

ANTITUMORAL COMPOUNDS

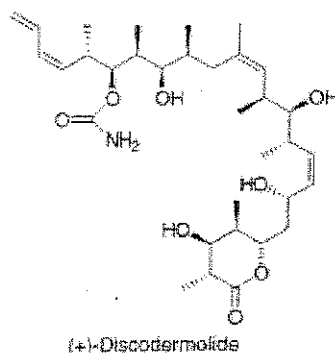
FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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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).

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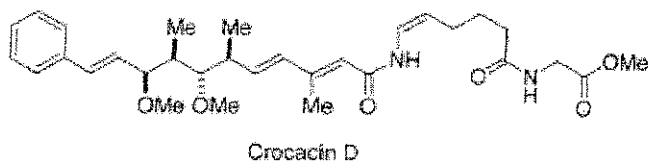
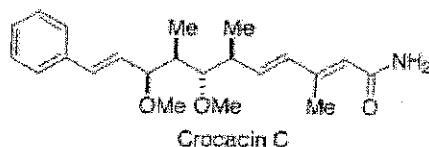
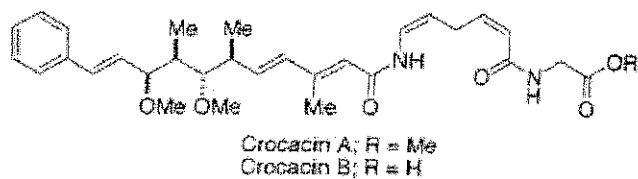
D1, Jones et al.; Journal of the Chemical Society; Volume 12; 1 January 1970; pages 1725–1737, concerns the microbial transformation of mycophenolic acid to form amidoacid analogues.

D2, WO 2005/014574 A1; Novartis AG; 17 February 2005, concerns substituted lactams and their use as anticancer agents.

D3, EP 0 111 105 A; Wellcome Foundation; 20 June 1984, concerns the use of unsaturated aromatic amides as pesticides.

D4, Gullledge et al.; Bioorganic & Medicinal Chemistry Letters; Volume 13; No. 17; 1 September 2003; pages 2907-2911 concerns microcystin analogues comprised only of Adda and a single additional amino acid that retain moderate activity as PP1/PP2A inhibitors.

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). Specifically, these compounds are crocacin A, B, C and D and are a group of electron transport inhibitors.



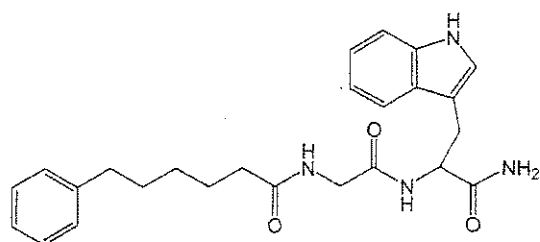
Crocacins A-D moderately inhibit the growth of a few Gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. The most active is crocacin D which showed a MIC of 1.4 ng/mL against the fungus *Saccharomyces cerevisiae* and strong toxicity (IC₅₀ of 0.06 mg/L)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

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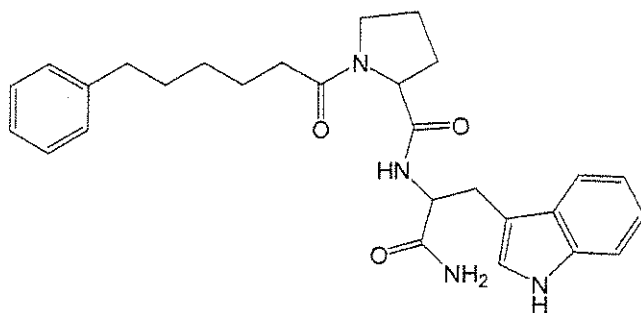
Gudasheva et al. (Russian Journal of Bioorganic Chemistry, 2007, 44(4), 413-420, and Pharmaceutical Chemistry Journal, 2006, 40(7), 367-372) reported the design of dipeptide compounds based on the structure of the endogenous tetrapeptide cholecystokinin-4 (CCK-4). In this regard, it is disclosed that L-thryptophan derivatives exhibited anxiolytic properties and the D-thryptophan derivatives, anxiogenic properties. Two of the dipeptide compounds disclosed by Gudasheva et al. are the following:

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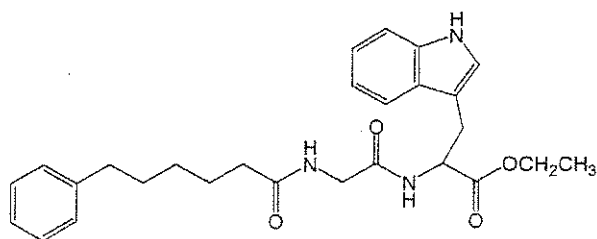


Compound R

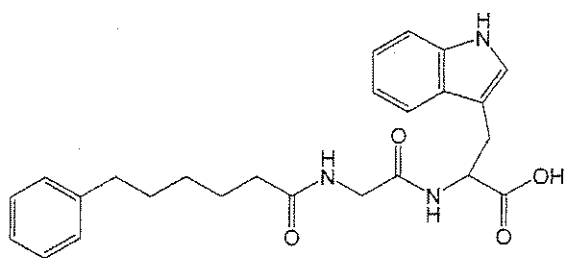


Compound U

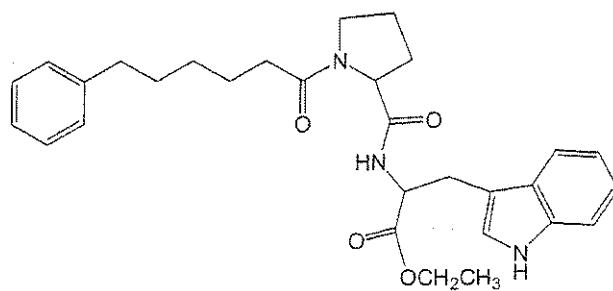
5 and the following compounds were disclosed as intermediates in the synthesis of compounds R and U:



