H NMR (CDCl₃, 300 MHz) δ : 3.74 (t, 2H, $J = 6.3$ Hz), 3.01 (m, 1H), 2.74 (t, 1H, $J = 4.6$ Hz), 2.48 (dd, 1H, $J = 5.1, 3.1$ Hz), 1.70 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

¹³C RMN (CDCl₃, 75 MHz) δ : 60.2, 50.2, 47.3, 36.1, 26.1, 18.4, -5.2.

30

Synthesis of intermediate 20



Propyne was condensed at -78°C and dissolved in anhydrous THF (165 mL). n-Butyllithium was added dropwise under Ar over 30 min, and the resultant white suspension was stirred for an additional 30 min at -78°C . A solution of (+) (R)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxirane **19** (23.7 g) in anhydrous THF (125 mL) was then added dropwise followed by addition of BF_3OEt_2 . The mixture was stirred for 1 h at -78°C and for an additional hour at 0°C . The reaction was quenched with saturated aqueous solution of NH_4Cl (150 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over NaSO_4 , filtered and concentrated. Flash chromatography (hexane/ EtOAc 10:1 to 1:1) provided 22.7 g, (yield: 80%) of alcohol **20** as a colourless oil.

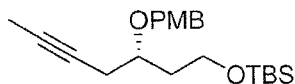
$[\alpha]_{\text{D}} = +5.6$ ($c = 0.1$, CHCl_3).

^1H -RMN (500 MHz, CDCl_3) δ : 3.75-3.90 (m, 3H), 3.47 (d, 1H, $J = 2.7$ Hz, OH), 2.34 (m, 2H), 1.79, (t, 3H, $J = 2.4$ Hz), 1.75 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C -RMN (125 MHz, CDCl_3) δ : 77.8, 75.8, 70.7, 62.4, 37.6, 27.6, 26.1, 18.3, 3.7, -5.3, -5.4.

MS (ES) m/z 243.2 $[\text{M}+\text{H}]^+$, 265.2 $[\text{M}+\text{Na}]^+$

Synthesis of intermediate 21a



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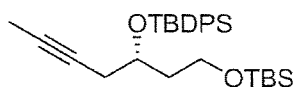
A solution of intermediate **20** (22.7 g) and *p*-methoxybenzyltrichloroacetimidate (PMBTCA) in DCM was treated with $\text{Sc}(\text{OTf})_3$. The mixture was stirred at room temperature for 2 h (TLC checking) and the reaction was concentrated in vacuo and purified by

30

column chromatography (hexane/EtOAc 50:1 to 15:1) to give **21a** as yellow oil (18.3 g; yield: 55 %).

¹H NMR (CDCl₃, 300 MHz) δ: 7.25 (d, 2H, *J* = 8.7 Hz), 6.90 (d, 2H, *J* = 8.7 Hz), 4.45 (m, 2H), 3.80 (s, 3H), 3.65 (m, 3H), 2.40 (m, 2H), 1.82 (m, 2H), 1.79 (t, 3H, *J* = 2.4 Hz), 0.92 (s, 9H), 0.05 (s, 6H).

Synthesis of intermediate 21b



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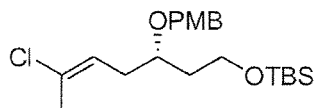
A solution of alcohol **20** (2.88 g, 11.9 mmol), tert-butyldiphenylsilyl chloride (4.39 mL, 16.89 mmol), and 4-(dimethylamino)pyridine (43.6 mg) in N,N-dimethylformamide (DMF) (14 mL) was stirred overnight at room temperature. The mixture was diluted with water and extracted with Et₂O, and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether **21b** (5.3 g, yield: 93%) as a colourless liquid.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.66 (m, 4H), 7.40-7.34 (m, 6H), 3.99-3.95 (m, 1H), 3.70-3.62 (m, 2H), 2.23-2.22 (m, 2H), 1.84-1.81 (m, 2H), 1.69 (t, 3H, *J* = 2.7 Hz), 1.05 (s, 9H), 0.84 (s, 9H), 0.01 (s, 6H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 136.1; 134.6; 129.7; 127.8; 77.8; 76.2; 69.9; 60.1; 39.6; 27.5; 27.2; 26.2; 19.6; 18.5; 3.7; -5.1.

Synthesis of intermediate 22a

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To a solution of **21a** in anhydrous toluene, under Ar and at 0°C Schwartz's reagent (Bis(cyclopentadienyl)zirconium(IV) chloride hydride,

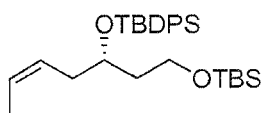
Cp₂ZrHCl) was added and the reaction was stirred 5 min at room temperature. The reaction temperature was increased to 50°C over a period of 20 min and stirred at 50°C for 2.30 h. During this time the reaction solution turned of orange colour. The reaction was cooled to 5 0°C and N-chlorosuccinimide was added in one portion. Stirring was continued for 30 min at room temperature and the reaction was diluted with Hexane/EtOAc (95:5; 500 mL). Removing of the solid by filtration and evaporation of volatiles provided **22a** as yellow oil which was used without further purification (15.1 g; yield: 86 %).

10 $[\alpha]_D = +20.5$ (c = 1, CHCl₃).

¹H NMR (CDCl₃, 300 MHz) δ : 7.25 (d, 2H, $J = 8.7$ Hz), 6.87 (d, 2H, $J = 8.7$ Hz), 5.64 (td, 1H, $J = 7.8, 0.9$ Hz), 4.45 (q, 2H, $J = 11.1$ Hz), 3.80 (s, 3H), 3.70 (m, 2H), 3.62 (m, 1H), 2.27 (t, 2H, $J = 6.9$ Hz), 2.03 (s, 3H), 1.70 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

15 ¹³C RMN (75 MHz, CDCl₃) δ : 159.4, 130.9, 130.7, 129.6, 124.2, 114.0, 75.2, 71.4, 59.8, 55.5, 37.7, 33.8, 26.1, 21.2, 18.5, -5.1.

Synthesis of intermediate 22b



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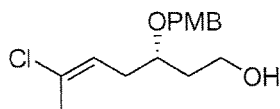
A flask containing a mixture of **21b** (4.73 g, 9.85 mmol), quinoline (0.582 mL, 4.92 mmol) and lindlar catalyst (2.18 g) in ethyl acetate was evacuated and flushed with H₂. The reaction mixture was stirred at 25 room temperature under H₂ (1 atm) for 2 h and then filtered through a plug of celite. The plug was rinsed with ethyl acetate and the combined filtrates were washed with 0.1 % HCl. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford intermediate **22b** (4.27 g, yield: 90%) as a colourless oil that was used without further 30 purification.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.70-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.48 (m, 1H), 5.36-5.27 (m, 1H), 3.95-3.87 (m, 1H), 3.71-3.55 (m, 2H), 2.16 (dd, 2H, $J = 6.9, 6.3$ Hz), 1.73-1.66 (m, 2H), 1.41 (dd, 3H, $J = 6.6, 1.2$ Hz), 1.05 (s, 9H), 0.84 (s, 9H), -0.02 (s, 6H).

5 ^{13}C -RMN (CDCl_3 , 75 MHz) δ : 136.2; 134.8; 129.8; 127.8; 126.4; 125.8; 70.9; 60.4; 39.6; 34.8; 27.3; 26.2; 19.7; 18.5; 13.1; -5.1.

Synthesis of intermediate 23a

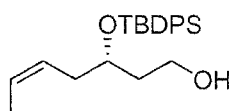
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To a solution of **22a** (23 g) in anhydrous THF under Ar and at 0°C a solution of Tetrabutylammonium fluoride (TBAF) was added dropwise over a period of 20 min (the solution turned red). The reaction mixture
 15 was stirred at room temperature for 2h, and then was quenched with saturated aqueous solution of NH_4Cl (200 mL). The combined layers were separated and the aqueous phase was extracted thoroughly with EtOAc (3 x 150 mL). The combined organic layers were dried over NaSO_4 , filtered and concentrated. Flash chromatography (hexane
 20 /EtOAc 4:1 to 1:1) provided **23a** as a colourless oil (11.9 g; yield: 73 %).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.25 (d, 2H, $J = 8.7$ Hz), 6.86 (d, 2H, $J = 8.7$ Hz), 5.62 (t, 1H, $J = 7.8$ Hz), 4.45 (m, 2H), 3.80 (s, 3H), 3.70 (m, 3H), 2.35 (m, 2H), 2.03 (s, 3H), 1.75 (m, 2H).

25 Synthesis of intermediate 23b

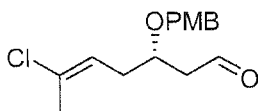


PPTS (837.7 mg, 3.33 mmol) was added in one portion to a solution of **22b** (4 g, 8.33 mmol) in ethanol (80 mL). The reaction mixture was stirred at room temperature for 7 h and then was concentrated. The residue was diluted in DCM and washed with a saturated solution of NaHCO₃. The organic layer was extracted, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether **23b** (2.12 g, yield: 69%) as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ : 7.73-7.69 (m, 4H), 7.44-7.36 (m, 6H), 5.44-5.38 (m, 1H), 5.21-5.17 (m, 1H), 4.01-3.94 (m, 1H), 3.84-3.76 (m, 1H), 3.69-3.64 (m, 1H), 2.32-2.14 (m, 2H), 1.89-1.78 (m, 1H), 1.70-1.60 (m, 1H), 1.37 (d, 3H, J = 6.9 Hz), 1.07 (s, 9H).

¹³C-RMN (CDCl₃, 75 MHz) δ : 136.2; 134.1; 130.0; 127.8; 126.3; 125.9; 72.3; 60.1; 37.7; 34.3; 27.2; 19.5; 13.0.

15 Synthesis of intermediate 24a

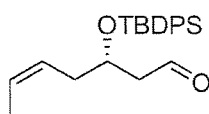


(Diacetoxyiodo)benzene (BAIB) (11.5 g, 35.7 mmol) was added to a solution of alcohol **23a** (9.2 g, 32.4 mmol) and 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) (515 mg, 3.3 mmol) in dichloromethane anhydrous (92 mL). The reaction mixture was stirred at room temperature for 20 h until the alcohol was no longer detectable (TLC), and then it was quenched with a saturated aqueous solution of NH₄Cl and extracted with DCM (3 x 100 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 4:1 to 1:1) to afford **24a** as colourless oil (6.3 g; yield: 70%).

^1H NMR (CDCl_3 , 300 MHz) δ : 9.78 (s, 1H), 7.25 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, $J = 8.7$ Hz), 5.64 (t, 1H, $J = 7.8$ Hz), 4.45 (q, 2H, $J = 11.1$ Hz), 4.02 (m, 1H), 3.80 (s, 3H), 2.60 (m, 2H), 2.35 (m, 2H), 2.03 (s, 3H).

^{13}C RMN (CDCl_3 , 75 MHz) δ : 201, 159.6, 132.1, 130.1, 129.7, 122.8,
5 114.1, 73.3, 71.5, 55.5, 48.3, 33.5, 21.3.

Synthesis of intermediate 24b



10

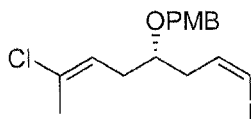
BAIB (1.97 g, 6.11 mmol) was added to a solution of alcohol **23b** (2.05 g, 5.56 mmol) and TEMPO (86.87 mg, 0.56 mmol) in 25 mL of DCM. The reaction mixture was stirred at room temperature for 16-18 h until the alcohol was no longer detectable (TLC), and then it was quenched with a
15 saturated aqueous solution of NH_4Cl , and extracted with DCM. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/DCM 5:1 to 1:2) to give **24b** (1.733 mg, yield: 79%) as a colourless oil.

20 ^1H NMR (CDCl_3 , 300 MHz) δ : 9.72 (t, 1H, $J = 2.7$ Hz), 7.74-7.67 (m, 4H), 7.48-7.37 (m, 6H), 5.56-5.45 (m, 1H), 5.32-5.23 (m, 1H), 4.29-4.20 (m, 1H), 2.51-2.48 (m, 2H), 2.31-2.27 (m, 2H), 1.43 (dd, 3H, $J = 6.9, 1.5$ Hz), 1.06 (s, 9H).

^{13}C -RMN (CDCl_3 , 75 MHz) δ : 202.3; 136.1; 134.0; 130.1; 127.9; 127.4;
25 125.1; 69.4; 50.1; 35.1; 27.2; 19.5; 13.1.

Synthesis of intermediate 25a

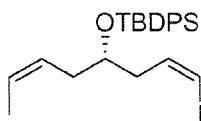
60



To a suspension of iodomethyltriphenylphosphonium iodide (16.6 g; 31 mmol) in anhydrous THF (126 mL), at room temperature, a 1M solution
5 of NaHMDS in THF (31.27 mL) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78°C and a solution of **24a** (6.3 g, 22 mmol) in THF (82 mL) was then added. The reaction mixture was stirred at -78°C for 2 h, and at room temperature for 5 min, diluted
10 with hexane and filtered through a plug of celite. The plug was rinsed with hexane and the combined filtrates were evaporated under reduced pressure and the resulting oil was purified by column chromatography (Hexane/EtOAc 12:1 to 8:1) affording **25a** as yellow oil (5.6 g; yield: 62%).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.25 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, $J =$
15 8.7 Hz), 6.25 (m, 2H), 5.64 (t, 1H, $J = 7.8$ Hz), 4.42 (m, 2H), 3.80 (s, 3H), 3.55(m, 1H), 2.40 (m, 2H), 2.25 (m, 2H), 2.03 (s, 3H).

Synthesis of intermediate 25b



20

To a suspension of iodomethyltriphenylphosphorane (3.32 g, 6.38 mmol) in THF (60 mL) at room temperature 6.83 mL of a 1M solution of NaHMDS (6.38 mmol) in THF was slowly added. After stirring for 2 min,
25 the yellow mixture was cooled to -78°C and a solution of **24b** (1.67 g, 4.56 mmol) in THF (40 mL) was then added. The reaction mixture was stirred at -78°C for 90 min, then at room temperature for 5 min, diluted with hexane and filtered through a plug celite/ SiO_2 . The plug

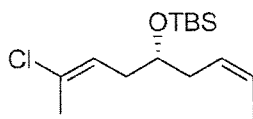
was rinsed with Hexane/EtOAc (10:1 to 5:1) to afford compound **25b** (2 g, yield: 89%) as a colourless oil that was used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.66 (m, 4H), 7.45-7.34 (m, 6H),
5 6.21-6.31 (m, 2H), 5.49-5.43 (m, 1H), 5.35-5.27 (m, 1H), 3.94-3.75 (m, 1H), 2.30-2.27 (m, 2H), 2.24-2.04 (m, 2H), 1.43 (d, 3H, *J* = 6.6 Hz), 1.06 (s, 9H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 138.2; 136.2; 134.3; 129.9; 127.8; 126.4; 126.0; 84.1; 71.9; 41.6; 34.5; 27.2; 19.6; 13.2.

10

Synthesis of intermediate 25c



15 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (3.6g, 16 mmol) was added to a solution of **25a** (5 g; 12 mmol) in DCM-H₂O (20:1) under Ar atmosphere at room temperature. After 1:30 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et₂O (200 mL) and washing with 1M NaOH (3 x 50 mL) and brine (50
20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. Chromatographic separation of *p*-methoxybenzaldehyde was facilitated by reduction to *p*-methoxybenzyl alcohol. Towards this end, a solution of the residue obtained in MeOH with NaBH₄ under Ar atmosphere was maintained at room temperature for 1 h. The reaction
25 mixture was then quenched by pouring into Et₂O (100 mL) and washing with 1 M HCl (40 mL) and brine (40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The resulting oil was purified on silica gel (Hexane/EtOAc 10:1 to 4:1) to provide the secondary alcohol as colourless oil. (2.8 g; yield: 80 %).

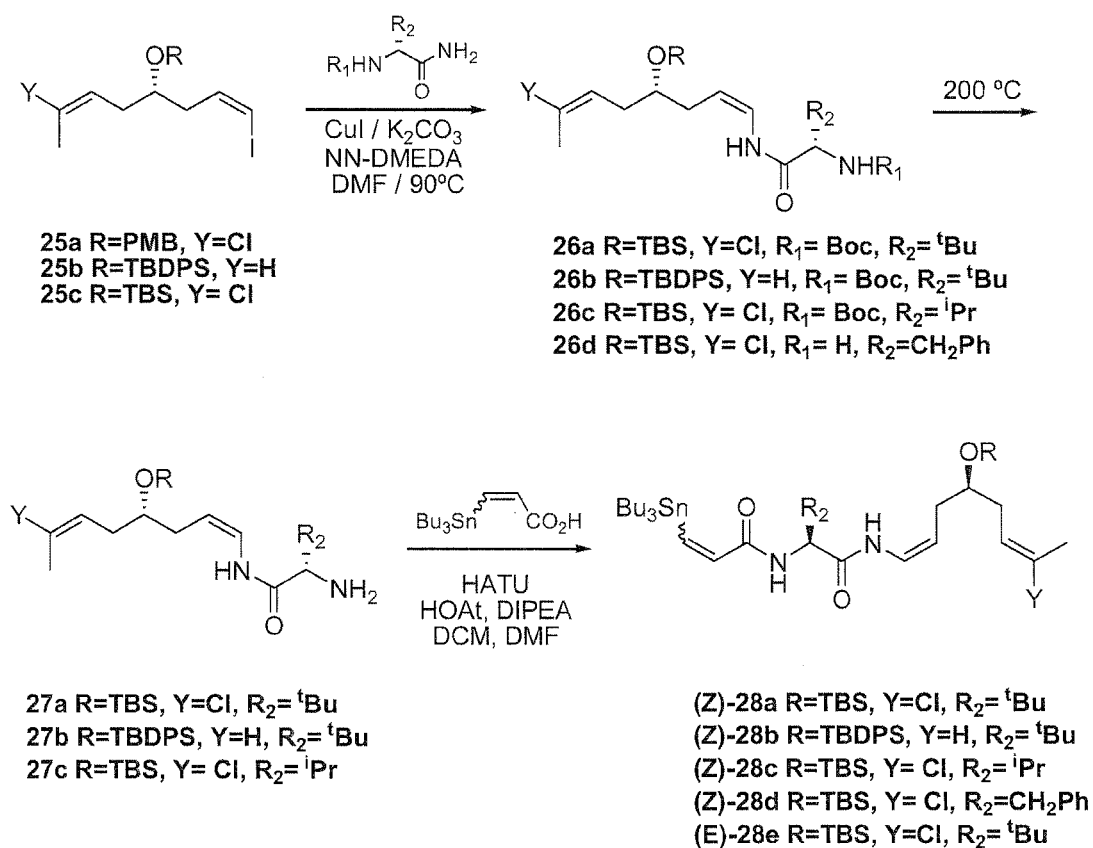
To a solution of secondary alcohol (2.8 g; 10 mmol) in anhydrous DCM, under Ar and at 0°C 2,6-lutidine was added dropwise, followed by addition of *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (TLC Hexane/DCM 4:1 showed no starting material). At this point the
5 crude mixture was quenched with 0.5M HCl (25 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried over NaSO₄, filtered and concentrated. Flash chromatography (Hexane /EtOAc 100:1 to 20:1) provided **25c** as a colourless oil (3.14 g;
10 yield: 80%).

¹H NMR (CDCl₃, 300 MHz) δ: 6.25 (m, 2H) 5.64 (t, 1H, *J* = 7.8 Hz), 3.82 (m, 1H), 2.38 (t, 2H, *J* = 6.0 Hz), 2.20 (t, 2H, *J* = 6.3 Hz), 2.03 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H).

¹³C RMN (CDCl₃, 75 MHz) δ: 137.7, 130.9, 124.3, 84.6, 70.6, 42.5, 36.6,
15 25.9, 21.3, 18.2, -4.4.

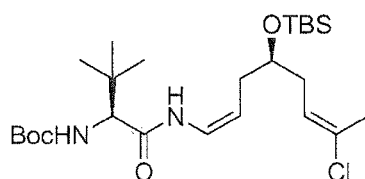
EXAMPLE 7: SYNTHESIS OF FRAGMENT BCD

Scheme 4 provides several examples of synthesis of fragment BCD, in
20 accordance with the nomenclature provided in Scheme 1.