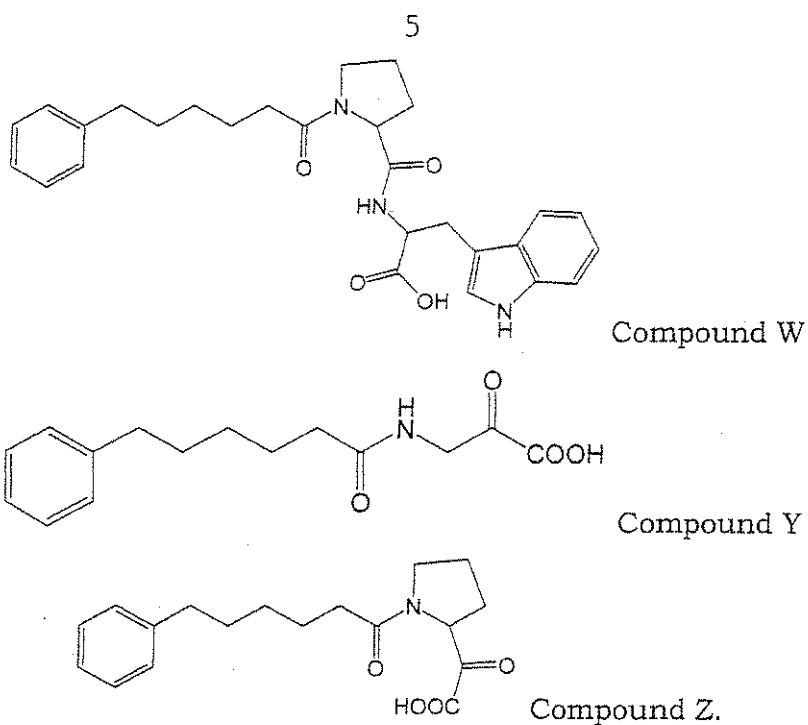
Compound S



Compound T



Compound V

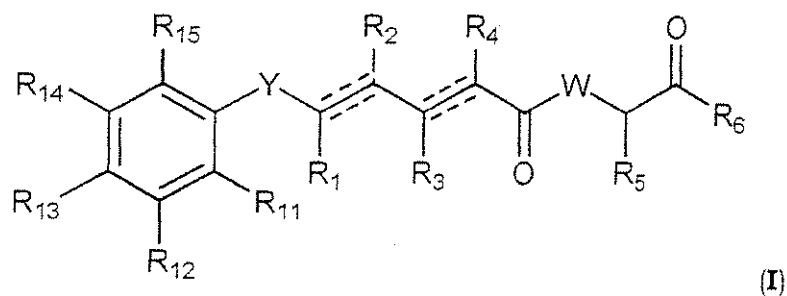


5. Cancer is a leading cause of death in animals and humans. Huge efforts have been and are still being undertaken in order to obtain an antitumor agent active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that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

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SUMMARY OF THE INVENTION

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



wherein Y is selected from $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$,
5 $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$, $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, and $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$;

each R_{ay} , R_{by} , and R_{cy} is independently selected from hydrogen,
10 substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted
 $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

each R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from hydrogen,
substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted
15 $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

R_6 is selected from NR_8R_9 , and OR_{10} ;

W is selected from O and NR_7 ;

15 R_7 is selected from hydrogen, COR_a , COOR_a , substituted or
unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$
alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, or R_7 and R_5
together with the corresponding N atom and C atom to which they are
20 attached may form a substituted or unsubstituted heterocyclic group;

R_8 is selected from hydrogen, COR_a , COOR_a , substituted or
unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$
alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl;

25 R_{10} is selected from hydrogen, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$
alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

each dotted line represents an optional additional bond with the proviso
30 that one or more additional bonds are present, but when a triple bond
exists between the C atoms to which R_1 and R_2 are attached, R_1 and R_2

are absent, and when a triple bond exists between the C atoms to which R₃ and R₄ are attached, R₃ and R₄ are absent;

R₉ is selected from hydrogen, COR_a, COOR_a, substituted or
 5 unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

each R₁₁, R₁₂, R₁₃, R₁₄, and R₁₅ are independently selected from
 hydrogen, halogen, OR_a, COR_a, COOR_a, OCOR_a, OCOOR_a, OCONR_aR_b,
 10 CONR_aR_b, OS(O)R_a, OSO₂R_a, OP(O)(R_a)OR_b, OSiR_aR_bR_c, NR_aR_b,
 NR_aCOR_b, NR_aCONR_aR_b, NR_aS(O)R_b, NR_aSO₂R_b, NR_aC(=NR_a)NR_aR_b, SR_a,
 S(O)R_a, SO₂R_a, S(O)NR_aR_b, SO₂NR_aR_b, S(O)OR_a, SO₂OR_a, substituted or
 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂
 alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; and

15 each R_a, R_b, and R_c 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
 20 group.

In another aspect, the present invention is also directed to a
 compound of formula I, or a pharmaceutically acceptable salt,
 tautomer, or stereoisomer thereof, for use as medicament.

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In another aspect, the present invention is also directed to a
 compound of formula I, or a pharmaceutically acceptable salt,
 tautomer, or stereoisomer thereof, for use as medicament for treating
 cancer.