Scheme 4

5 Synthesis of intermediate 26a



A resealable Schlenk tube was charged with copper (I) iodide (148 mg,
 0.78 mmol), potassium carbonate (1.076 g, 7.78 mmol) and Boc-*tert*-
 LeuCONH₂ (prepared following the procedure described in Pozdnev, V.
 F., *Tetrahedron Letters* 1995, 36, 7115-7118) (0.96 g, 4.15 mmol),
 evacuated and filled with argon. *N,N*-Dimethylethylenediamine
 (DMEDA) (0.166 mL, 1.55 mmol), vinyl iodide **25c** (1.04g, 2.59 mmol)

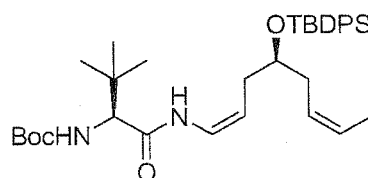
and dry DMF (15 mL) were added under argon. The Schlenk tube was sealed, heated at 90°C for 16-18h and cooled to room temperature. The resultant mixture was diluted with EtOAc and quenched with water. The organic layer was washed with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/ EtOAc, 20:1 to 15:1). Intermediate **26a** (670 mg, yield, 53%) was obtained as an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 7.72 (d, 1H, *J* = 9.9 Hz), 6.70 (t, 1H, *J* = 9.6 Hz), 5.54 (t, 1H, *J* = 7.8 Hz), 5.35 (d, 1H, *J* = 9.0 Hz), 4.76 (q, 1H, *J* = 7.8 Hz), 3.89 (d, 1H, *J* = 9.0 Hz), 3.73-3.68 (m, 1H), 2.12 (m, 4H), 1.98 (s, 3H), 0.971 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz) δ: 168.9, 156.0, 131.1, 123.9, 122.6, 108.2, 79.9, 71.6, 62.5, 36.5, 34.8, 33.8, 28.1, 26.7, 25.9, 21.2, 18.3, -4.3, -4.4.

15

Synthesis of intermediate 26b

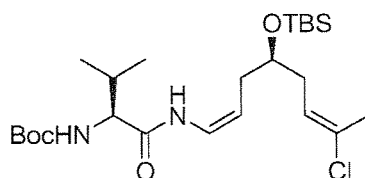


A resealable Schlenk tube was charged with copper (I) iodide (232.4 mg, 1.22 mmol), potassium carbonate (1.688 g, 12.23 mmol) and Boc-*tert*-LeuCONH₂ (2.474 g, 6.12 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (0.26 mL, 2.45 mmol), vinyl iodide **25b** (2 g, 4.08 mmol) and dry DMF (35 mL) were added under argon. The Schlenk tube was sealed, heated at 90°C for 16-18h and cooled to room temperature. The resultant mixture was diluted with EtOAc and quenched with water. The organic layer was washed with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel

(Hexane/ EtOAc, 20:1 to 15:1). Intermediate **26b** (1.06 g, yield: 44 %) was obtained as an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.67 (m, 4H), 7.43-7.35 (m, 6H), 7.13 (d, 1H, *J* = 10.5 Hz), 6.67 (dd, 1H, *J* = 10.2, 9.6 Hz), 5.56-5.45 (m, 1H),
5 5.36-5.28 (m, 2H), 4.86-4.78 (m, 2H), 3.88-3.77 (m, 1H), 2.26-2.04 (m, 4H), 1.44 (d, 3H, *J* = 6.9 Hz), 1.43 (s, 9H), 1.06 (s, 9H), 0.96 (s, 9H).

Synthesis of intermediate 26c



10

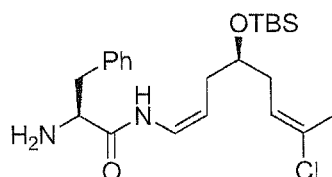
A resealable Schlenk tube was charged with copper (I) iodide (40.4 mg, 0.213 mmol), potassium carbonate (294 mg, 2.13 mmol) and Boc-Val-CONH₂ (prepared following the procedure described in Pozdnev, V. F.,
15 *Tetrahedron Letters* 1995, 36, 7115-7118) (230 mg, 1.06 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (45 μL, 0.426 mmol), vinyl iodide **25c** (283 mg, 0.71 mmol) and dry DMF (35 mL) were added under argon. The Schlenk tube was sealed, heated at 90°C for 16-18h and cooled to room temperature. The resultant mixture
20 was diluted with EtOAc and quenched with water. The organic layer was washed with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 7:1 to 3:1). Intermediate **26c** (270 g, yield: 77 %) was obtained as an oil.

25 ¹H NMR (CDCl₃, 300 MHz) δ: 7.80 (d, 1H, *J* = 9.3), 6.79-6.73 (m, 1H), 5.58 (t, 1H, *J* = 7.5 Hz), 5.02 (br s, 1H), 4.85-4.76 (m, 1H), 3.93 (dd, 1H, *J* = 8.4, 6.0 Hz), 3.80-3.73 (m, 1H), 2.12-2.22 (m, 5H), 2.02 (s, 3H), 1.45 (s, 9H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 169.3, 131.1, 124.0, 122.7, 108.9, 71.6, 36.5, 33.8, 30.6, 28.5, 26.1, 21.3, 19.6, 18.3, 17.9, -4.3, -4.4.

Synthesis of intermediate 26d

5

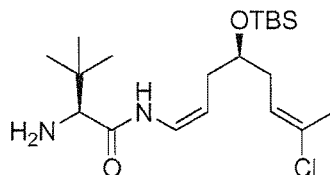


A resealable Schlenk tube was charged with copper (I) iodide (14.2 mg, 0.075 mmol), potassium carbonate (104 mg, 0.75 mmol) and Fmoc-Phe-
10 CONH_2 (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (145 mg, 0.375 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (16 μL , 0.15 mmol) vinyl iodide **25c** (100 mg, 0.25 mmol) and dry DMF (2.5 mL) were added under argon. The Schlenk tube was sealed, heated at
15 90°C for 16-18h and cooled to room temperature. The resultant mixture was diluted with EtOAc and quenched with water. The organic layer was washed with water and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 4:1 to 1:1). Intermediate
20 **26d** (46 mg, yield: 42 %) was obtained as an oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 9.19 (d, 1H, $J = 11.1$ Hz), 7.36-7.21 (m, 5H), 6.77 (ddd, 1H, $J = 10.2, 9.3, 0.9$), 5.60 (br t, 1H, $J = 7.8$ Hz), 4.82-4.78 m, 1H), 3.79-3.71 (m, 1H), 3.67 (dd, 1H, $J = 9.6, 3.9$ Hz), 3.32 (dd, 1H, $J = 13.8, 3.9$ Hz), 2.69 (dd, 1H, $J = 13.8, 9.6$ Hz), 2.20-2.11 (m,
25 4H), 1.99 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 171.9, 137.9, 130.9, 129.5, 129.1, 127.2, 124.1, 122.5, 107.9, 71.4, 56.6, 40.9, 36.3, 33.6, 26.1, 21.3, 18.3, -4.4, -4.5.

MS (ES) m/z 437.1 $[\text{M}+\text{H}]^+$, 459.0 $[\text{M}+\text{Na}]^+$

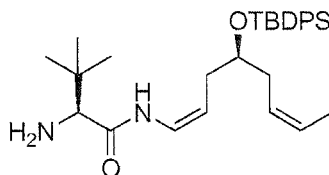
Synthesis of intermediate 27a

5

A solution of amino protected derivative **26a** (670 mg, 1.33 mmol) in ethylene-glycol (30 mL) was heated at 200 °C for 10-20 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were dried over Na₂SO₄, filtrated and concentrated in vacuo to afford the primary amine **27a** (510 mg, yield: 95 %) as a yellow oil which was used without further purification.

15 ¹H NMR (CDCl₃, 300 MHz) δ: 8.77 (d, 1H, *J* = 9.9 Hz), 6.71 (t, 1H, *J* = 9.6 Hz), 5.56 (t, 1H, *J* = 7.8 Hz), 4.71 (m, 1H), 3.72 (m, 1H), 3.14 (s, 1H), 2.14 (m, 4H), 1.97 (s, 3H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 6H).
¹³C RMN (CDCl₃, 75 MHz) δ: 171.2, 131.0, 124.1, 122.5, 107.1, 71.5, 64.3, 36.2, 34.5, 33.8, 26.5, 26.0, 21.2, 18.2, -4.4, -4.5.

20

Synthesis of intermediate 27b

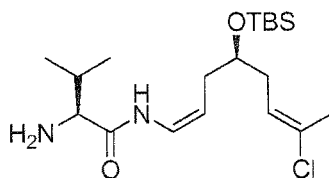
25 A solution of amino protected derivative **26b** (847 mg, 1.43 mmol) in ethylene-glycol (50 mL) was heated at 200 °C for 10-20 min. The reaction mixture was then cooled at room temperature, diluted with

DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were dried over Na₂SO₄, filtrated and concentrated in vacuo to afford the
5 primary amine **27b** (435 mg, 62%) as a white foam after purification by flash chromatography (Hexane/EtOAc 10:1 to 1:2).

¹H NMR (CDCl₃, 300 MHz) δ : 8.50 (d, 1H, J = 10.8 Hz), 7.70-7.66 (m, 4H), 7.45-7.33 (m, 6H), 6.67 (dd, 1H, J = 11.1, 9.3 Hz), 5.48-5.40 (m, 1H), 5.36-5.28 (m, 1H), 4.79 (dd, 1H, J = 16.2, 7.5 Hz), 3.87-3.79 (m,
10 1H), 3.08 (s, 1H), 2.22-2.14 (m, 4H), 1.43 (d, 3H, J = 6.9 Hz), 1.05 (s, 9H), 0.97 (s, 9H).

¹³C-RMN (CDCl₃, 75 MHz) δ : 171.0; 136.1; 134.5; 129.8; 127.8; 126.3; 126.2; 122.1; 107.6; 72.6; 64.4; 34.0; 34.4; 32.8; 27.2; 26.9; 19.6; 13.2.

15 Synthesis of intermediate 27c



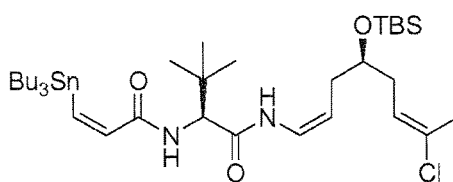
A solution of amino protected derivative **26c** (255 mg, 0.52 mmol) in
20 ethylene-glycol (15 mL) was heated at 200 °C for 10-20 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were
25 dried over Na₂SO₄, filtrated and concentrated in vacuo to afford the primary amine **27c** (170 mg, 85%) as a yellow oil which was used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ : 9.27 (d, 1H, J = 10.2), 6.76 (dd, 1H, J = 11.1, 9.6 Hz), 5.61 (t, 1H, J = 7.8 Hz), 4.80-4.72 (m, 1H), 3.81-3.73 (m,

1H), 3.31 (d, 1H, $J = 3.6$ Hz) 2.44-2.33 (m, 1H), 2.20-2.16 (m, 4H), 2.03 (s, 3H), 1.59 (br s, 2H), 1.00 (d, 3H, $J = 6.9$ Hz), 0.89 (s, 9H), 0.82 (d, 3H, $J = 6.9$ Hz), 0.05 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 172.1, 131.1, 124.1, 122.5, 107.4, 71.5,
5 36.5, 33.7, 30.8, 26.0, 21.3, 20.0, 16.1, -4.3, -4.4.

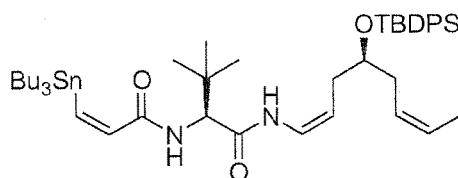
Synthesis of intermediate 28a



10

To a solution of amine **27a** (918 mg, 2.27 mmol) in DCM/DMF (10:1, 39.6 mL), a solution of (Z)-3-tributylstannylpropenoic acid (1028 mg, 2.84 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0 °C. Diisopropylethylamine (DIPEA) (0.6 mL, 3.4 mmol),
15 1-Hydroxy-7-azabenzotriazole (HOAt) (310 mg, 2.27 mmol), and N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) (860 mg, 2.27 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a
20 saturated aqueous solution of NH_4Cl , poured into water and extracted with DCM. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **28a** (1110 mg; yield: 66%) as an oil.

25 ^1H NMR (CDCl_3 , 300 MHz) δ : 7.63 (d, 1H, $J = 10.5$ Hz), 6.97 (d, 1H, $J = 12.3$ Hz), 6.75 (d, 1H, $J = 12.3$ Hz), 6.72 (t, 1H, $J = 9.5$ Hz), 6.50 (d, 1H, $J = 9.0$ Hz), 5.56 (t, 1H, $J = 6.6$ Hz), 4.83 (q, 1H, $J = 9.0$ Hz), 4.41 (d, 1H, $J = 9.6$ Hz) 3.76 (m, 1H), 2.17 (m, 4H), 2.01 (s, 3H), 1.45 (m, 6H), 1.25 (m, 8H), 1.0 (s, 9H), 0.88 (s, 9H), 0.84 (m, 13H), 0.06 (s, 6H).

Synthesis of intermediate 28b

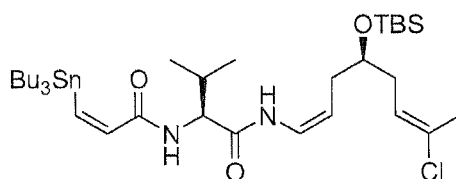
5

To a solution of amine **27b** (575 mg, 1.17 mmol) in DCM/DMF (4:1, 12.5 mL), a solution of (Z)-3-tributylstannylpropenoic acid (505.6 mg, 1.4 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0 °C. DIPEA (0.243 mL, 1.76mmol), 7-hydroxybenzotriazole
10 (HOBt) (189.2 mg, 1.4 mmol), and HATU (532.28 mg, 1.4 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over Na₂SO₄,
15 filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **28b** (780.4 mg; yield: 77%) as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.68 (m, 4H), 7.43-7.36 (m, 6H), 7.02 (d, 1H, *J* = 12.3 Hz), 7.00 (d, 1H, *J* = 10.8 Hz), 6.75 (d, 1H, *J* = 12.3 Hz),
20 6.66 (t, 1H, *J* = 9.3 Hz), 6.26 (d, 1H, *J* = 9.6 Hz), 5.57-5.34 (m, 1H), 5.38-5.28 (m, 1H), 4.83 (dd, 1H, *J* = 16.5, 7.8 Hz), 4.31 (d, 1H, *J* = 9.6 Hz), 3.89-3.82 (m, 1H), 2.26-2.02 (m, 4H), 1.50-1.42 (m, 6H), 1.43 (d, 3H, *J* = 6.9 Hz), 1.33-1.20 (m, 6H), 1.06 (s, 9H), 0.96 (s, 9H), 0.95-0.83 (m, 15H).

25 ¹³C-RMN (CDCl₃, 75 MHz) δ: 168.0; 166.2; 153.8; 136.3; 136.1; 134.3; 130.0; 127.8; 126.7; 126.0; 121.6; 109.0; 72.6; 60.7; 35.7; 34.0; 32.7; 29.5; 27.7; 27.2; 26.7; 19.5; 14.0; 13.2; 11.8.

Synthesis of intermediate 28c

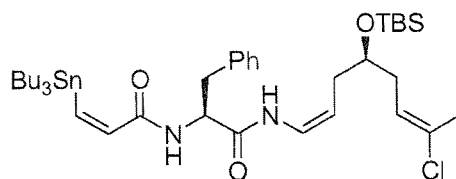


To a solution of amine **27c** (170 mg, 0.437 mmol) in DCM/DMF (10:1, 7.7 mL), a solution of (Z)-3-tributylstannylpropenoic acid (197.2 mg, 0.546 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0 °C. DIPEA (0.11 mL, 0.655 mmol), HOAt (59.4 mg, 0.437 mmol), and HATU (166 mg, 0.437 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **28c** (250 mg, yield: 78%) as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ: 7.94 (d, 1H, *J* = 10.8 Hz), 7.00 (d, 1H, *J* = 12.3 Hz), 6.75 (d, 1H, *J* = 12.3 Hz), 6.72 (t, 1H, *J* = 9.5 Hz), 6.50 (d, 1H, *J* = 9.0 Hz), 5.56 (t, *J* = 6.6 Hz, 1H), 4.83 (q, 1H, *J* = 9.0 Hz), 4.41 (t, 1H, *J* = 9.0 Hz), 3.76 (m, 1H), 2.17 (m, 4H), 2.01 (s, 3H), 1.45 (m, 7H), 1.25 (m, 8H), 0.88 (s, 9H), 0.84 (m, 19H), 0.06 (s, 6H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 169.2, 166.8, 153.8, 136.2, 131.1, 123.9, 122.6, 108.7, 71.6, 59.2, 36.5, 33.7, 31.4, 29.5, 29.4, 27.6, 26.1, 21.3, 19.5, 18.5, 18.3, 14.0, 11.8, -4.3, -4.4.

25 Synthesis of intermediate 28d



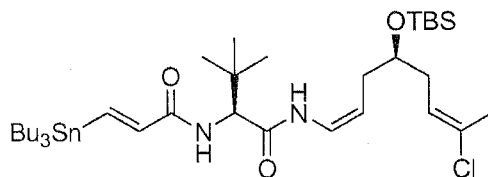
To a solution of amine **26d** (44 mg, 0.1 mmol) in DCM/DMF (10:1, 1.3 mL), a solution of (Z)-3-tributylstannylpropenoic acid (45 mg, 0.125 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0°C. DIPEA (26 μ L, 0.15 mmol), HOAt (13.6 mg, 0.1 mmol), and HATU (38 mg, 0.1 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **28d** (60 mg, yield: 80%) as an oil.

¹H NMR (CDCl₃, 300 MHz) δ : 7.43 (d, 1H, J = 10.8 Hz), 7.34-7.22 (m, 5H), 7.02 (d, 1H, J = 12.3 Hz), 6.70 (d, 1H, J = 12.3 Hz), 6.66 (dd, 1H, J = 9.9, 9.3 Hz), 6.34 (d, 1H, J = 7.8 Hz), 5.51 (dd, 1H, J = 8.1, 7.5 Hz), 4.81-4.71 (m, 2H), 3.68-3.59 (m, 1H), 3.18 (dd, 1H, J = 13.5, 6 Hz), 2.69 (dd, 1H, J = 13.5, 8.4 Hz), 2.11-2.04 (m, 2H), 2.01 (s, 3H), 1.96-1.87 (m, 1H), 1.80-1.70 (m, 1H), 1.53-1.43 (m, 8H), 1.31-1.24 (m, 10H), 0.89-0.85 (m, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz) δ : 168.5, 166.5, 154.4, 136.7, 135.9, 131.0, 129.5, 129.1, 127.4, 124.0, 122.3, 108.8, 71.5, 55.1, 38.8, 36.6, 33.3, 29.5, 29.4, 27.6, 26.0, 21.3, 18.2, 14.0, 11.8, -4.3, -4.5.

MS (ES) m/z 781.2 [M+H]⁺, 803.2 [M+Na]⁺

Synthesis of intermediate 28e



To a solution of amine **27a** (30 mg, 0.075 mmol) in DCM/DMF (10:1, 1
5 mL), a solution of (E)-3-tributylstannylpropenoic acid (33.5 mg, 0.095
mmol) in dry DCM was added, under argon atmosphere, and then was
cooled at 0°C. DIPEA (19 μ L, 0.11 mol), HOAt (10 mg, 0.075 mmol), and
HATU (27.5 mg, 0.075 mmol) were added to the solution and after 30
min the cold bath was removed. The reaction mixture was stirred at
10 room temperature for 2h, quenched with a saturated aqueous solution
of NH₄Cl, poured into water and extracted with DCM. The combined
organic phases were dried over Na₂SO₄, filtered and concentrated. The
residue was purified by flash chromatography (Hexane/EtOAc 6:1) to
give amide **28e** (25 mg, yield: 45%) as an oil.