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In a further aspect, the present invention is also directed to the use of compounds of formula I, or pharmaceutically acceptable salts, tautomers, or stereoisomers thereof, in the treatment of cancer, or in the preparation of a medicament for the treatment of cancer.

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Other aspects of the invention are methods of treatment, and compounds for use in these methods. Therefore, the 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 of formula I, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

In a yet further aspect, the present invention is also directed to a compound of formula I, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, for use as anticancer agent.

In another aspect, the present invention is directed to pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, together with a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

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

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

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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 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.

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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 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.

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We define alkenynyl group as an alkyl group containing one or more double bonds and one or more triple bonds, and preferred alkenynyl groups are those having from 4 to about 12 carbon atoms. One more preferred class of alkenynyl groups has from 6 to about 10 carbon atoms.

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Suitable aryl groups in the compounds of the present invention 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

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or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted phenanthryl and substituted or unsubstituted anthryl.

5 Suitable heterocyclic groups include heteroaromatic and 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, most preferably 5, 6 or 7 ring atoms. Suitable heteroaromatic groups in the
10 compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms 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,
15 imidazolyl, indolyl, isoindolyl, indazolyl, indoliziny, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic
20 groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidyl, oxetanyl, thietanyl, homopiperidyl,
25 oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-
30 azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinoliziny.

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', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR',
5 OCONR'R', CONHR', CONR'R', protected OH, 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, wherein each of the R' groups is independently selected from the
10 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 unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves
15 substituted, the substituents may be chosen from the foregoing list.

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

20 Suitable protecting groups for OH are well known for the skilled person in the art. A general review of protecting groups in organic chemistry is provided by Wuts, PGM and Greene TW in Protecting Groups in Organic Synthesis, 4th Ed. Wiley-Interscience, and by Kocienski PJ in Protecting Groups, 3rd Ed. Georg Thieme Verlag. These
25 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 ethers the protecting group for the OH can be selected from methyl,
30 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,
 guaiacolmethyl, [(*p*-phenylphenyl)oxy]methyl, *t*-butoxymethyl, 4-
 pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-
 cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl,
 5 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *o*-bis(2-acetoxyethoxy)methyl,
 tetrahydropyranyl, fluoros tetrahydropyranyl, 3-bromotetrahydropyranyl,
 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-
 10 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 -
 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-
 15 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-
 phenylisopropyl, 1-(2-cyanoethoxy)ethyl, 2-trimethylsilylethyl, 2-
 (benzylthio)ethyl, 2-phenylselenylethyl, *t*-butyl, cyclohexyl, 1-methyl-1'-
 cyclopropylmethyl, allyl, prenyl, cinnamyl, 2-phenallyl, propargyl, *p*-
 20 chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-
 tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-
 dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl,
 pentadienylnitrobenzyl, pentadienylnitropiperonyl, halobenzyl, 2,6-
 dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluoros
 25 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-
 30 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 -naphthylidiphenylmethyl, *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*-(imidazolylethyl)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, benzisothiazolyl *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]methylbenzoate, 2-[(4-methoxytritylthio)oxy]methylbenzoate, 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 *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, 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-(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 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-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 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 groups having said function may be known by the skilled person in the art, and they are to be understood to be also encompassed by the present invention.

The term "pharmaceutically acceptable salts, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, 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 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. 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 the acid addition salts include mineral acid addition salts such as, for
5 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, methanesulfonate and *p*-toluenesulfonate. Examples of the alkali addition salts include inorganic salts such as, for
10 example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylethanolamine, triethanolamine and basic aminoacids salts.

15 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.

20 Any compound that is a prodrug of a compound of formula I is not within the scope and spirit of the invention. The term "prodrug" as used in this application is defined here as meaning a chemical compound having undergone a chemical derivation such as substitution or addition of a further chemical group to change (for pharmaceutical use) any of its
25 physico-chemical properties, such as solubility or bioavailability, e.g. ester and ether derivatives of an active compound that yield the active compound per se after administration to a subject. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-
30 Larsen et al., Textbook of Drugdesign and Discovery, Taylor & Francis (April 2002).

Any compound referred to herein is intended to represent such 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 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 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 stereoisomerism of the other double bonds of the molecule. The single isomers and mixtures of isomers fall within the scope of the present invention.

20

Furthermore, compounds referred to herein may exist as 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 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

30

mixtures thereof, are considered within the scope of the present invention.

To provide a more concise description, some of the quantitative
5 expressions given herein are not qualified with the term "about". It is 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 skilled in the
10 art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

In compounds of general formula **I**, particularly preferred Y is -
CHR_{ay}-, -CR_{ay}=CR_{by}-, and -CHR_{ay}-CR_{by}=CR_{cy}-, wherein R_{ay}, R_{by}, and R_{cy}
15 are as defined before.

Particularly preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₆ alkyl, and
20 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
25 sec-butyl. Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂
30 alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, 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 and methyl are the most preferred R_{ay}, R_{by}, and R_{cy} groups. Specifically, when Y is -CHR_{ay}- then particularly preferred R_{ay} is methyl, when Y is -CR_{ay}=CR_{by}- then particularly preferred R_{ay} is hydrogen and particularly preferred R_{by} is methyl, and when Y is -CHR_{ay}-CR_{by}=CR_{cy}- then particularly preferred R_{ay} is hydrogen or methyl, particular preferred R_{by} is hydrogen, and particularly preferred R_{cy} is methyl.