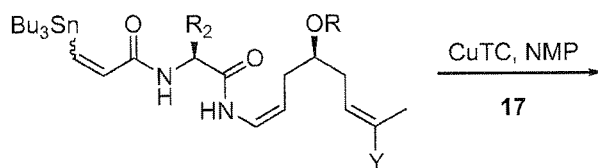
15 ¹H NMR (CDCl₃, 300 MHz) δ : 7.68 (d, 1H, J = 9.2 Hz), 7.52 (d, 1H, J =
18.9 Hz), 6.73 (t, 1H, J = 9.2 Hz), 6.28 (d, 1H, J = 10.8 Hz), 6.25 (d, 1H,
 J = 18.9 Hz), 5.60 (t, 1H, J = 7.2 Hz), 4.83 (q, 1H, J = 9.2 Hz), 4.40 (d,
1H, J = 9.6 Hz), 3.77 (m, 1H), 2.17 (m, 4H), 2.01 (s, 3H), 1.45 (m, 6H),
1.25 (m, 8H), 1.0 (s, 9H), 0.88 (s, 9H), 0.84 (m, 13H), 0.06 (s, 6H).

20

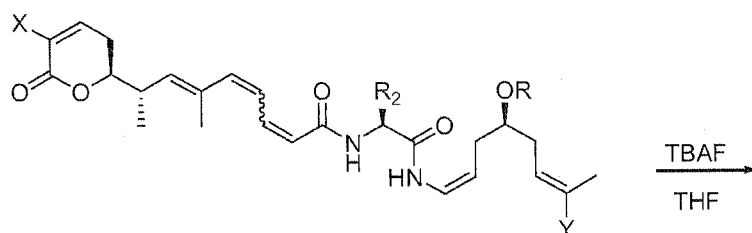
EXAMPLE 8

Scheme 5 provides the synthesis of several compounds of the invention.

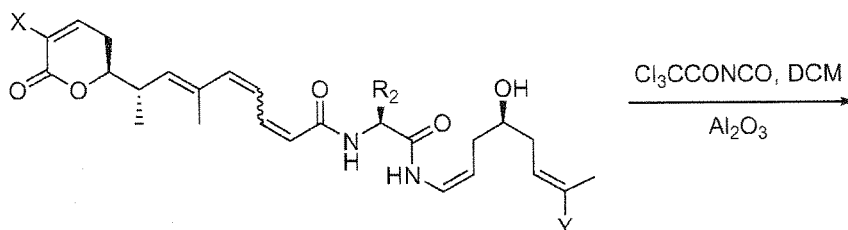
25



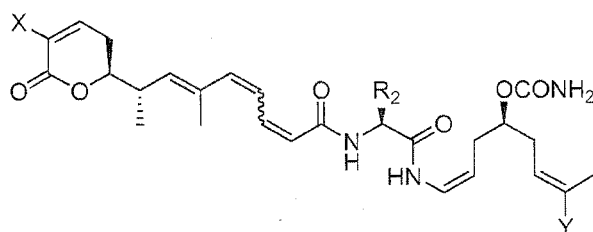
- (Z)-28a R=TBS, Y=Cl, R₂=^tBu
 (Z)-28b R=TBDPS, Y=H, R₂=^tBu
 (Z)-28c R=TBS, Y=Cl, R₂=ⁱPr
 (Z)-28d R=TBS, Y=Cl, R₂=CH₂Ph
 (E)-28e R=TBS, Y=Cl, R₂=^tBu



- (7E,9Z,11Z)-29a R=TBS, R₂=^tBu, X=OMe, Y=Cl
 (7E,9Z,11Z)-29b R=TBDPS, R₂=^tBu, X=OMe, Y=H
 (7E,9Z,11Z)-29c R=TBS, R₂=ⁱPr, X=OMe, Y=Cl
 (7E,9Z,11Z)-29d R=TBS, R₂=CH₂Ph, X=OMe, Y=Cl
 (7E,9Z,11E)-29e R=TBS, R₂=^tBu, X=OMe, Y=Cl
 (7E,9Z,11Z)-29f R=TBS, R₂=^tBu, X=H, Y=Cl

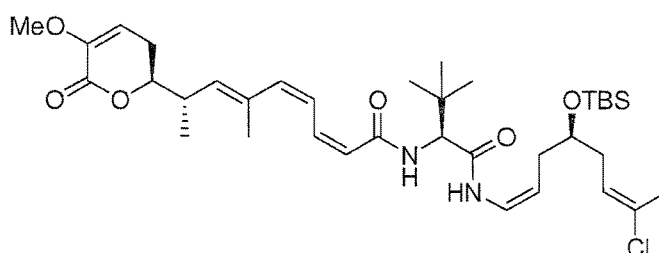


- (7E,9Z,11Z)-30a R₂=^tBu, X=OMe, Y=Cl
 (7E,9Z,11Z)-30b R₂=^tBu, X=OMe, Y=H
 (7E,9Z,11Z)-30c R₂=ⁱPr, X=OMe, Y=Cl
 (7E,9Z,11Z)-30d R₂=CH₂Ph, X=OMe, Y=Cl
 (7E,9Z,11E)-30e R₂=^tBu, X=OMe, Y=Cl
 (7E,9Z,11Z)-30f R₂=^tBu, X=H, Y=Cl



- (7E,9Z,11Z)-Compound 1 R₂=^tBu, X=OMe, Y=Cl
 (7E,9Z,11Z)-Compound 4 R₂=^tBu, X=OMe, Y=H
 (7E,9Z,11Z)-Compound 5 R₂=ⁱPr, X=OMe, Y=Cl
 (7E,9Z,11Z)-Compound 31 R₂=CH₂Ph, X=OMe, Y=Cl
 (7E,9Z,11E)-Compound 8 R₂=^tBu, X=OMe, Y=Cl

Scheme 5

Synthesis of compound 29a

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To a solution of alkenylstannane **28a** (1.1 g, 1.47 mmol) and **17a** (0.62 g, 1.77 mmol) in 1-methyl-2-pyrrolidinone (NMP) (14.7 mL) at 0°C, Copper thiophenecarboxylate (CuTC) (422 mg, 2.2 mmol) was added.

- 10 The reaction was stirred at 0°C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3x15 mL). The organic solution was dried and evaporated to give the crude product which was purified
- 15 by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene **29a** (0.66 g, yield: 66%) as an oil.

- ¹H NMR (CDCl₃, 300 MHz) δ: 7.89 (d, 1H, *J* = 10.8 Hz), 7.22 (dd, 1H, *J* = 12.3, 11.4 Hz), 6.86 (dd, 1H, *J* = 11.7, 11.4 Hz), 6.70 (dd, 1H, *J* = 9.9, 9.3 Hz), 6.35 (d, 1H, *J* = 9.3 Hz), 6.13 (d, 1H, *J* = 11.4 Hz), 5.66 (d, 1H, *J* = 11.4 Hz), 5.60 (dd, 1H, *J* = 5.4, 3.9 Hz), 5.55 (br t, 1H, *J* = 7.8 Hz), 5.26 (d, 1H, *J* = 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, *J* = 9.3 Hz), 4.20-4.16 (m, 1H), 3.77-3.69 (m, 1H), 3.63 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 2H), 2.19-2.13 (m, 4H), 2.00 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H, *J* = 6.9 Hz), 1.02 (s, 9H), 0.86 (s, 9H), 0.4 (s, 3H), 0.03 (s, 3H).
- 20

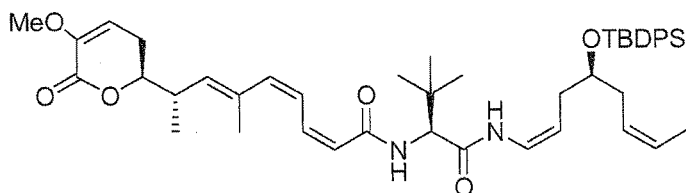
¹³C-RMN (CDCl₃, 75 MHz) δ: 168.5; 166.4; 161.8; 145.4; 140.3, 137.3; 134.4; 134.3; 131.0, 124.3; 124.1, 122.4; 121.2; 108.7; 108.4; 82.0;

25

71.6; 60.6; 55.6; 37.5; 36.5, 35.1; 33.8; 26.5; 26.0; 21.3, 18.3, 17.4, 16.9, -4.3, -4.4.

Synthesis of compound 29b

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To a solution of alkenylstannane **28b** (780.4 mg, 0.904 mmol) and **17a** (377.4 mg, 1.085 mmol) in NMP (9 mL) at 0°C, Copper
10 thiophenecarboxylate (258.5 mg, 1.36 mmol) was added. The reaction
was stirred at 0°C for 45 min and 20 min at room temperature. Then,
the crude mixture was filtered through a plug of neutral alumina,
washed with EtOAc/Ether 50:50 and the combined filtrates were
washed with HCl 0.5N (3 x 10 mL). The organic solution was dried and
15 evaporated to give the crude product which was purified by column
chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene **29b** (459.7
mg, yield: 66%) as an oil.

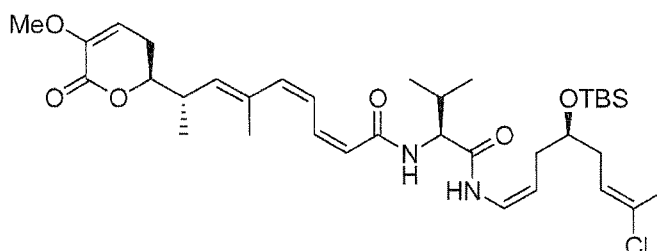
¹H NMR (CDCl₃, 300 MHz) δ: 7.66-7.64 (m, 4H), 7.43-7.32 (m, 7H), 7.23 (t, 1H, *J* = 11.7 Hz), 6.85 (t, 1H, *J* = 11.7 Hz), 6.62 (dd, 1H, *J* = 10.5, 9.3 Hz), 6.41 (d, 1H, *J* = 9.3 Hz), 6.11 (d, 1H, *J* = 11.7 Hz), 5.66 (d, 1H, *J* = 11.4 Hz), 5.60 (dd, 1H, *J* = 5.7, 5.1 Hz), 5.49-5.41 (m, 1H), 5.32-5.27 (m, 1H), 5.25 (d, 1H, *J* = 9.9 Hz), 4.83-4.75 (m, 1H), 4.32 (d, 1H, *J* = 9.3 Hz), 4.22-4.15 (m, 1H), 3.83-3.78 (m, 1H), 3.62 (s, 3H), 2.86-2.78 (m, 1H), 2.40-2.35 (m, 2H), 2.20-2.04 (m, 4H), 1.81 (s, 3H), 1.40 (d, 3H, *J* = 6.9 Hz), 1.13 (d, 3H, *J* = 6.9 Hz), 1.03 (s, 9H), 0.97 (s, 9H).

¹³C-RMN (CDCl₃, 75 MHz) δ: 168.3; 166.3; 161.8; 145.4; 140.2, 137.3; 136.1; 134.8; 134.4; 134.3; 129.9; 127.8; 126.4; 126.1; 124.4; 121.7;

121.2; 108.4; 109.1; 82.0; 72.6; 60.6; 55.6; 37.5; 35.2; 32.7; 31.1; 27.2;
26.8, 26.5; 19.5; 17.4; 16.9; 13.1.

Synthesis of compound 29c

5



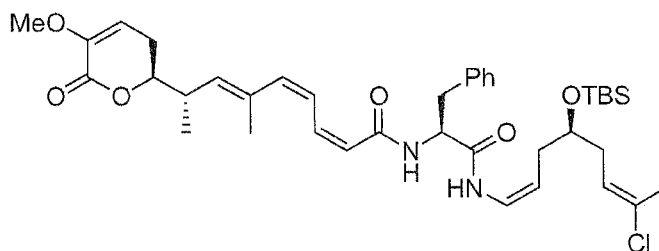
To a solution of alkenylstannane **28c** (250 mg, 0.34 mmol) and **17a**
(142 mg, 0.409 mmol) in NMP (2.5 mL) at 0°C, Copper
10 thiophenecarboxylate (97 mg, 0.51 mmol) was added. The reaction was
stirred at 0°C for 45 min and 20 min at room temperature. Then, the
crude mixture was filtered through a plug of neutral alumina, washed
with EtOAc/Ether 50:50 and the combined filtrates were washed with
HCl 0.5N (3 x 10 mL). The organic solution was dried and evaporated to
15 give the crude product which was purified by column chromatography
(Hexane/EtOAc 10:1 to 6:1) to give triene **29c** (150 mg, yield: 67%) as
an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 8.21 (d, 1H, *J* = 10.8 Hz), 7.28 (t, 1H, *J* =
11.7 Hz), 6.88 (dd, 1H, *J* = 11.7, 11.4 Hz), 6.72 (dd, 1H, *J* = 10.2, 9.3
20 Hz), 6.42 (d, 1H, *J* = 8.4 Hz), 6.15 (d, 1H, *J* = 11.7 Hz), 5.66 (d, 1H, *J* =
11.4 Hz), 5.61 (dd, 1H, *J* = 5.7, 3.6 Hz), 5.56 (br t, 1H, *J* = 8.1 Hz), 5.27
(d, 1H, *J* = 9.9 Hz), 4.85-4.77 (m, 1H), 4.30 (dd, 1H, *J* = 8.1, 7.5 Hz),
4.24-4.16 (m, 1H), 3.79-3.72 (m, 1H), 3.66 (s, 3H), 2.88-2.80 (m, 1H),
2.42-2.37 (m, 2H), 2.18-2.14 (m, 5H), 2.00 (s, 3H), 1.83 (s, 3H), 1.14 (d,
25 3H *J* = 6.9 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.86 (s,
9H), 0.4 (s, 6H).

^{13}C -RMN (CDCl_3 , 75 MHz) δ : 169.2 166.8; 161.8; 145.4; 140.5, 137.7; 134.6; 134.3; 131.0, 124.3; 124.2, 122.6; 121.2; 108.6; 108.4; 82.0; 71.5; 58.9; 55.6; 37.5; 36.4; 33.8; 30.8, 26.5; 26.1; 21.3, 19.6, 18.5, 18.3, 17.4, 16.9, -4.3, -4.4.

5

Synthesis of compound 29d



10 To a solution of alkenylstannane **28d** (60 mg, 0.08 mmol) and **17a** (32.4 mg, 0.09 mmol) in NMP (1 mL) at 0°C, Copper thiophenecarboxylate (22 mg, 0.12 mmol) was added. The reaction was stirred at 0°C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed

15 with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3 x 10 mL). The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 4:1 to 1:1) to give triene **29d** (13 mg, yield: 25%) as an oil.

20 ^1H NMR (CDCl_3 , 300 MHz) δ : 7.59 (d, 1H, J = 11.1 Hz), 7.33-7.24 (m, 5H), 7.23 (t, 1H, J = 11.7 Hz), 6.90 (dd, 1H, J = 11.7, 11.4 Hz), 6.66 (dd, 1H, J = 10.5, 9 Hz), 6.24 (d, 1H, J = 7.2 Hz), 6.17 (d, 1H, J = 12.0 Hz), 5.63-5.58 (m, 2H), 5.51 (td, 1H, J = 7.8, 1.2 Hz), 5.28 (d, 1H, J = 10.8 Hz), 4.79-4.67 (m, 2H), 4.24-4.17 (m, 1H), 3.66 (s, 3H), 3.65-3.62 (m,

25 1H), 3.22 (dd, 1H, J = 13.5, 6.3 Hz), 3.04 (dd, 1H, J = 13.8, 8.4 Hz), 2.89-2.81 (m, 1H), 2.43-2.37 (m, 2H), 2.11-2.04 (m, 2H), 2.00 (s, 3H),

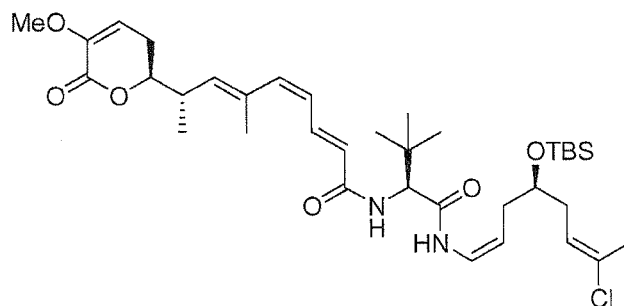
1.84 (s, 3H), 1.93-1.72 (m, 2H), 1.16 (d, 3H, $J = 6.9$ Hz), 0.86 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.4, 166.5, 161.7, 145.5, 140.8, 138.1, 136.8, 134.5, 134.3, 131.0, 129.5, 129.1, 127.4, 124.2, 124.1, 122.3, 120.4, 108.7, 108.3, 82.0, 71.4, 55.7, 54.9, 38.3, 37.5, 36.6, 33.4, 26.5, 26.0, 21.3, 18.2, 17.4, 16.9, -4.3, -4.4.

MS (ES) m/z 711.2 $[\text{M}+\text{H}]^+$

Synthesis of compound 29e

10



To a solution of alkenylstannane **28e** (50 mg, 0.067 mmol) and **17a** (28 mg, 0.08 mmol) in NMP (1 mL) at 0°C, Copper thiophenecarboxylate (19.1 mg, 0.10 mmol) was added. The reaction was stirred at 0°C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3 x 10 mL). The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene **29e** (33 mg, yield: 50%) as an oil.

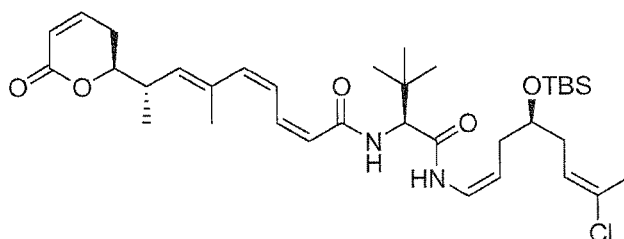
^1H NMR (CDCl_3 , 300 MHz) δ : 7.73 (d, 1H, $J = 11.4$ Hz), 7.70 (dd, 1H, $J = 14.1, 11.7$ Hz), 6.71 (dd, 1H $J = 9.9, 9.7$ Hz), 6.30 (d, 1H, $J = 9.3$ Hz), 6.13 (d, 1H, $J = 12.9$ Hz), 6.04 (dd, 1H, $J = 11.7, 11.4$ Hz), 5.93 (d, 1H, $J = 15.0$ Hz), 5.63 (br t, 1H, $J = 4.5$ Hz), 5.58-5.53 (m, 1H), 5.34 (d, 1H, $J = 9.9$ Hz), 4.85-4.78 (m, 1H), 4.41 (d, 1H, $J = 9.3$), 4.24-4.16 (m, 1H),

3.77-3.72 (m, 1H), 3.64 (s, 3H), 2.90-2.78 (m, 1H), 2.45-2.41 (m, 2H), 2.19-2.12 (m, 4H), 2.01 (s, 3H), 1.91 (s, 3H), 1.16 (d, 3H, $J = 6.6$ Hz), 1.02 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.5, 166.1, 161.8, 145.4, 140.7, 138.0, 135.3, 134.9, 131.1, 125.8, 124.9, 124.0, 122.4, 108.7, 108.5, 81.9, 71.6, 60.9, 55.6, 37.6, 36.5, 35.2, 33.8, 29.9, 26.8, 26.1, 21.3, 18.3, 17.3, 16.9, -4.3, -4.4.