Particularly preferred R₁, R₂, R₃, R₄, and R₅ are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₁, R₂, R₃, R₄, and R₅ 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 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', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, 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, 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 R₁, R₂, R₃, R₄, and R₅ groups. Specifically, particularly preferred R₁, R₂, R₃, and R₄ are hydrogen. And particularly preferred R₅ are methyl, isopropyl, and tert-butyl.

15

Particularly preferred W is NR₇ wherein R₇ is as defined before. Particularly preferred R₇ is hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₇ is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen is the most preferred.

20

In another embodiment, it is particularly preferred that R₇ and R₅ together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted heterocyclic group. In this regard, preferred heterocyclic group is a heteroalicyclic group containing one, two or three heteroatoms selected from N, O or S atoms, most preferably one N atom, and having from 5 to about 10 ring atoms, most preferably 5, 6 or 7 ring atoms. A pyrrolidine group is the most preferred.

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Particularly preferred R_6 is NR_8R_9 and OR_{10} wherein R_8 , R_9 , and R_{10} are as defined before, and even more preferred R_6 is NR_8R_9 .

Particularly preferred R_8 is hydrogen.

5

Particularly preferred R_9 is hydrogen, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, and substituted or unsubstituted C_4 - C_{12} alkenynyl. The preferred substituted alkenyl, substituted alkynyl and substituted
10 alkenynyl may present not only one but two or more substituents. 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-
15 dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-dienyl are the most preferred alkenyl groups. On the other hand, more preferred alkynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-7-ynyl, oct-6-ynyl, oct-5-ynyl, oct-4-ynyl, oct-3-ynyl, oct-2-ynyl, oct-1-ynyl, non-8-ynyl,
20 non-7-ynyl, non-6-ynyl, non-5-ynyl, non-4-ynyl, non-3-ynyl, non-2-ynyl, non-1-ynyl, hept-6-ynyl, hept-5-ynyl, hept-4-ynyl, hept-3-ynyl, hept-2-ynyl, and hept-1-ynyl are the most preferred alkynyl groups. On the other hand, more preferred alkenynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon
25 atoms. Oct-1-en-7-ynyl, oct-1-en-6-ynyl, oct-1-en-5-ynyl, oct-1-en-4-ynyl, oct-1-en-3-ynyl, non-1-en-8-ynyl, non-1-en-7-ynyl, non-1-en-6-ynyl, non-1-en-5-ynyl, non-1-en-4-ynyl, non-1-en-3-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, and hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said
30 alkenyl, alkynyl and alkenynyl groups are OR' , $=O$, SR' , SOR' , SO_2R' , NO_2 , NHR' , $NR'R'$, $=N-R'$, $NHCOR'$, $N(COR')_2$, $NHSO_2R'$, $NR'C(=NR)NR'R'$, CN , halogen, COR' , $COOR'$, $OCOR'$, $OCONHR'$, $OCONR'R'$, $CONHR'$,

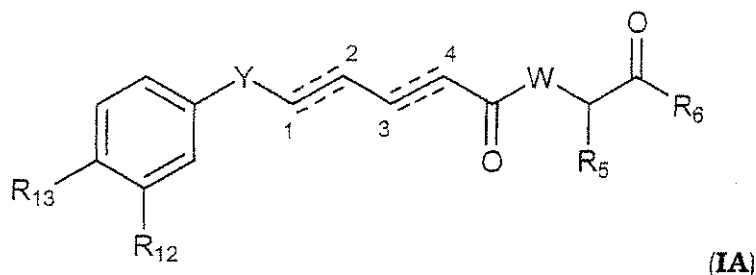
CONR'R', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from 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. More preferred substituents for the above mentioned alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCOR', OCONHR', OCONR'R', CONHR', CONR'R', 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 alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCONHR', OCONR'R', CONHR', CONR'R', 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 fluorosilyl, 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 alkenyl, alkynyl and alkenynyl groups.

Particularly preferred R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are hydrogen, OR_a , $OCOR_a$, and $OSiR_aR_bR_c$, wherein R_a , R_b , and R_c are as defined above. Specifically, particular preferred R_{11} , R_{14} , and R_{15} are hydrogen, particular preferred R_{12} is hydrogen and OR_a , and particular preferred R_{13} is hydrogen, OR_a , and $OSiR_aR_bR_c$. Particular preferred R_a , R_b , and R_c are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Even more preferred R_a , R_b , and R_c 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, being hydrogen, methyl, and tert-butyl the most preferred.

Particularly preferred is the presence of one additional bond between the C atoms to which R_1 and R_2 are attached, and the presence of one or two additional bonds between the C atoms to which R_3 and R_4 are attached. 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, preferred compounds of general formula **I** are those also having general formula **IA** or pharmaceutically acceptable salts, tautomers, or stereoisomers thereof



wherein Y is selected from $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$, $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, and $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$;

each R_{ay} , R_{by} , and R_{cy} is independently selected from hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

R_5 is selected from hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

R_6 is selected from NR_8R_9 , and OR_{10} ;

W is selected from O and NR_7 ;

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, or R_7 and R_5 together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

each R_8 and R_9 are independently selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or

unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

R₁₀ is selected from hydrogen, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each R₁₂ and R₁₃ are independently selected from hydrogen, halogen, OR_a, COR_a, COOR_a, OCOR_a, OCOOR_a, OCONR_aR_b, CONR_aR_b, OS(O)R_a, OSO₂R_a, OP(O)(R_a)OR_b, OSiR_aR_bR_c, NR_aR_b, NR_aCOR_b, NR_aCONR_aR_b, NR_aS(O)R_b, NR_aSO₂R_b, NR_aC(=NR_a)NR_aR_b, SR_a, S(O)R_a, SO₂R_a, S(O)NR_aR_b, SO₂NR_aR_b, S(O)OR_a, SO₂OR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each R_a, R_b, and R_c 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; and

each dotted line represents an optional additional bond with the proviso that one or more additional bonds are present.

In compounds of general formula **IA**, particularly preferred Y is -CHR_{ay}-, -CR_{ay}=CR_{by}-, and -CHR_{ay}-CR_{by}=CR_{cy}-, R_{ay}, R_{by}, and R_{cy} are as defined before.

Particularly preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R_{ay}, R_{by}, and R_{cy} 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 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',
 5 SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or
 10 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
 15 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*-
 20 hydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen and methyl are the most preferred R_{ay}, R_{by}, and R_{cy} groups. Specifically, when Y is -CHR_{ay}- then particularly preferred R_{ay} is methyl, when Y is -CR_{ay}=CR_{by}- then particularly preferred R_{ay} is hydrogen and particularly preferred R_{by} is
 25 methyl, and when Y is -CHR_{ay}-CR_{by}=CR_{cy}- then particularly preferred R_{ay} is hydrogen or methyl, particular preferred R_{by} is hydrogen, and particularly preferred R_{cy} is methyl.

Particularly preferred R₅ is hydrogen and substituted or
 30 unsubstituted C₁-C₁₂ alkyl. More preferred R₅ is 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 unsubstituted isopropyl and substituted or unsubstituted butyl, including substituted or unsubstituted tert-butyl, substituted or unsubstituted isobutyl and substituted or unsubstituted sec-butyl.

5 Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, 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, 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 R₅ groups, and even most preferred methyl, isopropyl, and tert-butyl.

25

Particularly preferred W is NR₇ wherein R₇ is as defined before. Particularly preferred R₇ is hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₇ is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl.

30 Hydrogen is the most preferred.

In another embodiment, it is particularly preferred that R₇ and R₅ together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted heterocyclic group. In this regard, preferred heterocyclic group is a heteroalicyclic group containing one, two or three heteroatoms selected from N, O or S atoms, most preferably one N atom, and having from 5 to about 10 ring atoms, most preferably 5, 6 or 7 ring atoms. A pyrrolidine group is the most preferred.

10 Particularly preferred R₆ is NR₈R₉ and OR₁₀ wherein R₈, R₉, and R₁₀ are as defined before, and even more preferred R₆ is NR₈R₉.

Particularly preferred R₈ is hydrogen.

15 Particularly preferred R₉ is hydrogen, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl. The preferred substituted alkenyl, substituted alkynyl, and substituted alkenynyl may present not only one but two or more substituents. 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. On the other hand, more preferred alkynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-7-ynyl, oct-6-ynyl, oct-5-ynyl, oct-4-ynyl, oct-3-ynyl, oct-2-ynyl, oct-1-ynyl, non-8-ynyl, non-7-ynyl, non-6-ynyl, non-5-ynyl, non-4-ynyl, non-3-ynyl, non-2-ynyl, non-1-ynyl, hept-6-ynyl, hept-5-ynyl, hept-4-ynyl, hept-3-ynyl, hept-2-ynyl, and hept-1-ynyl are the most preferred alkynyl groups. On the other hand, more preferred alkenynyl groups are those having from

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6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-1-en-7-ynyl, oct-1-en-6-ynyl, oct-1-en-5-ynyl, oct-1-en-4-ynyl, oct-1-en-3-ynyl, non-1-en-8-ynyl, non-1-en-7-ynyl, non-1-en-6-ynyl, non-1-en-5-ynyl, non-1-en-4-ynyl, non-1-en-3-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, and hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said alkenyl, alkynyl and alkenynyl groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, 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, 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. More preferred substituents for the above mentioned alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCOR', OCONHR', OCONR'R', CONHR', CONR'R', 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 alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCONHR', OCONR'R', CONHR', CONR'R', 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

10 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-

15 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 alkenyl, alkynyl and alkenynyl

20 groups.

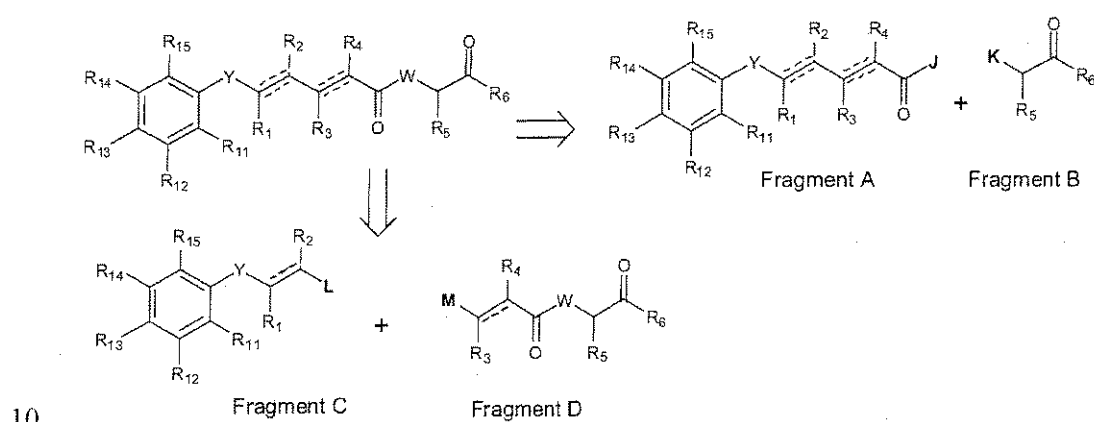
Particularly preferred R₁₂ and R₁₃ are hydrogen, OR_a, OCOR_a, and OSiR_aR_bR_c, wherein R_a, R_b, and R_c are as defined above. Even more preferred R₁₂ is hydrogen and OR_a, and more preferred R₁₃ is hydrogen,

25 OR_a, and OSiR_aR_bR_c. Particular preferred R_a, R_b, and R_c are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Even more preferred R_a, R_b, and R_c are hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl, being hydrogen, methyl, and tert-butyl

30 the most preferred.