Synthesis of compound 29f

10



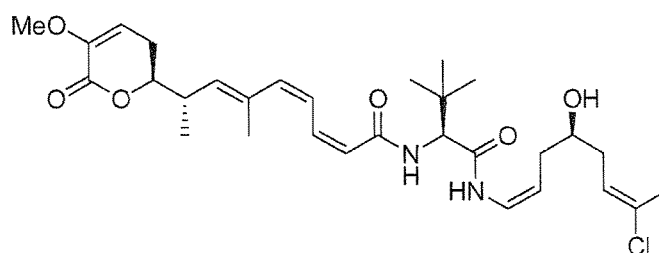
To a solution of alkenylstannane **28a** (60 mg, 0.083 mmol) and **17b** (29 mg, 0.09 mmol) in NMP (0.9 mL) at 0°C, Copper thiophenecarboxylate (24 mg, 0.12 mmol) was added. The reaction was stirred at 0°C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3 x 10 mL). The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give amide **29f** (27 mg, yield: 50%) as an oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.62 (d, 1H, $J = 10.5$ Hz), 7.25 (dd, 1H, $J = 12.6, 11.4$ Hz), 6.94-6.84 (m, 2H), 6.73 (dd, 1H, $J = 10.5, 9.0$ Hz), 6.23 (d, 1H, $J = 9.3$ Hz), 6.17 (d, 1H, $J = 11.4$ Hz), 6.06-6.01 (m, 1H), 5.66 (d, 1H, $J = 11.4$ Hz), 5.60-5.55 (m, 1H), 5.29 (d, 1H, $J = 9.9$ Hz), 4.88-4.80 (m, 1H), 4.34 (d, 1H, $J = 9.3$ Hz), 4.27-4.19 (m, 1H), 3.79-3.72 (m, 1H), 2.90-2.81 (m, 1H), 2.36-2.30 (m, 2H), 2.21-2.13 (m, 4H), 2.03 (s, 3H),

1.85 (s, 3H), 1.17 (d, 3H, $J = 6.6$ Hz), 1.03 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

Synthesis of compound 30a

5

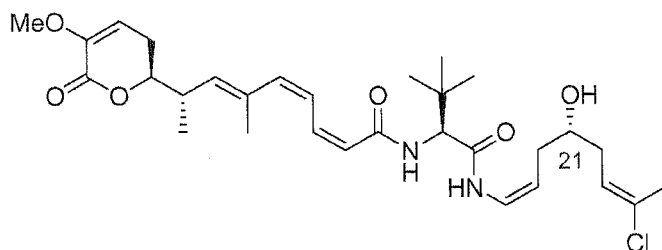


To a solution of **29a** (275 mg, 0.41 mmol) in THF (6 mL) under N_2 and at room temperature, TBAF 1M in THF (0.82 mL, 0.82 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30a** (175 mg; yield: 76 %) as a white solid.

1H NMR ($CDCl_3$, 300 MHz) δ : 9.00 (d, 1H, $J = 10.2$ Hz), 7.25 (dd, 1H, $J = 12.0, 11.4$ Hz), 6.86 (dd, 1H, $J = 11.7, 11.4$ Hz), 6.72 (dd, 1H, $J = 9.6, 8.7$ Hz), 6.68 (d, 1H, $J = 8.7$ Hz), 6.13 (d, 1H, $J = 11.7$ Hz), 5.68 (d, 1H, $J = 11.4$ Hz), 5.63-5.58 (m, 2H), 5.27 (d, 1H, $J = 10.2$ Hz), 4.85-4.76 (m, 1H), 4.42 (d, 1H, $J = 9.3$ Hz), 4.25-4.17 (m, 1H), 3.70-3.69 (m, 1H), 3.63 (s, 3H), 3.48 (br s, 1H), 2.89-2.75 (m, 1H), 2.42-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.04 (s, 3H), 1.82 (s, 3H), 1.14 (d, 3H, $J = 6.6$ Hz), 1.03 (s, 9H).

The isomer **(21S)-** of **Compound 30a** was obtained when the synthetic process was performed starting from racemic fragment D. The final mixture of isomers [(21S)-Compound 30a and (21R)-Compound 30a] was separated by semipreparative reversed phase HPLC (SymmetryPrep C18

7 μ m, 7.8 x 150 mm, gradient H₂O:MeCN from 50 to 60% MeCN in 30 min, UV detection, flow 2.5 mL/min, [rt ((21*S*)-30a): 15.4 min, rt ((21*R*)-30a):14.7 min]) and **(21*S*)-Compound 30a** was obtained in pure form:



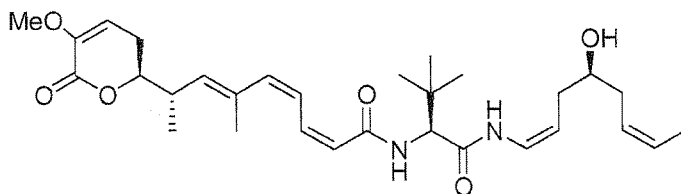
5

¹H NMR (CDCl₃, 300 MHz) δ : 8.62 (d, 1H, J = 10.2 Hz), 7.28-7.22 (m, 1H), 6.93-6.86 (m, 1H), 6.81-6.75 (m, 1H), 6.32 (d, 1H, J = 9.0 Hz), 6.17 (d, 1H, J = 11.7 Hz), 5.68-5.58 (m, 3H), 5.28 (d, 1H, J = 10.2 Hz), 4.93-4.84 (m, 1H), 4.32 (d, 1H, J = 9.3 Hz), 4.25-4.17 (m, 1H), 3.78-3.67 (m, 1H), 3.66 (s, 3H), 2.89-2.81 (m, 1H), 2.43-2.38 (m, 2H), 2.28-2.20 (m, 4H), 2.08 (s, 3H), 1.84 (s, 3H), 1.16 (d, 3H J = 6.9 Hz), 1.02 (s, 9H).

10

Synthesis of compound 30b

15



To a solution of **29b** (586 mg, 0.76 mmol) in THF (7.5 mL) under N₂ and at room temperature, TBAF 1M in THF (1.53 mL, 2 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash

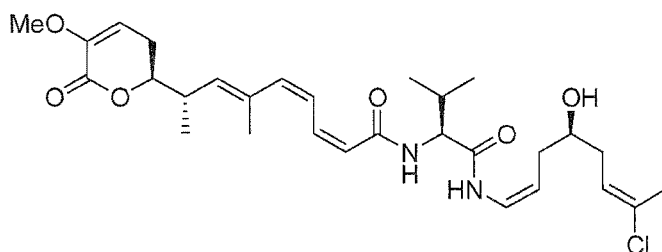
20

chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30b** (320 mg, yield: 80 %) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ : 8.95 (d, 1H, J = 10.2 Hz), 7.25 (t, 1H, J = 12.0 Hz), 6.85 (t, 1H, J = 11.7 Hz), 6.73 (t, 1H, J = 9.6 Hz), 6.57 (d, 1H, J = 8.7 Hz), 6.12 (d, 1H, J = 11.4 Hz), 5.67 (d, 1H, J = 11.4 Hz), 5.61 (dd, 1H, J = 5.4, 3.9 Hz), 5.63-5.58 (m, 1H), 5.44-5.35 (m, 1H), 5.26 (d, 1H, J = 9.9 Hz), 4.86 (q, 1H, J = 8.1 Hz), 4.38 (d, 1H, J = 9.3 Hz), 4.24-4.16 (m, 1H), 3.81-3.71 (m, 1H), 3.64 (s, 3H), 2.96-2.92 (m, 1H), 2.86-2.79 (m, 1H), 2.41-2.37 (m, 2H), 2.28-2.14 (m, 4H), 1.82 (s, 3H), 1.61 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H).

¹³C-RMN (CDCl₃, 75 MHz) δ : 168.7; 166.6; 161.8; 145.4; 140.3; 137.5; 134.4; 134.3; 127.7; 126.0; 124.4; 123.7; 121.1; 108.9; 108.4; 82.0; 72.1; 60.9; 55.7; 37.6; 35.0; 34.8; 33.2; 26.9; 26.5; 17.4; 16.9; 13.3.

15 Synthesis of compound 30c



To a solution of **29c** (150 mg, 0.23 mmol) in THF (4.8 mL) under N₂ and at room temperature, TBAF 1M in THF (0.45 mL, 0.45 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30c** (90 mg, yield: 73 %) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ : 9.16 (d, 1H, J = 10.2 Hz), 7.26 (dd, 1H, J = 12.0, 11.1 Hz), 6.87 (dd, 1H, J = 11.7, 11.4 Hz), 6.79-6.70 (m, 2H), 6.14

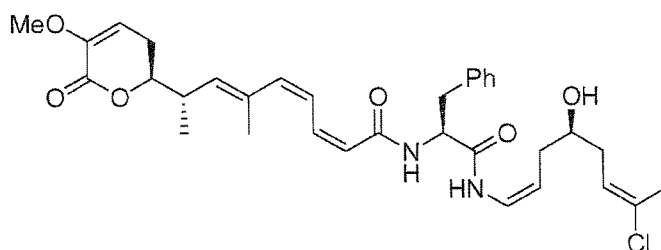
(d, 1H, $J = 11.7$ Hz), 5.68 (d, 1H, $J = 11.7$ Hz), 5.63-5.58 (m, 2H), 5.27 (d, 1H, $J = 9.6$ Hz), 4.85-4.76 (m, 1H), 4.35 (dd, 1H, $J = 8.4, 7.5$ Hz), 4.24-4.17 (m, 1H), 3.70-3.69 (m, 1H), 3.63 (s, 3H), 3.43 (br s, 1H), 2.89-2.76 (m, 1H), 2.42-2.36 (m, 2H), 2.21-2.14 (m, 4H), 2.03 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H $J = 6.9$ Hz), 0.96 (d, 6H, $J = 6.6$ Hz).

^{13}C -RMN (CDCl_3 , 75 MHz) δ : 169.7, 167.1, 161.8, 145.4, 140.5, 137.8, 134.6, 134.2, 131.6, 124.4, 123.9, 123.8, 120.7, 108.5, 108.4, 82.0, 59.1, 55.7, 37.5, 36.4, 33.5, 31.0, 26.5, 21.3, 19.5, 18.7, 17.4, 16.8.

MS (ES) m/z 549.0 $[\text{M}+\text{H}]^+$, 571.1 $[\text{M}+\text{Na}]^+$

10

Synthesis of compound 30d



15 To a solution of **29d** (11 mg, 0.02 mmol) in THF (0.32 mL) under N_2 and at room temperature, TBAF 1M in THF (0.03 mL, 0.03 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 ,
20 filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30d** (6 mg, yield: 65%) as a white solid.

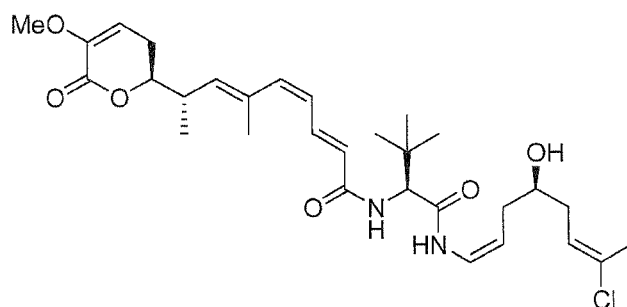
^1H NMR (CDCl_3 , 300 MHz) δ : 8.54 (d, 1H, $J = 9.9$ Hz), 7.34-7.23 (m, 5H), 7.20 (t, 1H, $J = 11.7$ Hz), 6.89 (dd, 1H, $J = 11.7, 11.4$ Hz), 6.72 (dd, 1H, $J = 9.9, 9.3$ Hz), 6.27 (d, 1H, $J = 8.1$ Hz), 6.17 (d, 1H, $J = 11.7$ Hz), 5.63-5.53 (m, 3H), 5.28 (d, 1H, $J = 10.2$ Hz), 4.84-4.76 (m, 1H), 4.75-4.68 (m, 1H), 4.25-4.17 (m, 1H), 3.66 (s, 3H), 3.67-3.65 (m, 1H), 3.18

(dd, 1H, $J = 13.8, 6.3$ Hz), 3.06 (dd, 1H, $J = 13.8, 8.1$ Hz), 2.89-2.81 (m, 1H), 2.43-2.38 (m, 2H), 2.15-2.10 (m, 3H), 2.06 (s, 3H), 1.92-1.87 (m, 1H), 1.84 (s, 3H), 1.16 (d, 3H, $J = 6.6$ Hz).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.6, 166.6, 160.8, 145.8, 140.8, 138.1, 136.8, 134.6, 134.2, 129.6, 129.0, 127.2, 124.1, 124.0, 123.4, 120.4, 108.3, 108.2, 82.0, 71.6, 55.7, 55.0, 38.4, 37.5, 36.4, 33.0, 26.5, 21.3, 17.4, 16.9.

MS (ES) m/z 597.2 $[\text{M}+\text{H}]^+$.

10 Synthesis of compound 30e



To a solution of **29e** (32 mg, 0.047 mmol) in THF (1 mL) under N_2 and at room temperature, TBAF 1M in THF (0.094 mL, 0.094 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30e** (14 mg, yield: 55%) as a white foam.

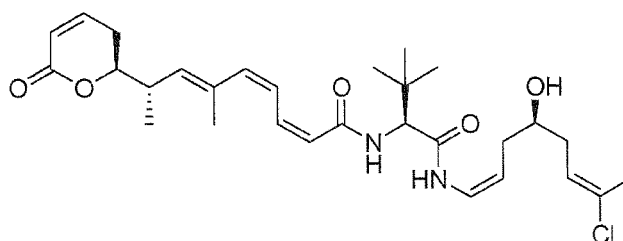
^1H NMR (CDCl_3 , 500 MHz) δ : 8.97 (d, 1H, $J = 10.2$ Hz), 7.71 (dd, 1H $J = 14.7, 11.7$ Hz), 6.74 (dd, 1H $J = 9.3, 9.9$ Hz), 6.57 (d, 1H, $J = 9.0$ Hz), 6.15 (d, 1H, $J = 11.7$ Hz), 6.03 (dd, 1H, $J = 11.7, 11.4$ Hz), 5.95 (d, 1H, $J = 14.7$ Hz), 5.65-5.58 (m, 2H), 5.35 (d, 1H, $J = 9.9$ Hz), 4.87-4.78 (m, 1H), 4.42 (d, 1H, $J = 9.3$), 4.25-4.18 (m, 1H), 3.72-3.68 (m, 1H), 3.65 (s,

3H), 3.25 (br s, 1H), 2.87-2.79 (m, 1H), 2.45-2.40 (m, 2H), 2.23-2.12 (m, 4H), 2.04 (s, 3H), 1.89 (s, 3H), 1.15 (d, 3H, $J = 6.6$ Hz). 1.03 (s, 9H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.8, 166.5, 161.68, 145.3, 140.9, 138.2, 135.4, 134.7, 132.0, 125.68, 124.6, 123.9, 123.6, 108.6, 108.4, 81.9, 71.7, 61.3, 55.7, 37.5, 36.5, 36.3, 34.9, 33.3, 26.9, 26.7, 21.3, 17.0, 16.7.

MS (ES) m/z 563.3 $[\text{M}+\text{H}]^+$, 585.2 $[\text{M}+\text{Na}]^+$

Synthesis of compound 30f

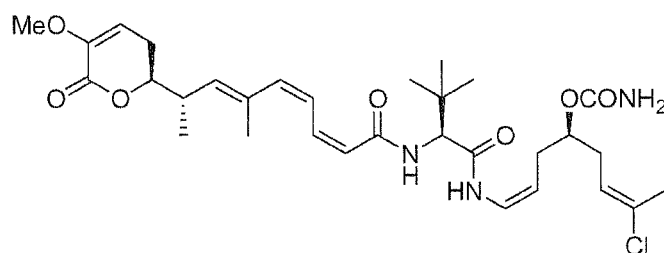


To a solution of **29f** (28 mg, 0.04 mmol) in THF (1 mL) under N_2 and at room temperature, TBAF 1M in THF (0.09 mL, 0.09 mmol) was added.

The reaction was stirred at room temperature for 18 hours and then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **30f** (17 mg; yield: 75 %) as a white solid.

^1H NMR (CDCl_3 , 300 MHz) δ : 9.05 (d, 1H, $J = 10.2$ Hz), 7.35 (m, 2H), 7.0 (dd, 1H, $J = 11.7, 11.4$ Hz), 6.73 (dd, 1H, $J = 9.6, 8.7$ Hz), 6.56 (d, 1H, $J = 8.7$ Hz), 6.05 (m, 3H), 5.63-5.58 (m, 2H), 5.30 (d, 1H, $J = 10.2$ Hz), 4.78 (m, 1H), 4.50 (d, 1H, $J = 9.3$ Hz), 3.68 (m, 1H), 3.48 (br s, 1H), 2.45 (m, 1H), 2.42-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.04 (s, 3H), 1.82 (s, 3H), 1.14 (d, 3H $J = 6.6$ Hz), 1.03 (s, 9H).

Synthesis of compound 1



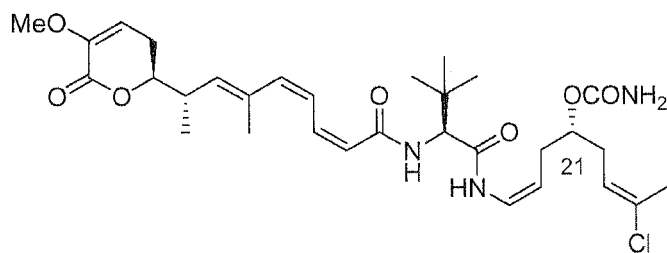
To a solution of **30a** (300 mg, 0.53 mmol) in Dichloromethane (7.5 mL)
5 at 0°C, trichloroacetyl isocyanate (TCAI) (76 µl, 0.64 mmol) was added.
The reaction was stirred at 0°C for 30 min and then neutral aluminium
oxide was added. The mixture was stirred for 5-30 min and then was
soaked into a pad of aluminium oxide. The product was washed out
using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in
10 vacuo to give the crude product which was purified by column
chromatography (Hexane/EtOAc 2:1 to 1:2). **Compound 1** (0.26 g,
yield: 81%) was obtained as a white solid and exhibited physical and
spectroscopic characteristics (¹H, ¹³C RMN and MS) equivalent to those
reported in Example 2.

15

The isomer **(21S)-** of **Compound 1** was obtained by either of these two
methods:

A.- following the same procedure starting from the mixture of isomers
(21R)- and **(21S)-Compound 30a** and final separation of **(21S)-**
20 **Compound 1** by semipreparative reversed phase HPLC (SymmetryPrep
C18 7 µm, 7.8 x 150 mm, gradient H₂O:MeOH from 50 to 100% MeOH
in 30 min, UV detection, flow 2.5 mL/min, [rt ((21S)-1): 19.2 min, rt
((21R)-1): 19.8 min]).

B.- following the same procedure as disclose for compound 1, but
25 starting from pure **(21S)-Compound 30a**.

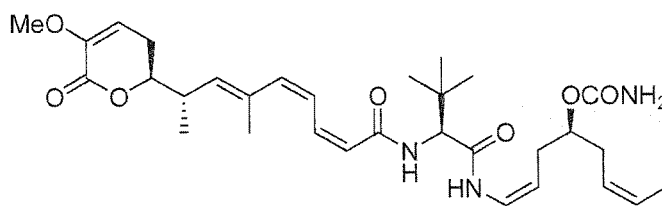


(21S)-Compound 1

¹H NMR (CDCl₃, 500 MHz) δ : 8.69 (d, 1H, J = 10.5 Hz), 7.30 (t, 1H, J = 11.5 Hz), 6.90 (t, 1H, J = 11.5 Hz), 6.86-6.82 (m, 1H), 6.34 (d, 1H, J = 9.0 Hz), 6.17 (d, 1H, J = 11.5 Hz), 5.66 (d, 1H, J = 11.5 Hz), 5.64-5.62 (m, 1H), 5.59-5.56 (m, 1H), 5.29 (d, 1H, J = 9.5 Hz), 4.81-4.77 (m, 1H), 4.50-4.45 (m, 1H), 4.42 (d, 1H, J = 9.5 Hz), 4.25-4.20 (m, 1H), 3.66 (s, 3H), 2.89-2.81 (m, 1H), 2.44-2.31 (m, 5H), 2.24-2.17 (m, 1H), 2.06 (s, 3H), 1.84 (s, 3H), 1.16 (d, 3H, J = 6.5 Hz), 1.04 (s, 9H).

¹³C-RMN (125 MHz, CDCl₃) δ : 168.4, 166.1, 157.2, 148.3, 145.2, 140.2, 137.4, 134.1, 134.0, 132.0, 124.7, 124.2, 122.4, 120.7, 108.1, 104.7, 81.8, 75.0, 60.8, 55.4, 37.2, 34.8, 32.5, 30.3, 26.7, 26.2, 21.0, 17.1, 16.6.