Particularly preferred is the presence of one additional bond between C₁ and C₂, and/or the presence of one or two additional bonds between C₃ and C₄. In addition, the stereochemistry of each double bond may exist as (E) or (Z). The single isomers and mixtures of the
5 isomers fall within the scope of the present invention.

The compounds of the invention can be obtained synthetically by joining different fragments as indicated in the Scheme A.



Scheme A

where R₁, R₂, R₃, R₄, R₅, R₆, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, Y and W are the
15 desired groups or an appropriate protecting group as needed, and J, K, L, and M are appropriate reacting or leaving groups.

The compounds of the invention can be obtained by either of the following strategies:

20

1) Fragments A and B can be coupled following standard procedures in organic chemistry (*i.e.* Bodanszky M and Bodanszky A, *The Practice of Peptide Synthesis*, Springer-Verlag, 1993).

2) Fragments C and D can be coupled following standard procedures of organometallic chemistry (*i.e.* R.B. Crabtree, "The Organometallic Chemistry of the Transition Metals", 2nd Ed., Wiley, Nueva York, 1994).

5

Fragments A, B, C and D can be independently prepared following standard procedures in organic synthesis.

Deprotection of the protecting groups 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).

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 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 the obtained compounds by usual procedures in synthetic organic chemistry which are known by a person skilled in the art.

25

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 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

30

stereoisomers once the compound has been synthesized by standard resolution techniques known to the skilled reader.

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

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

The term "carrier" refers to a diluent, adjuvant, excipient or vehicle with which the active ingredient is administered. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 1995.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions 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, 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 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.

5 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 the host, drug combinations, reaction sensitivities and severity of the
10 disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

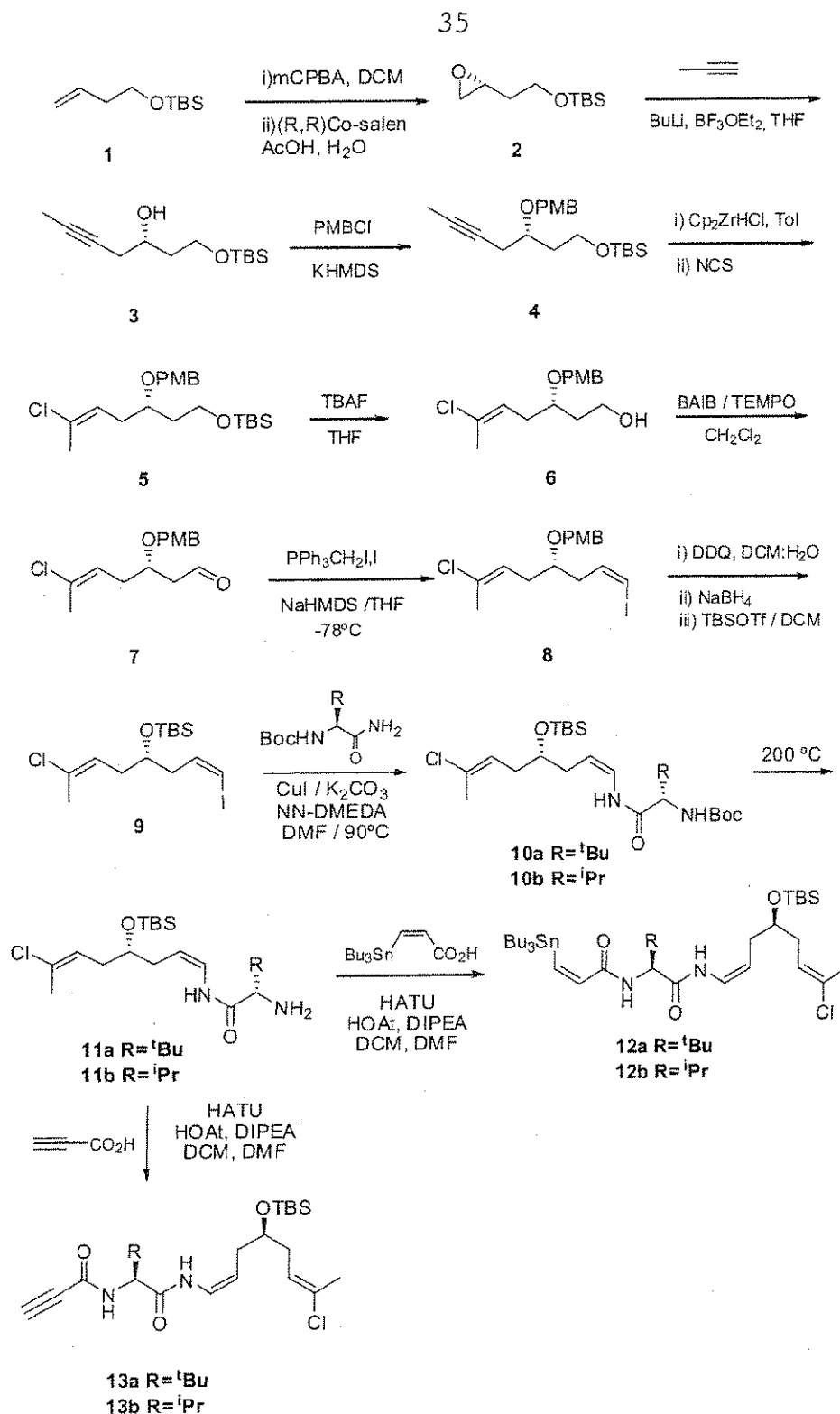
 The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs
15 may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