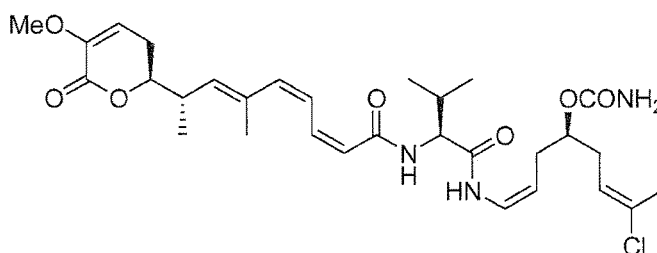
15 Synthesis of compound 4



To a solution of **30b** (56 mg, 0.105 mmol) in Dichloromethane (1 mL) at 0°C, trichloroacetyl isocyanate (15 μ L, 0.126 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in

vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2). **Compound 4** (57.6 mg, yield: 96%) was obtained as a white foam and exhibited physical and spectroscopic characteristics (^1H , ^{13}C RMN and MS) equivalent to those reported in Example 3.

Synthesis of compound 5



10

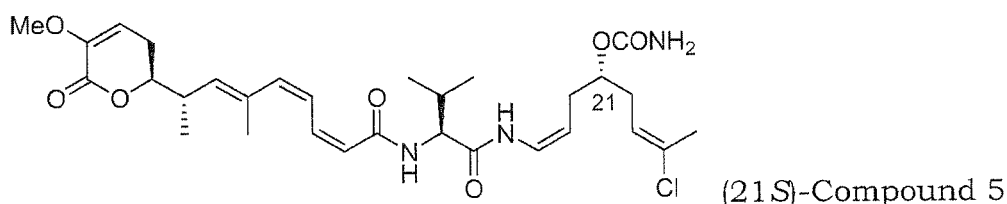
To a solution of **30c** (115 mg, 0.21 mmol) in Dichloromethane (2 mL) at 0°C, trichloroacetyl isocyanate (27 μl , 0.23 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2). **Compound 5** (71 mg, yield: 57%) was obtained as a white foam and exhibited physical and spectroscopic characteristics (^1H , ^{13}C RMN and MS) equivalent to those reported in Example 3.

The final mixture of isomers (15 mg) was separated by semipreparative reversed phase HPLC (SymmetryPrep C18 7 μm , 7.8 x 150 mm, gradient H_2O :MeOH from 50 to 70% MeOH in 75 min, UV detection, flow 2.5 mL/min, [rt ((15*R*)-7): 18.15 min, rt ((15*S*)-7)]: 19.62 min) and it was

25

obtained 3.1 mg of pure **(15R)-Compound 7** and 2.9 mg of pure **(15S)-Compound 7**:

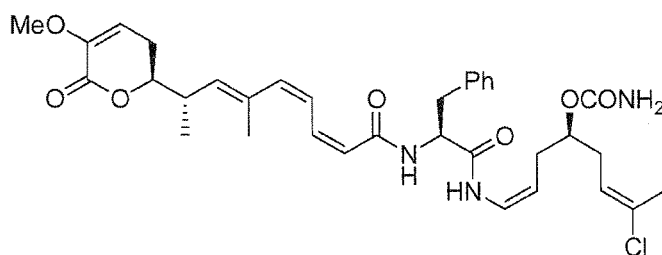
The isomer **(21S)-** of **Compound 5** was isolated when **5** was purified by semipreparative reversed phase HPLC (SymmetryPrep C8, gradient H₂O:MeCN from 45 to 50% MeCN in 30 min, UV detection, flow 4.7 mL/min, [rt ((21S)-5):21.6 min, rt ((21R)-5): 23.6 min). Starting from a sample (50 mg) which was containing both isomers, after the above mentioned separation it was obtained 39 mg of pure (21R)-Compound 5 and 6.1 mg of pure (21S)-Compound 5.



¹H NMR (CDCl₃, 500 MHz) δ : 8.74 (d, 1H, J = 10.5 Hz), 7.29 (dd, 1H, J = 11.7, 11.4 Hz), 6.94 (dd, 1H, J = 11.7, 11.4 Hz), 6.84 (dd, 1H, J = 10.5, 9.3 Hz), 6.22 (m, 2H), 5.68 (d, 1H, J = 11.5 Hz), 5.63 (m, 2H), 5.42 (d, 1H, J = 9.3 Hz), 4.81 (m, 1H), 4.52 (m, 1H), 4.41 (m, 1H), 4.23 (m, 1H), 3.66 (s, 3H), 2.91 (m, 1H), 2.49-2.38 (m, 3H), 2.35-2.31 (m, 2H), 2.24-2.17 (m, 2H), 2.05 (s, 3H), 1.82 (s, 3H), 1.15 (d, 3H, J = 6.6 Hz), 0.99 (d, 3H, J = 6.9 Hz) 0.96 (d, 3H, J = 6.9 Hz).

MS (ES) m/z 592.3 [M+H]⁺

Synthesis of compound 31

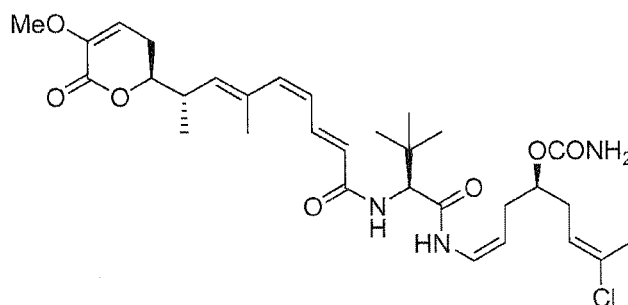


To a solution of **30d** (5 mg, 0.008 mmol) in Dichloromethane (0.7 mL) at 0°C, trichloroacetyl isocyanate (1.1 μ l, 0.009 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2). **Compound 31** (3.5 mg, yield: 66%) was obtained as a white solid

^1H NMR (CDCl_3 , 300 MHz) δ : 8.43 (d, 1H, J = 10.5 Hz), 7.29-7.19 (m, 6H), 6.91 (dd, 1H, J = 11.7, 11.4 Hz), 6.77 (br dd, 1H, J = 10.2, 9.6 Hz), 6.51 (d, 1H, J = 8.1 Hz), 6.16 (d, 1H, J = 11.4 Hz), 5.69-5.63 (m, 2H), 5.59-5.54 (m, 1H), 5.31 (d, 1H, J = 9.3 Hz), 5.12 (br s, 1H), 4.91-4.84 (m, 1H), 4.76-4.70 (m, 1H), 4.31-4.13 (m, 2H, CH-5), 3.66 (s, 3H), 3.20 (dd, 1H, J = 13.5, 6.9 Hz), 3.09 (dd, 1H, J = 13.5, 6.6 Hz), 2.89-2.81 (m, 1H), 2.48-2.35 (m, 2H), 2.28-2.23 (m, 3H), 2.05 (s, 3H), 2.01-1.90 (m, 1H), 1.81 (s, 3H), 1.15 (d, 3H, J = 6.6 Hz).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.9, 166.5, 161.9, 157.1, 145.4, 140.6, 137.9, 136.4, 134.4, 133.9, 132.1, 129.7, 128.8, 127.2, 124.6, 124.6, 122.7, 120.7, 108.5, 105.6, 82.1, 74.8, 55.7, 54.6, 38.7, 37.2, 33.1, 30.5, 26.2, 21.2, 17.3, 16.4.

Synthesis of compound 8



To a solution of **30e** (13 mg, 0.023 mmol) in Dichloromethane (1.7 mL) at 0°C, trichloroacetyl isocyanate (3 μ l, 0.025 mmol) was added. The
5 reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in
10 vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2). **Compound 8** (14.3 mg, yield: 100%) was obtained as a white solid and exhibited physical and spectroscopic characteristics (^1H , ^{13}C RMN and MS) equivalent to those reported in Example 4.

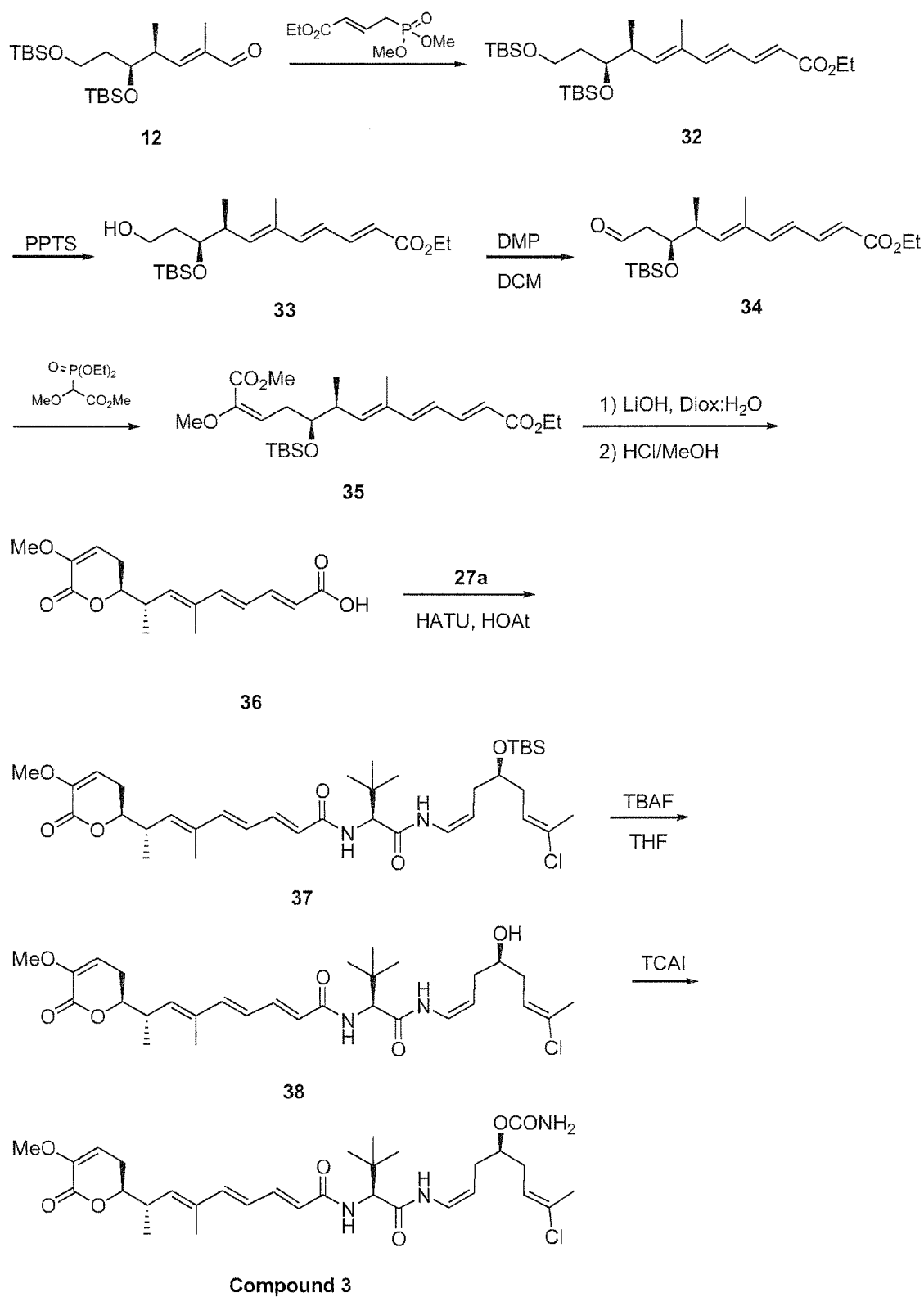
15

EXAMPLE 9

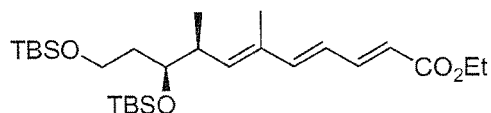
Scheme 6 depicts a synthetic process for several compounds of the invention.

20

93



Scheme 6

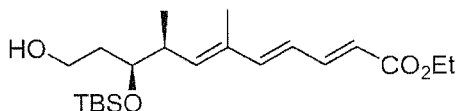
Synthesis of intermediate 32

5

To a solution of triethyl 4-phosphonocrotonate (3.7 g, 14.66 mmol) and 18-crown-6 (6.2 g, 23.46 mmol) in dry THF (59 mL) stirred under argon atmosphere at -78°C KHMDs (28.1 mL, 14.07 mmol) was added dropwise. After 15 min aldehyde **12** (2.35 g, 5.86 mmol) was added dropwise and stirred for 20 hours at room temperature. Then, the reaction was quenched with saturated NH₄Cl solution (200 mL), and diluted with EtOAc. The organic phase was dried (Na₂SO₄) and evaporated at reduced pressure. Purification by column chromatography (Hexane/EtOAc 20:1 to 10:1) afforded 2.7 g (yield: 93 %) of triene **32**.

¹H-RMN (300 MHz, CDCl₃) δ: 7.31 (dd, 1H, *J* = 11.2, 15.3 Hz), 6.53 (d, 1H, *J* = 15.0 Hz), 6.21 (dd, 1H, *J* = 11.7, 13.8 Hz), 5.84 (d, 1H, *J* = 15.1 Hz), 5.61 (d, 1H, *J* = 9.6 Hz), 4.17 (m, 2H), 3.72 (m, 1H), 3.63 (m, 2H), 2.61 (m, 1H), 1.78 (s, 3H), 1.67 (m, 2H), 1.26 (m, 3H), 0.94 (d, 3H, *J* = 6.7 Hz), 0.87 (s, 18H), 0.01 (m, 12H).

20

Synthesis of intermediate 33

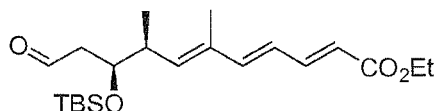
25

To a solution of **32** (3.75 g, 7.54 mmol) in EtOH (38 mL), pyridinium *p*-toluenesulfonate (663 mg, 2.64 mmol) was added. The reaction mixture was stirred at room temperature for 17 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by

column chromatography (Hexane/EtOAc 4:1 to 1:1) affording 2.11 g (yield: 73%) of alcohol **33**.

¹H-RMN (300 MHz, CDCl₃) δ: 7.31 (dd, 1H, *J* = 10.8, 15.0 Hz), 6.52 (d, 1H, *J* = 15.3 Hz), 6.23 (dd, 1H, *J* = 11.1, 15.0 Hz), 5.86 (d, 1H, *J* = 15.3 Hz), 5.52 (d, 1H, *J* = 9.9 Hz), 4.18 (q, 2H, *J* = 7.5 Hz), 3.72 (m, 3H), 2.73 (m, 1H), 1.82 (s, 3H), 1.68 (m, 2H), 1.28 (t, 3H, *J* = 7.2 Hz), 0.98 (d, 3H, *J* = 6.6 Hz), 0.88 (s, 9H), 0.08 (m, 6H).

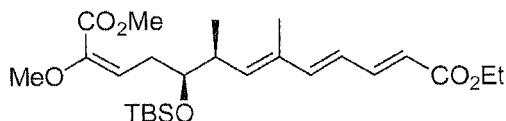
Synthesis of intermediate 34



The alcohol **33** (130 mg, 0.34 mmol) was stirred at room temperature in DCM (3.4 mL) under an inert atmosphere and periodinane (DMP) (288.5 mg, 0.68 mmol) was added in one portion. The reaction was stirred until completion (TLC, about 1 hour) and then was quenched with NaHCO₃ (saturated solution), extracted with DCM, washed with brine, dried over magnesium sulphate, filtered and concentrated in vacuum. The product was purified by column chromatography eluting with EtOAc/Hexane 1:4 to yield about 125 mg (yield: 96%) of aldehyde **34** as a colourless oil.

¹H-RMN (300 MHz, CDCl₃) δ: 9.79 (s, 1H), 7.31 (dd, 1H, *J* = 11.1, 15.3 Hz), 6.52 (d, 1H, *J* = 15.3 Hz), 6.25 (dd, 1H, *J* = 11.1, 15.3 Hz), 5.87 (d, 1H, *J* = 15.3 Hz), 5.48 (d, 1H, *J* = 10.5 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 4.03 (m, 1H), 2.69 (m, 1H), 2.54 (m, 2H), 1.80 (s, 3H), 1.29 (t, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.9 Hz), 0.88 (s, 9H), 0.06 (m, 6H).

Synthesis of intermediate 35

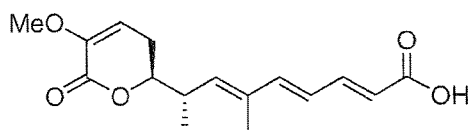


To a solution of phosphonate (170 mg, 0.67 mmol) and 18-crown-6 (357 mg, 1.35 mmol) in dry THF (10 mL) stirred under argon atmosphere at –
 5 78°C KHMDS (1.34 ml, 0.67 mmol) was added dropwise. After 15 min a solution of aldehyde **34** (170 mg, 0.45 mmol) in dry THF (8.5 mL) was added dropwise over a period of 30 min and stirred at –78°C for 90 min. Then, the reaction was quenched with saturated NH₄Cl solution, warmed to room temperature and diluted with Dichloromethane. The
 10 organic phase was dried (Na₂SO₄) and evaporated at reduced pressure. Purification by column chromatography (Hexane/EtOAc 20:1 to 10:2) afforded 170 mg (yield: 82%) of (*E*)-**35**.

¹H-RMN (300 MHz, CDCl₃) δ: 7.29 (dd, 1H, *J* = 10.8, 15.3 Hz), 6.50 (d, 1H, *J* = 15.3 Hz), 6.19 (dd, 1H, *J* = 10.8, 15.0 Hz), 5.83 (d, 1H, *J* = 15.3 Hz), 5.48 (d, 1H, *J* = 10.2 Hz), 5.33 (t, 1H, *J* = 7.2 Hz), 4.17 (m, 2H),
 15 3.71 (s, 3H), 3.61 (m, 1H), 3.58 (s, 3H), 2.73 (m, 1H), 2.57 (m, 2H), 1.71 (s, 3H), 1.25 (m, 3H), 0.97 (d, 3H, *J* = 6.7 Hz), 0.88 (s, 9H), 0.03 (m, 6H).

Synthesis of intermediate 36

20



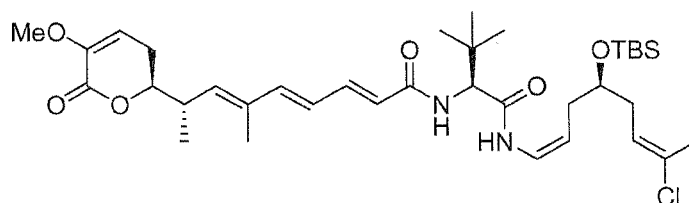
LiOH (15.8 mg, 0.66 mmol) was added to a solution of ester **35** (140 mg, 0.30 mmol) in 20 % water/Dioxane (7 mL) and the mixture was stirred
 25 for 4 hours at 60°C. The mixture was cooled, diluted with DCM and washed with HCl (0.5N, 10 mL). The aqueous phase was repeatedly extracted with DCM and the combined organic layers were dried over

Na₂SO₄, filtered and evaporated to afford the crude di-acid which was used in the next step without further purification.

Concentrated HCl (43 μ L) was added to a solution of crude in MeOH (5.2 mL) and the resulting mixture was stirred for 1 hour at room temperature. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (Hexane/EtOAc 1:4 to EtOAc/MeOH 5:1) affording 72 mg (yield: 70%) of acid **36** as a colourless oil.

¹H-RMN (300 MHz, CDCl₃) δ : 7.40 (dd, 1H, J = 10.8, 15.0 Hz), 6.57 (d, 1H, J = 15.0 Hz), 6.31 (dd, 1H, J = 11.4, 15.3 Hz), 5.89 (d, 1H, J = 15.0 Hz), 5.60 (m, 1H), 5.52 (d, 1H, J = 10.2 Hz), 4.22 (m, 1H), 3.64 (s, 3H), 2.90 (m, 1H), 2.38 (m, 2H), 1.84 (s, 3H), 1.15 (d, 3H, J = 6.9 Hz).

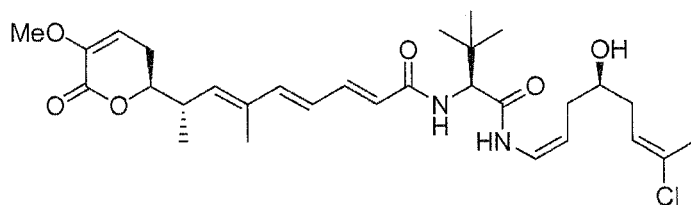
Synthesis of compound 37



To a solution of amine **27a** (37.6 mg, 0.093 mmol) in DCM/DMF (10:1, 1.3 mL), a solution of acid **36** (30 mg, 0.103 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0 °C. DIPEA (26 μ L, 0.14 mmol), HOAt (12.7 mg, 0.093 mmol), and HATU (35.4 mg, 0.093 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 3h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 2:1 to 1:4) to give amide **37** (34.7 mg, yield: 55%) as an oil.