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

EXAMPLE 1: SYNTHESIS OF FRAGMENTS 12 AND 13

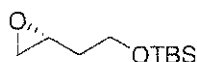
 Scheme 1 provides an example of the synthesis of fragments 12 and 13.
25



Scheme 1

Synthesis of intermediate 2

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To a solution of intermediate **1** (72.3 g, 0.39 mol) in anhydrous DCM (918 mL) at room temperature 3-Chloroperbenzoic acid (*m*-CPBA) (100 g, 0.58 mol) was added portionwise, and the mixture was stirred at room temperature for 18 h. The white precipitate was quenched with saturated aqueous 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 anhydrous Na₂SO₄ and concentrated in vacuo. The resulting oil was purified on silica gel (Hexane-EtOAc; 15:1) to provide epoxide as a colourless oil (64.5 g, 82%). To a solution of racemic epoxide (30 g, 0.15 mol) in anhydrous THF (7.5 mL) (*R,R*)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) [(*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 stirred for 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 eluent, provided chiral epoxide **(+)-2** (13.6 g, yield: 46%) as a colourless oil.

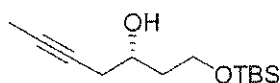
$[\alpha]_D = +14.1$ (c 1, CHCl₃).

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

Synthesis of intermediate 3

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Propyne (10 mL, 0.176 mol) was condensed at -78 °C and dissolved in anhydrous THF (165 mL). n-Butyllithium (75.1 mL, 0.188 mol) was added dropwise under N₂ over 30 min, and the resultant white
5 suspension was stirred for additional 30 min at -78 °C. A solution of (+) (R)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxirane **2** (23.7 g, 0.117 mol) in anhydrous THF (125 mL) was then added dropwise followed by addition of BF₃·OEt₂ (22.1 mL, 0.176 mol). The mixture was stirred for 1 h at -78 °C and for an additional hour at 0 °C. The reaction mixture was
10 quenched with saturated aqueous solution of NH₄Cl (150 mL) and extracted with Et₂O (3 x 150 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (hexane/EtOAc 10:1 to 1:1) provided alcohol **3** (22.7 g, yield: 80%) as a colourless oil.

15 $[\alpha]_D = +5.6$ (c 0.1, CHCl₃).

¹H-NMR (500 MHz, CDCl₃) 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).

¹³C-NMR (125 MHz, CDCl₃) δ : 77.8, 75.8, 70.7, 62.4, 37.6, 27.6, 26.1,
20 18.3, 3.7, -5.3, -5.4.

MS (ES) m/z 243.2 [M+H]⁺, 265.2 [M+Na]⁺.

Synthesis of intermediate 4

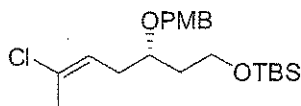


Over a solution of **3** (41.8 g, 0.173 mol) and 18-crown-6 ether (50.27 g, 0.190 mol) in anhydrous THF (1190 mL) at -78°C under N₂ atmosphere, a 0.5N solution of KHMDS in toluene (380 mL, 0.190 mol) was added
30 via addition funnel over a period of 30 min. The mixture was stirred at this temperature for 45 min, followed by addition of a solution of 4-methoxybenzyl chloride (PMBCl) (23.89 g, 0.176 mol) in anhydrous THF

(100 mL). After 2 h at -78 °C, the mixture was quenched with saturated aqueous solution of NH₄Cl (600 mL). The organic layer was separated and the aqueous phase was extracted exhaustively with EtOAc (3 x 500 mL). The combined organic layers were washed with saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄, filtered, and concentrated to afford **4** as yellow oil, which was used in the next steps without further purification (61.3 g, yield: 99%).

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 5



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To a solution of **4** (61.3 g, 0.169 mol) in anhydrous toluene (2.1 L), under N₂ atmosphere and at 0 °C Schwartz's reagent (Bis(cyclopentadienyl)zirconium(IV) chloride hydride, Cp₂ZrHCl) (130.3 g, 0.507 mol) 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 2.5 h. During this time the reaction solution turned of orange colour. The reaction was cooled to 0°C and N-chlorosuccinimide (58.45 g, 0.440 mol) 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 **5** as yellow oil which was used without further purification (15.1 g, yield: 86%).

[α]_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,

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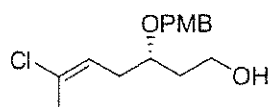
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3H), 3.70 (m, 2H), 3.62 (m, 1H), 2.27 (t, 2H, $J = 6.9$ Hz), 2.03 (s, 3H), 1.70 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz) 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.

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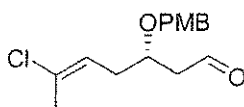
Synthesis of intermediate 6



- 10 To a solution of **5** (23 g, 0.058 mol) in anhydrous THF (288 ml) under N_2 and at 0 °C a solution of Tetrabutylammonium fluoride (TBAF) (115.3 mL, 0.115 mol) was added dropwise over a period of 20 min (the solution turned red). The reaction mixture was stirred at room temperature for 2 h, and then was quenched with saturated aqueous
- 15 solution of NH_4Cl (200 mL). The layers were separated and the aqueous phase was extracted exhaustively with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. Flash chromatography (hexane /EtOAc 4:1 to 1:1) provided **6** as a colourless oil (11.9 g, yield: 73%).
- 20 ^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).