^1H NMR (CDCl_3 , 500 MHz) δ : 7.88 (d, 1H J = 10.5 Hz), 7.26 (dd, 1H, J = 14.4, 11.4 Hz), 6.72 (dd, 1H, J = 9.9, 9.6 Hz), 6.50 (d, 1H, J = 15.3 Hz), 6.31-6.22 (m, 2H), 5.94 (d, 1H, J = 14.7 Hz), 5.61-5.54 (m, 2H), 5.44 (d, 1H, J = 9.9 Hz), 4.87-4.79 (m, 1H), 4.45 (d, 1H, J = 9.3), 4.24-4.16 (m, 1H), 3.77-3.44 (m, 1H), 3.64 (s, 3H), 2.96-2.2.81 (m, 1H), 2.39-2.35 (m, 2H), 2.16-2.15 (m, 4H), 2.01 (s, 3H), 1.82 (s, 3H), 1.14 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

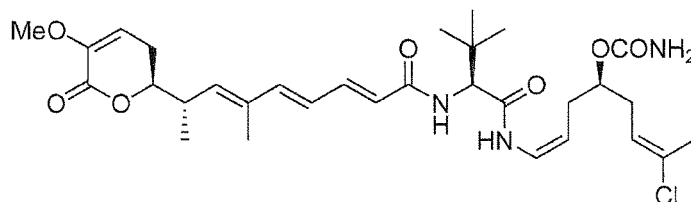
Synthesis of compound 38



To a solution of **37** (28 mg, 0.04 mmol) in THF (0.6 mL) under N_2 and at room temperature, TBAF 1M in THF (83 μL , 0.08 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **38** (22 mg, yield: 96%) as a white solid.

^1H NMR (CDCl_3 , 500 MHz) δ : 9.06 (d, 1H, J = 9.9 Hz), 7.24 (dd, 1H, J = 14.7, 10.5 Hz), 6.76 (d, 1H, J = 9.6 Hz), 6.74 (dd, 1H, J = 9.6, 9.6 Hz), 6.50 (d, 1H, J = 15.3 Hz), 6.25 (dd, 1H, J = 15.3, 11.1 Hz), 5.99 (d, 1H, J = 14.7 Hz), 5.65-5.60 (m, 2H), 5.45 (d, 1H, J = 9.9 Hz), 4.87-4.81 (m, 1H), 4.45 (d, 1H, J = 9.3), 4.24-4.16 (m, 1H), 3.74-3.64 (m, 1H), 3.64 (s, 3H), 3.22-3.17 (m, 1H), 2.95-2.2.82 (m, 1H), 2.40-2.35 (m, 2H), 2.23-2.16 (m, 4H), 2.05 (s, 3H), 1.81 (s, 3H), 1.13 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H).

Synthesis of compound 3

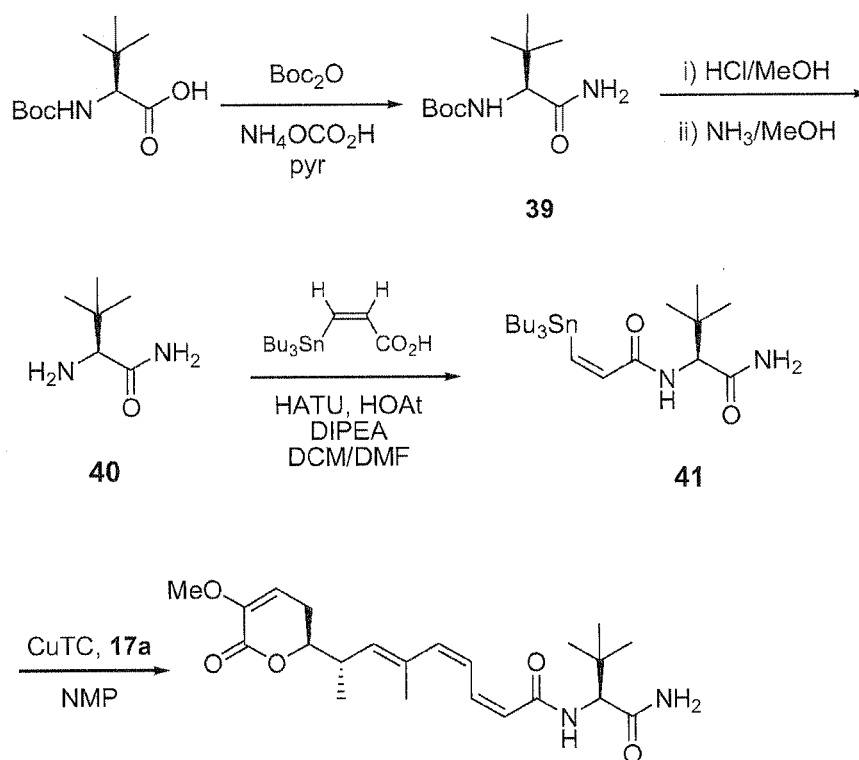


5

To a solution of compound **38** (20 mg, 0.04 mmol) in Dichloromethane (0.35 ml) at 0°C, trichloroacetyl isocyanate (5.1 µL, 0.04 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 1:1 to 1:3). Compound **3** (13.6 mg, yield: 63%) was obtained as a white foam and exhibited physical and spectroscopic characteristics (¹H, ¹³C RMN and MS) equivalent to those reported in Example 3.

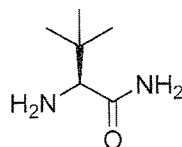
EXAMPLE 10

20 Scheme 7 depicts a synthetic process for compound 7.



Scheme 7

5 Synthesis of intermediate 40

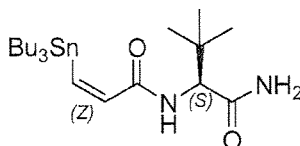


- 10 To a solution of Boc-*tert*-LeuCONH₂ **39** (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (1.9 g, 8.26 mmol) in MeOH, 66 mL of a solution 1.25 M of HCl in MeOH was added. The reaction mixture was stirred for 2 hours at room temperature and then was concentrated at reduced pressure.
- 15 The solid was then suspended in MeOH and neutralized with

concentrated ammonium hydroxide. The solvent was removed by rotary evaporation and the crude was dissolved in dichloromethane. The solution was dried over Na₂SO₄, filtered and concentrated to give 730 mg (yield: 68%) of the intermediate **40** as a white solid.

- 5 ¹H NMR (CDCl₃, 300 MHz) δ: 6.65-6.55 (br s, 1H), 5.65-5.55 (br s, 1H), 3.18 (s, 1H), 1.65-1.55 (br s, 2H), 1.05 (s, 9H).

Synthesis of intermediate 41

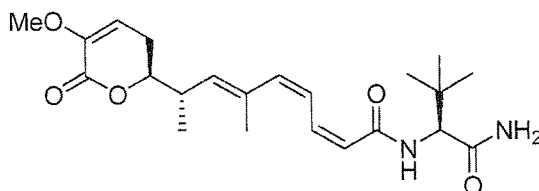


10

To a solution of amine **40** (100 mg, 0.77 mmol) in DCM/DMF (10:1, 7.7 mL), a solution of (Z)-3-tributylstannylpropenoic acid (306 mg, 0.85 mmol) in dry DCM was added, under argon atmosphere, and then was cooled at 0°C. DIPEA (0.27 mL, 1.54 mmol), HOAt (115.6 mg, 0.85 mmol), and HATU (323 mg, 0.85 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 10:1 to 1:1) to give amide **41** (228 mg, yield: 63%) as a white foam.

- 25 ¹H NMR (CDCl₃, 300 MHz) δ: 6.99 (d, 1H, *J* = 12.3 Hz), 6.77 (d, 1H, *J* = 12.3 Hz), 6.47 (d, 1H, *J* = 9.6 Hz), 6.38 (br s, 1H), 6.12 (br s, 1H), 4.46 (d, 1H, *J* = 9.9 Hz), 1.48-1.40 (m, 6H), 1.31-1.19 (m, 12H), 1.00 (s, 9H), 0.89-0.83 (m, 9H).

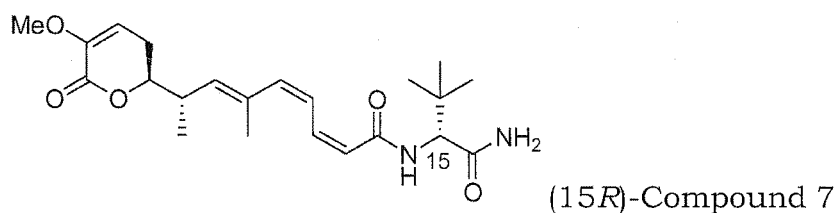
¹³C NMR (CDCl₃, 75 MHz) δ: 173.4, 166.6, 153.4, 136.6, 60.0, 35.0, 29.6, 27.6, 26.8, 14.0, 11.7.

Synthesis of compound 7

5

To a solution of alkenylstannane **41** (227.6 mg, 0.48 mmol) and **17a** (200.9 mg, 0.58 mmol) in NMP (5 mL) at 0°C, Copper thiophenecarboxylate (19.1 mg, 0.10 mmol) was added. The reaction was stirred at 0°C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.1%. The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (dichloromethane/MeOH 100:1 to 10:1) to give Compound **7** (65.7 mg, yield: 34%) as a white foam. This synthetic product exhibited physical and spectroscopic characteristics (¹H, ¹³C RMN and MS) equivalent to those reported in Example 3.

The isomer **(15R)-** of **Compound 7** was obtained when a racemic mixture of the amino acid (Boc-*tert*-LeuCONH₂) was used to carry out these reactions. The final mixture of isomers (15 mg) was separated by semipreparative reversed phase HPLC (SymmetryPrep C18 7 μm, 7.8 x 150 mm, gradient H₂O:MeOH from 50 to 70% MeOH in 75 min, UV detection, flow 2.5 mL/min, [rt ((15R)-7): 18.15 min, rt ((15S)-7): 19.62 min) and it was obtained 3.1 mg of pure **(15R)-Compound 7** and 2.9 mg of pure **(15S)-Compound 7**:



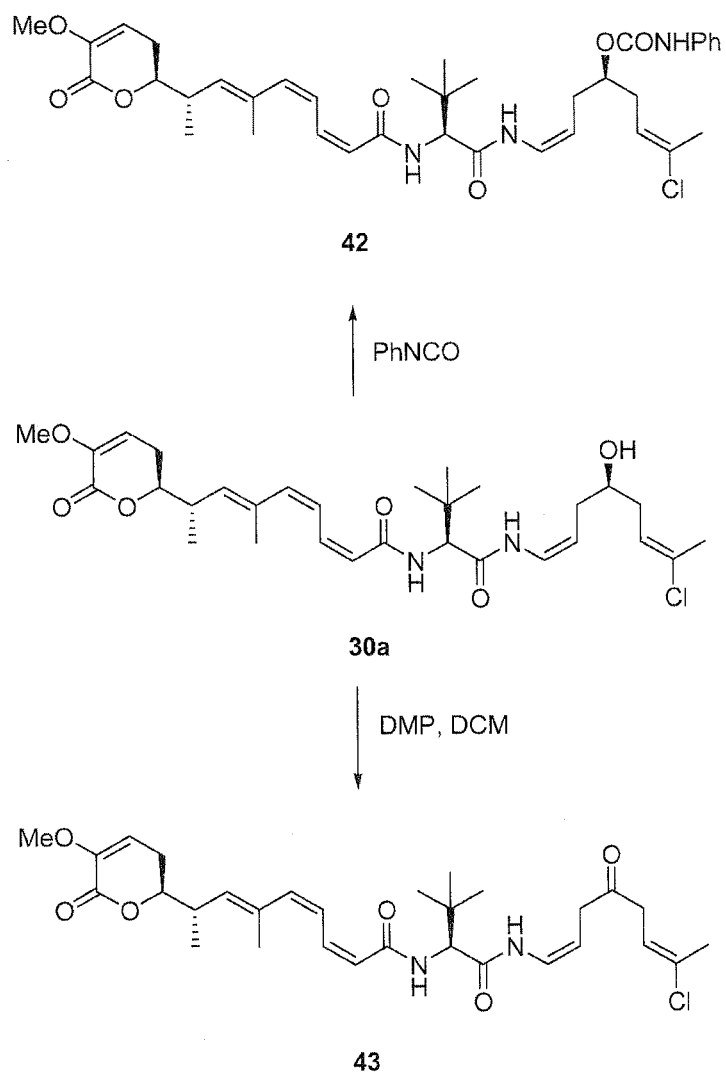
¹H NMR (MeOD, 500 MHz) δ : 7.23 (dd, 1H, J = 12.5, 11.5 Hz), 6.94 (dd, 1H, J = 12.5, 11.5 Hz), 6.18 (d, 1H, J = 12.0 Hz), 5.91-5.88 (m, 1H),
 5 5.86 (t, 1H, J = 4.5 Hz), 5.34 (d, 1H, J = 10.0 Hz), 4.33-4.28 (m, 1H), 3.64 (s, 3H), 2.92-2.88 (m, 1H), 2.47-2.44 (m, 2H), 1.85 (s, 3H), 1.17 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H).

¹³C NMR (MeOD, 125 MHz) δ : 175.3, 168.6, 164.0, 146.0, 140.8, 138.2, 135.4, 135.4, 125.5, 121.9, 111.1, 83.5, 61.8, 55.9, 38.4, 35.0, 27.2,
 10 27.1, 17.3, 16.8.

EXAMPLE 11

Scheme 8 depicts the processes for obtaining compounds 42 and 43.

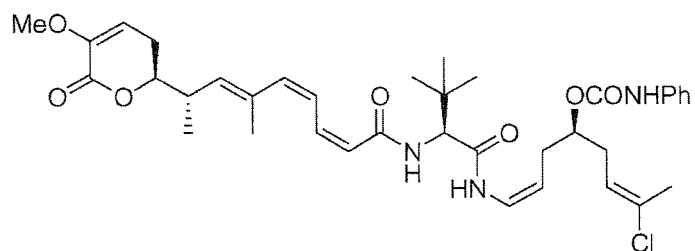
104



Scheme 8

Synthesis of compound 42

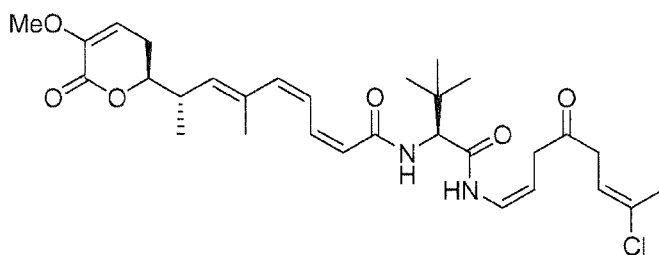
5



To a solution of alcohol **30a** (5 mg, 8.8 μ mol) in pyridine (0.45 mL), phenylisocyanate (29 mL, 0.27 mmol) was added. The reaction was stirred at room temperature for 20 hours and then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 1:1) to give compound **42** (2.7 mg, yield: 44%) as a white solid.

^1H NMR (CDCl_3 , 300 MHz) δ : 8.81-8.77 (m, 1H), 7.46-7.43 (m, 2H), 7.34-7.23 (m, 3H), 7.11-7.06 (m, 2H), 6.88-6.77 (m, 2H), 6.39 (d, 1H, J = 9.9 Hz), 6.10 (d, 1H, J = 11.7 Hz), 5.67-5.57 (m, 3H), 5.27 (d, 1H, J = 9.9 Hz), 4.85-4.78 (m, 1H), 4.62-4.56 (m, 1H), 4.54 (d, 1H, J = 9.3 Hz), 4.25-4.17 (m, 1H), 3.66 (s, 3H), 2.87-2.80 (m, 1H), 2.41-2.38 (m, 5H), 2.21-2.13 (m, 1H), 2.08 (s, 3H), 1.82 (s, 3H), 1.16 (d, 3H J = 6.6 Hz), 1.07 (s, 9H).

Synthesis of compound 43



20

Alcohol **30a** (5 mg, 8.88 μ mol) was stirred at room temperature in DCM (0.1 mL) under an inert atmosphere and periodinane (7.5 mg, 0.018 mmol) was added in one portion. The reaction was stirred until completion (TLC, about 1 hours) and then was quenched with NaHCO_3 (saturated solution), extracted with DCM, washed with brine, dried over magnesium sulphate, filtered and concentrated in vacuum. The product

was purified by column chromatography eluting with EtOAc/Hexane 1:1 to yield about 4.5 mg (yield: 90%) of ketone **43** as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ : 8.32 (d, 1H, J = 9.9 Hz), 7.31-7.23 (m, 1H), 6.91 (dd, 1H, J = 11.7, 11.4 Hz), 6.84 (dd, 1H, J = 9.9, 8.7 Hz), 6.26 (d, 1H, J = 8.7 Hz), 6.18 (d, 1H, J = 11.4 Hz), 5.78-5.73 (m, 1H), 5.68 (d, 1H, J = 11.4 Hz), 5.64-5.61 (m, 1H), 5.30-5.27 (m, 1H), 4.94-4.86 (m, 1H), 4.41 (d, 1H, J = 9.0 Hz), 4.25-4.17 (m, 1H), 3.66 (s, 3H), 3.18 (dd, 4H, J = 18.3, 7.2 Hz), 2.89-2.75 (m, 1H), 2.44-2.38 (m, 2H), 2.04 (s, 3H), 1.84 (s, 3H), 1.16 (d, 3H J = 6.9 Hz), 1.05 (s, 9H).

10

EXAMPLE 12: BIOASSAYS FOR THE DETECTION OF ANTITUMOR ACTIVITY

The aim of this assay is to evaluate the *in vitro* cytostatic (ability to delay or arrest tumor cell growth) or cytotoxic (ability to kill tumor cells) activity of the samples being tested.

CELL LINES

20

Name	N° ATCC	Species	Tissue	Characteristics
A549	CCL-185	human	lung	lung carcinoma (NSCLC)
HT29	HTB-38	human	colon	colorectal adenocarcinoma
MDA-MB-231	HTB-26	human	breast	breast adenocarcinoma

EVALUATION OF CYTOTOXIC ACTIVITY USING THE SBR COLORIMETRIC ASSAY

A colorimetric type of assay, using sulforhodamine B (SRB) reaction has been adapted for a quantitative measurement of cell growth and viability (following the technique described by Skehan P et al. J. Natl. Cancer Inst. 1990, 82, 1107-1112).

25

This form of assay employs SBS-standard 96-well cell culture microplates (Faircloth et al. Methods in cell science, 1988, 11(4), 201-205; Mosmann et al, Journal of. Immunological. Methods, 1983, 65(1-2), 55-
5 63). All the cell lines used in this study, derived from different types of human cancer, were obtained from the American Type Culture Collection (ATCC).

Cells were maintained in Dulbecco's Modified Eagle Medium
10 (DMEM) supplemented with 10% Fetal Bovine Serum (FBS), 2mM L-glutamine, 100 U/mL penicillin and 100 U/mL streptomycin at 37°C, 5% CO₂ and 98% humidity. For the experiments, cells were harvested from subconfluent cultures using trypsinization and resuspended in fresh medium before counting and plating.

15

Cells were seeded in 96 well microtiter plates at 5×10^3 cells per well in aliquots of 150 μ L, and allowed to attach to the plate surface for 18 hours in drug free medium. One control (untreated) plate of each cell line was fixed (as described below) and used for time zero reference
20 value. Afterwards, test samples were added to the cultures in ten serial dilutions, in aliquots of 50 μ L, ranging from 10 to 0.00262 μ g/mL. After 48 hours exposure, the antitumor effect was estimated by the SRB method: Briefly, cells were washed twice with PBS, fixed for 15 min in 1% glutaraldehyde solution, rinsed twice in PBS, and stained in 0.4%
25 SRB solution for 30 min at room temperature. Cells were then rinsed several times with 1% acetic acid solution and air-dried. SRB was then extracted in 10mM trizma base solution and the absorbance measured in an automated spectrophotometric plate reader at 490 nm. Cell survival was expressed as percentage of control cell growth. The final
30 effect of the sample being tested was estimated by applying the NCI algorithm (Boyd MR and Paull KD. Drug Dev. Res. 1995, 34, 91-104).

Using the mean $\pm$ SD of triplicate cultures, a dose-response curve was automatically generated using nonlinear regression analysis. Three reference parameters were calculated (NCI algorithm) by automatic interpolation: GI₅₀ = concentration that produces 50% growth inhibition; TGI = total growth inhibition (cytostatic effect) and LC₅₀ = concentration that produces 50% net cell killing (cytotoxic effect).

ANTI-MITOTIC ASSAY PROTOCOL

10 The mitotic ratio of the cell cultures (percentage of cells arrested in mitosis) was estimated using a specific 96-well microplate immunoassay that quantitatively detects a specific mitotic marker. HeLa cells (h-cervix carcinoma, ATCC# CCL-2) were incubated for 18 hours in the presence or absence of the samples being tested.

15 Afterwards, cells were washed with PBS and lysed on ice in 75 μ L of freshly prepared lysis buffer (1mM EGTA (pH 7.5), 0.5 mM PMSF and 1 mM NaVO₃) for 30 min. An aliquot of the cell extract (60 μ L) was transferred to a high-binding surface ELISA plate and dried in a speed-vac for 2 h at room temperature. Plates were then blocked in 100 μ L.

20 PBS-1% BSA for 30 min at 30°C and sequentially incubated with anti-MPM2 primary mouse monoclonal antibody (*Upstate Biotechnology*, cat # 05-368) for 18 h at 4°C and appropriate peroxidase-conjugated secondary antibody for 1h at 30°C. After intensive washing in 0.02% Tween-20, peroxidase reaction were performed using 30 μ L of TMB

25 (3,3',5,5'-tetramethyl-benzidine) for 30 min at 30°C. Reaction was stopped by adding 30 μ L of a 4% H₂SO₄ solution. Assay was quantified by measuring the O.D. at 450 nm in a microplate spectrophotometer. Results were expressed as IC₅₀, sample concentration that produces 50% mitotic arrest in treated cell cultures, as compared to control,

30 untreated cultures.

Tables 9 and 10 illustrate data on the biological activity of compounds of the present invention.

Table 9. Cytotoxicity assay - Activity Data (Molar)

		Compound 1	Compound 2	Compound 3	Compound 4
MDA-MB-231	GI ₅₀	4.45E-10	9.85E-09	9.24E-10	6.13E-10
	TGI	9.90E-10	2.15E-08	2.47E-09	1.49E-09
	LC ₅₀	2.80E-09	7.20E-08	9.57E-09	8.23E-09
HT29	GI ₅₀	4.62E-10	8.31E-09	4.45E-10	< 4.31E-10
	TGI	6.10E-10	1.09E-08	7.59E-10	9.28E-10
	LC ₅₀	9.90E-10	1.72E-08	> 1.65E-07	1.12E-09
A549	GI ₅₀	3.79E-10	8.63E-09	1.02E-09	5.95E-10
	TGI	1.09E-09	2.37E-08	4.29E-09	2.45E-09
	LC ₅₀	> 1.65E-07	1.65E-05	> 1.65E-07	> 1.64E-06

5

Table 9. (cont.)

		Compound 5	Compound 6	Compound 7	Compound 8
MDA-MB-231	GI ₅₀	1.03E-10	4.90E-10	4.20E-07	3.46E-09
	TGI	4.56E-10	3.21E-09	8.41E-07	1.01E-08
	LC ₅₀	4.90E-09	1.55E-08	2.45E-06	4.12E-08
HT29	GI ₅₀	4.39E-11	5.91E-10	4.20E-07	2.14E-09
	TGI	1.28E-10	1.01E-09	5.44E-07	3.13E-09
	LC ₅₀	> 1.69E-07	4.90E-09	8.16E-07	6.27E-09
A549	GI ₅₀	6.08E-11	7.60E-10	6.18E-07	3.63E-09
	TGI	3.21E-10	> 1.64E-06	1.19E-06	1.30E-08
	LC ₅₀	> 1.69E-07	> 1.64E-06	> 2.47E-06	> 1.65E-06

10

Table 9. (cont.)

		Compound 29a	Compound 29d	Compound 29e	Compound 30a
MDA- MB-231	GI50	1.18E-06	1.10E-06	1.14E-06	1.95E-09
	TGI	2.80E-06	1.39E-06	1.48E-06	9.41E-09
	LC50	6.20E-06	1.83E-06	2.07E-06	8.52E-08
HT29	GI50	6.05E-07	8.29E-07	2.07E-06	1.35E-09
	TGI	1.42E-06	8.72E-07	2.21E-06	2.13E-09
	LC50	4.43E-06	9.28E-07	2.36E-06	1.01E-08
A549	GI50	8.86E-07	4.64E-07	1.15E-06	2.31E-09
	TGI	3.40E-06	8.01E-07	1.77E-06	1.37E-07
	LC50	8.56E-06	1.38E-06	2.66E-06	> 1.78E-06

Table 9. (cont.)

		Compound 30b	Compound 30c	Compound 30d	Compound 30f
MDA- MB-231	GI ₅₀	2.08E-08	9.83E-10	3.10E-10	6.94E-07
	TGI	5.11E-07	5.83E-09	7.03E-10	1.07E-06
	LC ₅₀	5.11E-06	5.28E-08	> 1.67E-08	1.61E-06
HT29	GI ₅₀	9.84E-09	4.74E-10	1.32E-10	4.88E-07
	TGI	9.27E-08	8.38E-10	2.51E-10	7.13E-07
	LC ₅₀	4.73E-06	> 1.82E-07	> 1.67E-08	1.05E-06
A549	GI ₅₀	2.27E-08	7.10E-10	3.18E-10	4.88E-07
	TGI	3.22E-07	3.10E-09	1.06E-09	6.57E-07
	LC ₅₀	> 1.89E-05	> 1.82E-07	> 1.67E-08	9.19E-07

Table 9. (cont.)

		Compound 30e	Compound 31	Compound 37	Compound 38
MDA- MB-231	GI ₅₀	2.31E-08	7.50E-11	3.10E-06	6.04E-08
	TGI	6.57E-08	1.50E-10	5.61E-06	> 1.78E-07
	LC ₅₀	2.66E-07	3.59E-10	> 1.48E-05	> 1.78E-07
HT29	GI ₅₀	1.35E-08	4.06E-11	1.92E-06	3.91E-08
	TGI	2.13E-08	1.02E-10	2.95E-06	6.39E-08
	LC ₅₀	4.44E-08	> 1.56E-08	1.00E-05	> 1.78E-07
A549	GI ₅₀	3.55E-08	9.22E-11	3.54E-06	4.62E-08
	TGI	3.02E-07	2.19E-10	6.64E-06	6.75E-08
	LC ₅₀	3.55E-06	> 1.56E-08	1.39E-05	> 1.78E-07

Table 9. (cont.)

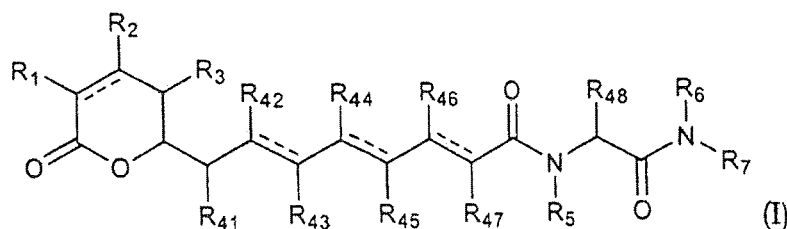
		Compound (21S)-1	Compound (21S)-5	Compound (15R)-7	Compound (21S)-30a
MDA- MB-231	GI ₅₀	1.65E-09	4.56E-09	7.66E-07	2.49E-09
	TGI	5.77E-09	1.86E-08	2.47E-06	2.13E-08
	LC ₅₀	3.46E-08	1.03E-07	> 2.47E-05	2.84E-07
HT29	GI ₅₀	8.91E-10	2.53E-09	3.46E-07	2.66E-09
	TGI	1.63E-09	2.87E-09	5.93E-07	3.02E-09
	LC ₅₀	2.31E-08	3.88E-09	1.31E-06	> 1.63E-06
A549	GI ₅₀	2.14E-09	6.92E-09	1.04E-06	3.73E-09
	TGI	4.29E-08	2.87E-08	3.46E-06	1.95E-07
	LC ₅₀	> 1.65E-06	> 1.69E-06	> 2.47E-05	> 1.63E-06

Table 10. Antimitotic assay – Activity Data (Molar) of Compounds 1 and 2.

	IC ₅₀
Compound 1	2.64E-8
Compound 2	2.64E-8

CLAIMS

1. A compound of general formula I



5

wherein R_1 is selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, NR_aR_b , NR_aCOR_b , and $NR_aC(NR_a)NR_aR_b$;

- each R_2 and R_3 are independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl;

each R_{41} , R_{42} , R_{43} , R_{44} , R_{45} , R_{46} , R_{47} and R_{48} are independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl;

- each R_5 , R_6 , and R_7 are independently selected from hydrogen, COR_a , $COOR_a$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, or R_5 and R_{48} together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

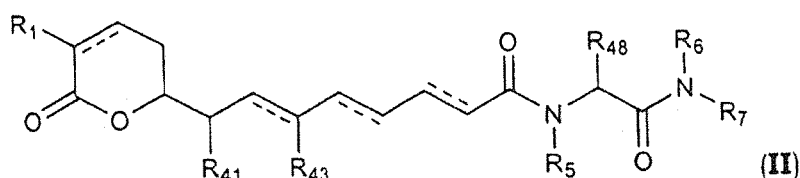
each R_a and R_b are independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic group;

and

each dotted line represent an optional additional bond;

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

2. A compound according to claim 1, having the following formula **II**



5

wherein R₁, R₄₁, R₄₃ and R₄₈, R₅, R₆, and R₇ are as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

3. A compound according to claim 1, wherein R₂ and R₃ are each
 10 independently selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

4. A compound according to claim 3, wherein R₂ and R₃ are
 15 hydrogen, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

5. A compound according to any of the preceding claims, wherein R₁ is selected from hydrogen, OR_a and OCOR_a, wherein R_a is selected from
 20 hydrogen and substituted or unsubstituted C₁-C₆ alkyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

6. A compound according to claim 5, wherein R₁ is hydrogen or methoxy, or a pharmaceutically acceptable salt, tautomer, or
 25 stereoisomer thereof.

7. A compound according to any of claims 1 and 3-6, wherein R₄₂, R₄₄, R₄₅, R₄₆, and R₄₇ groups are independently selected from hydrogen

and substituted or unsubstituted C₁-C₆ alkyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

8. A compound according to claim 7, wherein R₄₂, R₄₄, R₄₅, R₄₆, R₄₇
5 groups are independently selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted isopropyl and substituted or unsubstituted tert-butyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

10 9. A compound according to claim 8, wherein R₄₂, R₄₄, R₄₅, R₄₆, and R₄₇ are hydrogen, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

10. A compound according to any of the preceding claims, wherein
15 R₄₁, R₄₃, and R₄₈ groups are independently selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

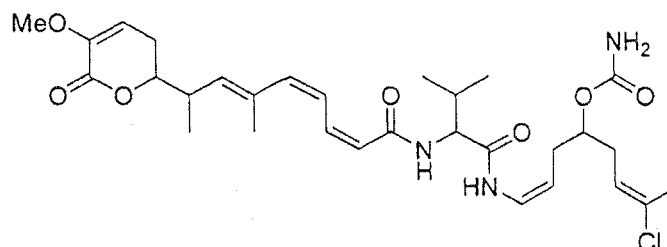
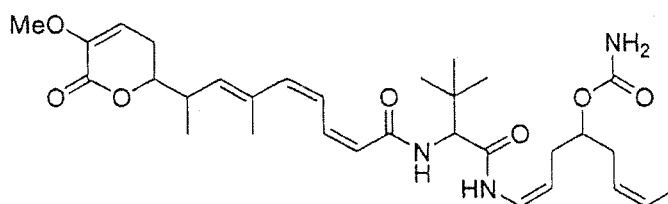
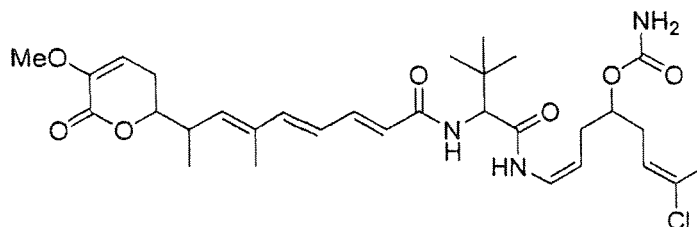
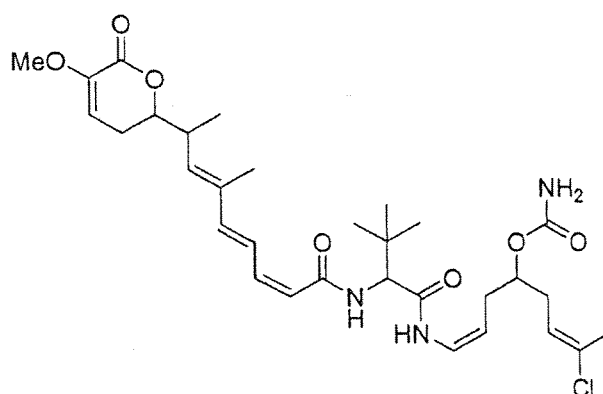
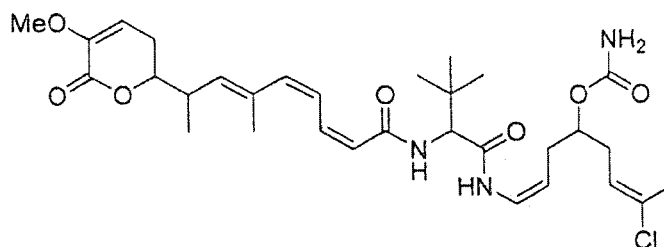
11. A compound according to claim 10, wherein R₄₁, R₄₃, and R₄₈
20 groups are independently selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted isopropyl and substituted or unsubstituted tert-butyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

25 12. A compound according to claim 11, wherein R₄₁ and R₄₃ are methyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

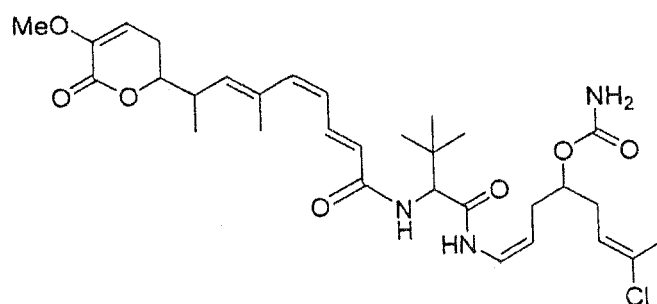
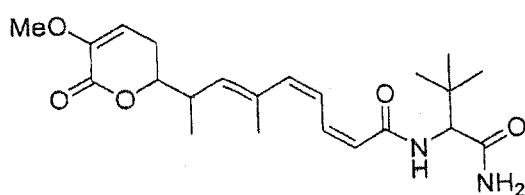
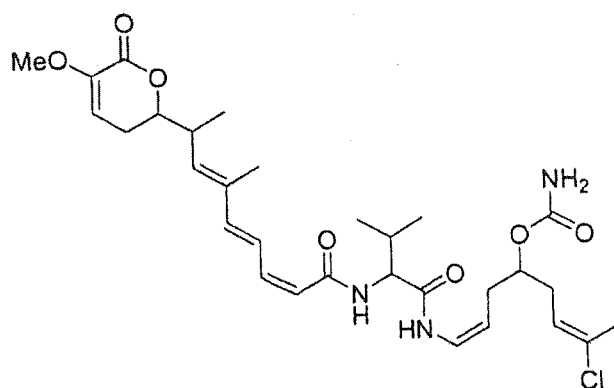
13. A compound according to claim 11 or 12, wherein R₄₈ is selected
30 from isopropyl, tert-butyl, and benzyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

14. A compound according to any of the preceding claims, wherein R_5 and R_6 are each independently selected from the group consisting of hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.
- 5 15. A compound according to claim 14, wherein R_5 and R_6 are hydrogen, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.
- 10 16. A compound according to any of the preceding claims, wherein R_7 is selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl and substituted or unsubstituted C_2 - C_{12} alkenyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.
- 15 17. A compound according to claim 16, wherein R_7 is selected from hydrogen and substituted C_2 - C_{12} alkenyl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.
- 20 18. A compound according to claim 17, wherein R_7 is an alkenyl group that is substituted in one or more positions with halogen, OR' , $=O$, $OCOR'$, $OCONHR'$, $OCON(R')_2$ and protected OH, wherein each of the R' groups is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, and substituted or
25 unsubstituted aryl, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.
- 30 19. A compound according to any of the preceding claims, wherein an additional bond is present in all the places indicated with a dotted line, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

20. A compound according to claim 1 or 2, having the following formula

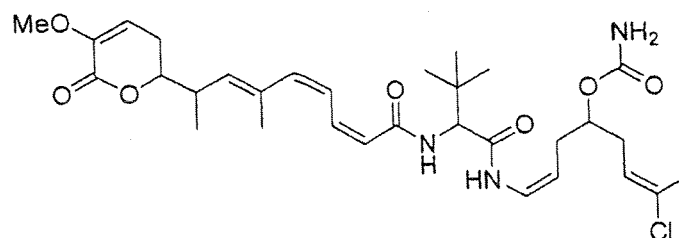


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5 or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

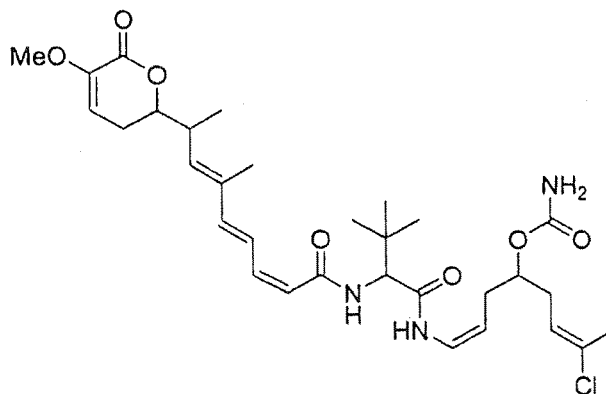
21. A compound according to claim 1 or 2, having the following formula



10

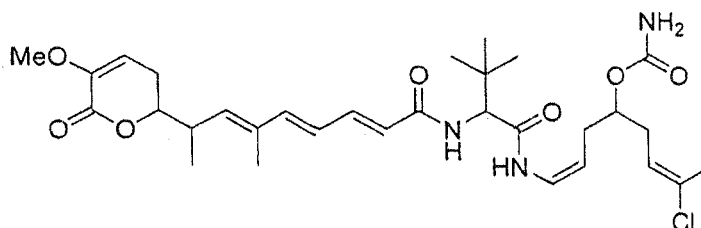
or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

22. A compound according to claim 1 or 2, having the following formula



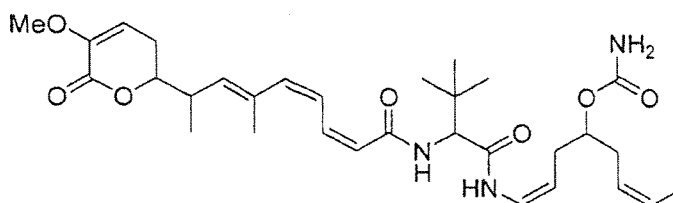
or a pharmaceutically acceptable salt, tautomer, or stereoisomer
5 thereof.

23. A compound according to claim 1 or 2, having the following formula



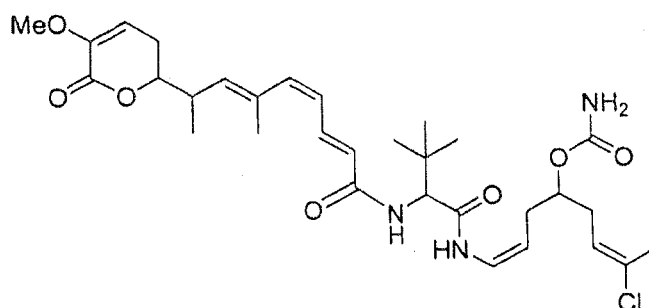
10 or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

24. A compound according to claim 1 or 2, having the following formula



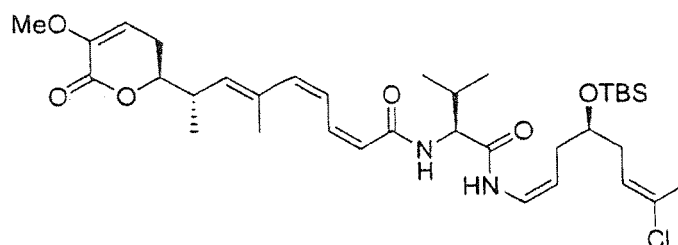
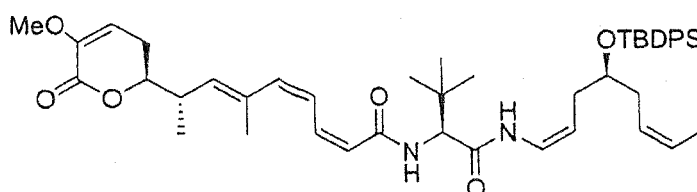
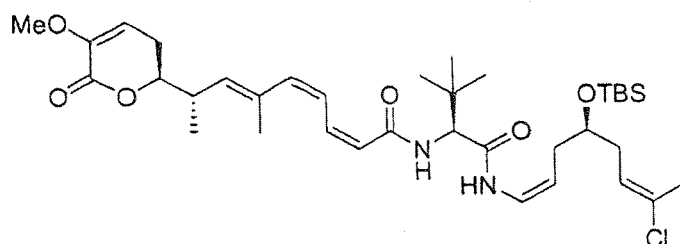
15 or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

28. A compound according to claim 1 or 2, having the following formula

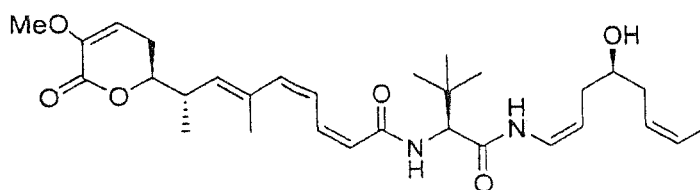
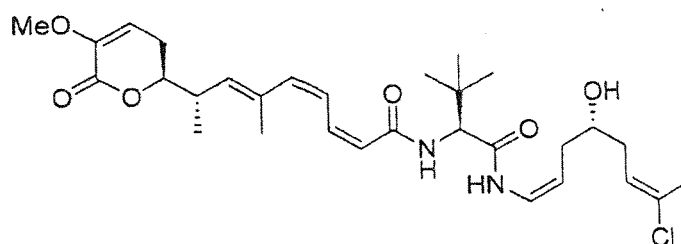
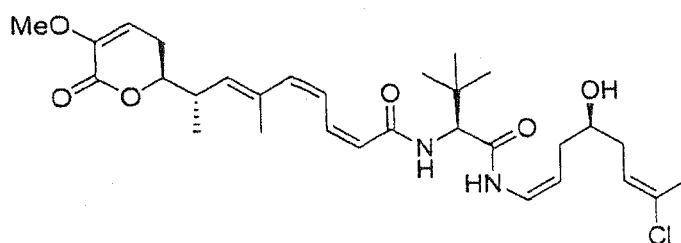
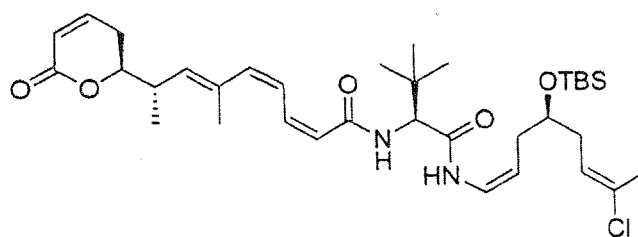
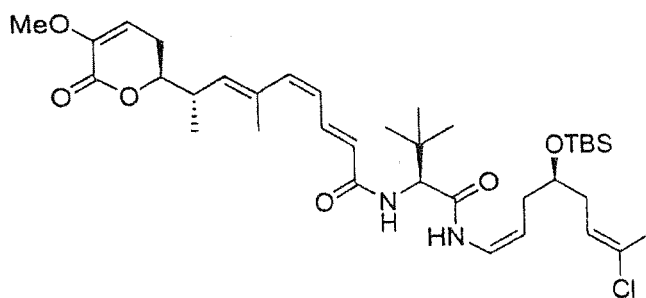
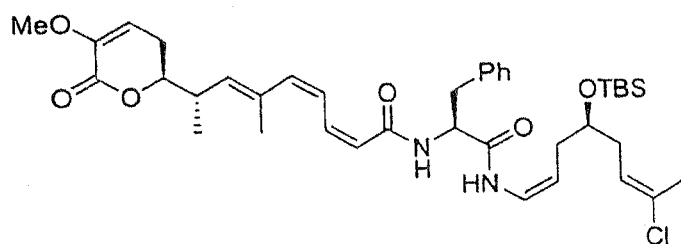


or a pharmaceutically acceptable salt, tautomer, or stereoisomer
5 thereof.

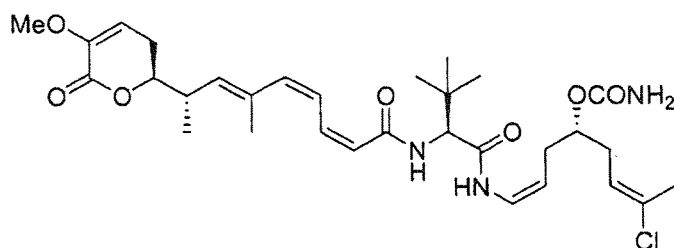
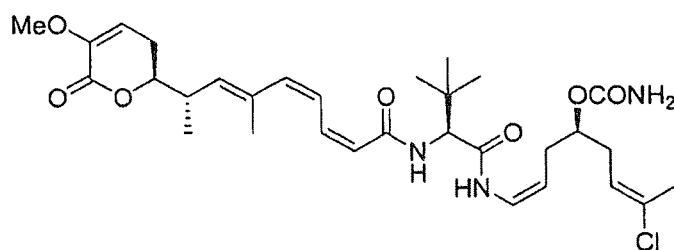
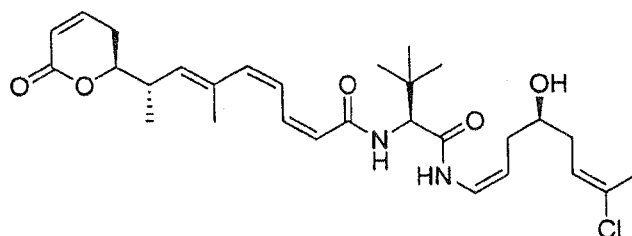
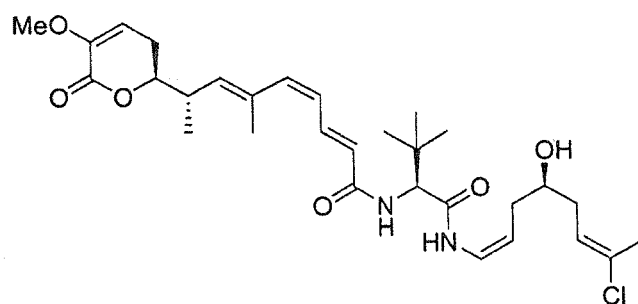
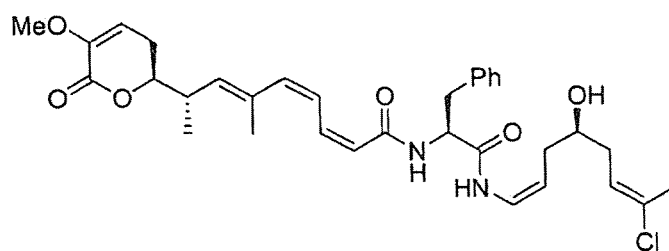
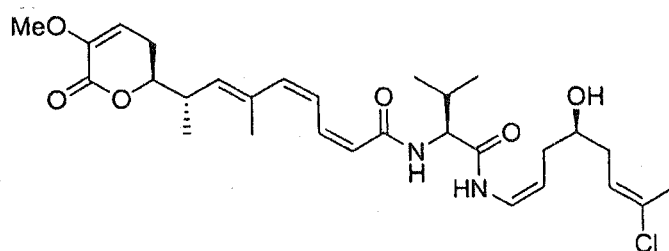
29. A compound according to claim 1 or 2, having the following formula



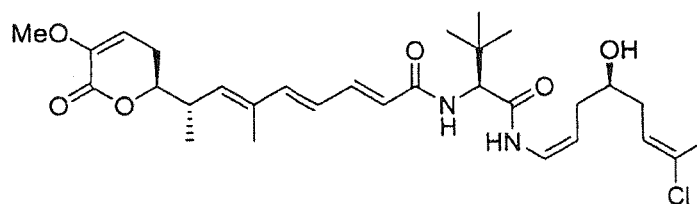
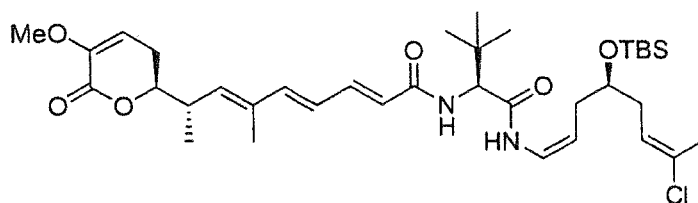
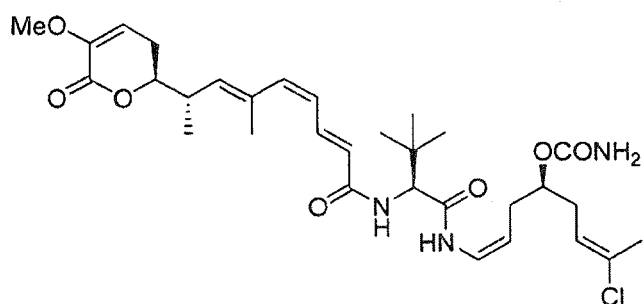
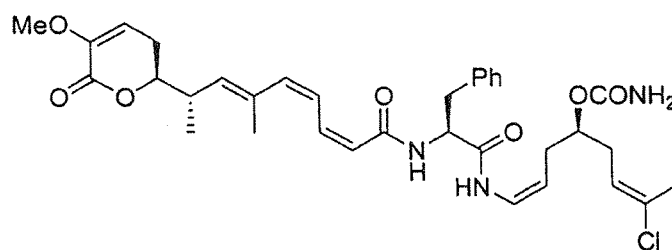
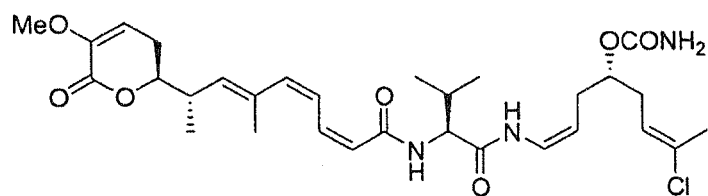
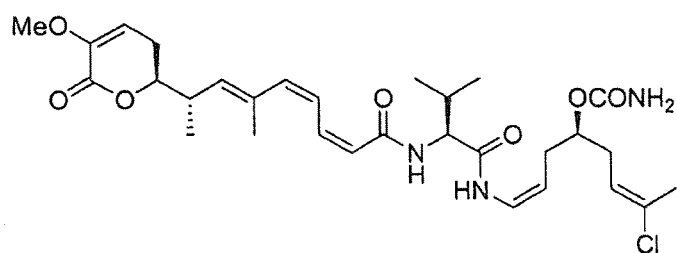
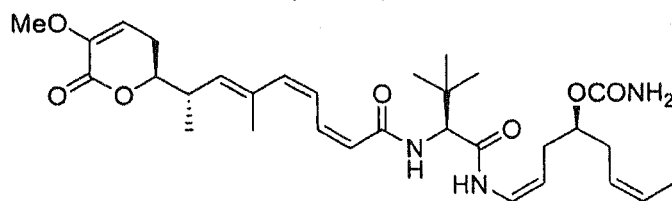
122



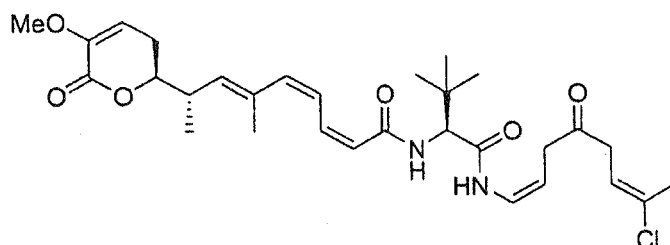
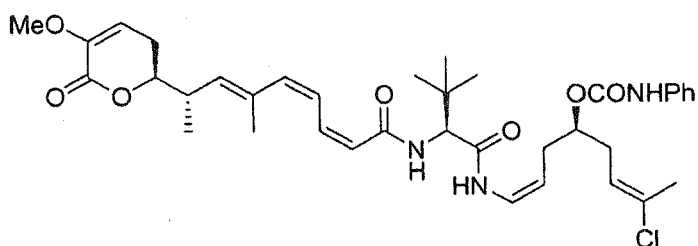
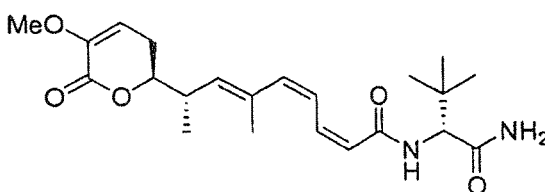
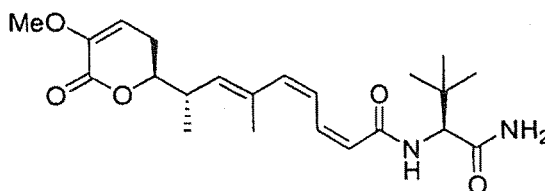
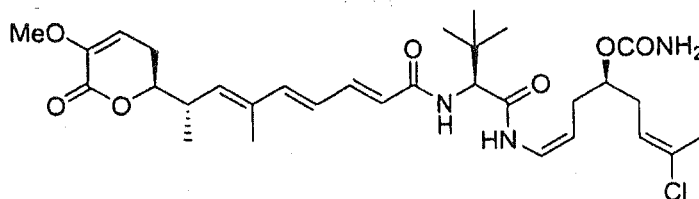
123



124



125

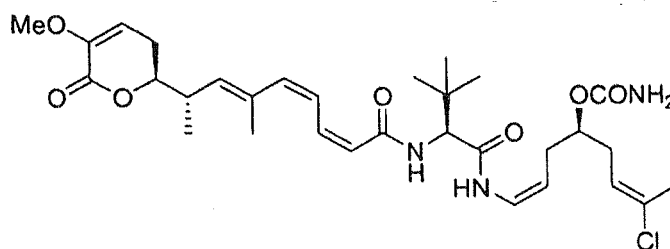


5

or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

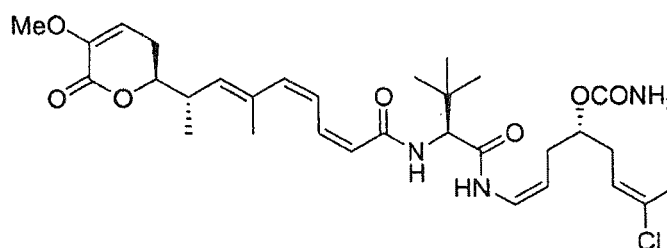
- 10 30. A compound according to claim 1 or 2, having the following formula

126



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

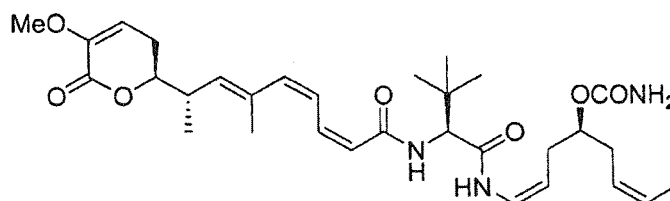
- 5 31. A compound according to claim 1 or 2, having the following formula



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

10

32. A compound according to claim 1 or 2, having the following formula

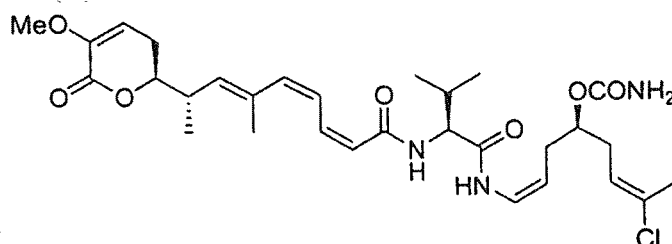


or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

15

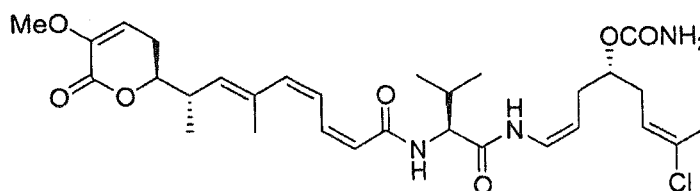
33. A compound according to claim 1 or 2, having the following formula

127



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

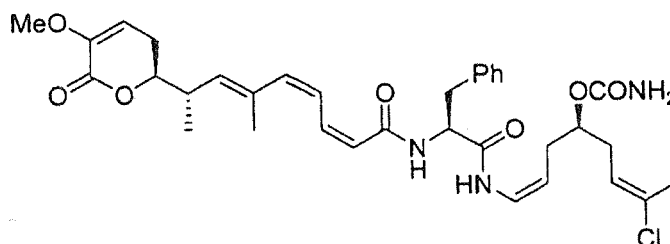
- 5 34. A compound according to claim 1 or 2, having the following formula



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

10

35. A compound according to claim 1 or 2, having the following formula

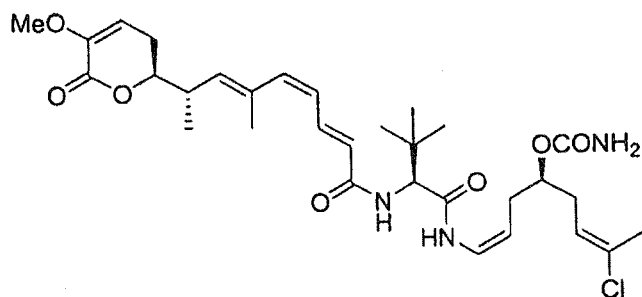


or a pharmaceutically acceptable salt, tautomer, or stereoisomer

15 thereof.

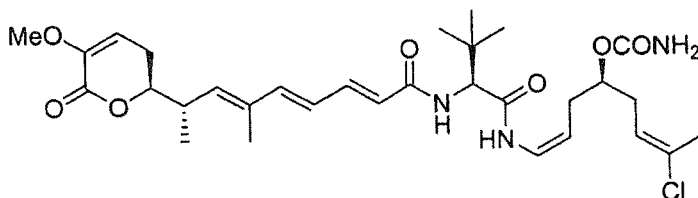
36. A compound according to claim 1 or 2, having the following formula

128



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

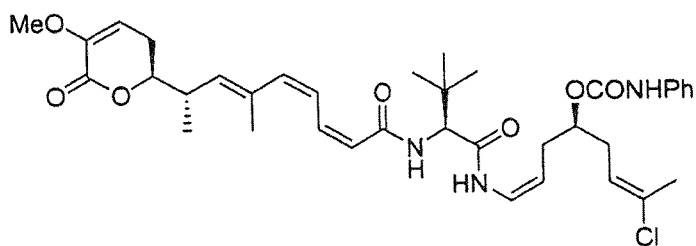
- 5 37. A compound according to claim 1 or 2, having the following formula



or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

10

38. A compound according to claim 1 or 2, having the following formula



- 15 or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

39. A pharmaceutical composition comprising a compound according to any of the preceding claims, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, and a pharmaceutically acceptable
20 diluent or carrier.

40. A compound or composition according to any of claims 1 to 39, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, for use as a medicament.

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41. A compound or composition according to any of claims 1 to 39, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, for use in the treatment of cancer.

10 42. Use of a compound or composition according to any of claims 1 to 39, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer.

15