Synthesis of intermediate 7

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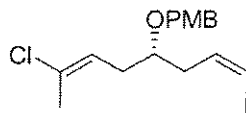
(Diacetoxyiodo)benzene (BAIB) (11.5 g, 35.7 mmol) was added to a solution of alcohol **6** (9.2 g, 32.4 mmol) and 2,2,6,6-

Tetramethylpiperidine 1-oxyl (TEMPO) (515 mg, 3.3 mmol) in anhydrous dichloromethane (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 NH_4Cl and extracted with DCM (3 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 4:1 to 1:1) to afford **7** as colourless oil (6.3 g, yield: 69%).

^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 NMR (CDCl_3 , 75 MHz) δ : 201, 159.6, 132.1, 130.1, 129.7, 122.8, 114.1, 73.3, 71.5, 55.5, 48.3, 33.5, 21.3.

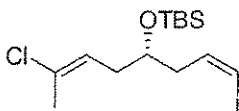
15 Synthesis of intermediate 8



To a suspension of iodomethyltriphenylphosphonium iodide (16.6 g, 31 mmol) in anhydrous THF (126 mL), at room temperature, a 1M solution of NaHMDS in anhydrous THF (31.27 mL, 31.27 mol) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78°C and a solution of **7** (6.3 g, 22 mmol) in anhydrous 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 with hexane and filtered through a plug of Celite®. The plug was rinsed with hexane, 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 **8** as a 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, $J = 8.7$ 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).

5 Synthesis of intermediate 9

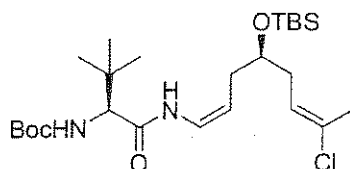


2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (3.6 g, 16 mmol) was added to a solution of **8** (5 g, 12 mmol) in DCM- H_2O (20:1, 98 mL) under N_2 atmosphere at room temperature. After 1.5 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et_2O (200 mL) and washing with 1M NaOH (3 x 50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated. Chromatographic separation of *p*-methoxybenzaldehyde was facilitated by reduction to *p*-methoxybenzyl alcohol. Towards this end, a solution of the obtained residue in MeOH (98 mL) with NaBH_4 (0.60 g, 16 mmol) under N_2 atmosphere was maintained at room temperature for 1 h. The reaction mixture was then quenched by pouring into Et_2O (100 mL) and washing with 1M HCl (40 mL) and brine (40 mL). The organic phase was dried over anhydrous Na_2SO_4 , 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 (38 mL) under N_2 atmosphere and at 0 °C, 2,6-lutidine (2.28 mL, 20 mmol) was added dropwise, followed by addition of *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (2.33 mL, 12 mmol). The reaction mixture was stirred for 2 h. At this point the crude 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 Na₂SO₄, filtered, and concentrated. Flash chromatography (Hexane /EtOAc 100:1 to 20:1) provided **9** as a colourless oil (3.14 g, 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 NMR (CDCl₃, 75 MHz) δ: 137.7, 130.9, 124.3, 84.6, 70.6, 42.5, 36.6, 25.9, 21.3, 18.2, -4.4.

10 Synthesis of intermediate 10a



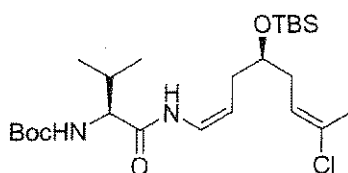
A resealable Schlenk tube was charged with copper (I) iodide (148 mg, 0.78 mmol), potassium carbonate (1.076 g, 7.78 mmol) and Boc-*tert*-LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (0.96 g, 4.15 mmol), evacuated and filled with N₂. *N,N*-Dimethylethylenediamine (DMEDA) (0.166 mL, 1.55 mmol), vinyl iodide **9** (1.04g, 2.59 mmol) and anhydrous DMF (15 mL) were added under N₂. The Schlenk tube was sealed, heated at 90 °C for 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 anhydrous 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 **10a** (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*

43

= 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), 1.40 (s, 9H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (CDCl_3 , 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.

Synthesis of intermediate 10b

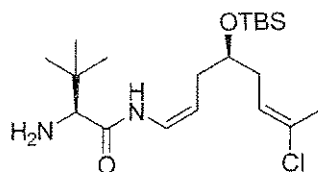


10

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., *Tetrahedron Letters* 1995, 36, 7115-7118) (230 mg, 1.06 mmol),
 15 evacuated and filled with N₂. *N,N*-Dimethylethylenediamine (45 μL , 0.426 mmol), vinyl iodide **9** (283 mg, 0.71 mmol) and anhydrous DMF (35 mL) were added under N₂. 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
 20 layer was washed with water and dried over anhydrous 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 **10b** (270 g, yield: 77%) was obtained as an oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.80 (d, 1H, J = 9.3 Hz), 6.79-6.73 (m, 1H),
 25 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).

30 Synthesis of intermediate 11a



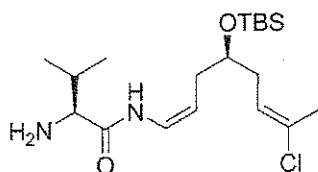
A solution of amino protected derivative **10a** (670 mg, 1.33 mmol) in
5 ethylenglycol (30 mL) was heated at 200 °C for 15 min. The reaction
mixture was then cooled at room temperature, diluted with DCM,
quenched with brine and poured into water. A few drops of 3M NaOH
were added until the solution reached pH 14 and then was extracted
thoroughly with DCM. The combined organic phases were dried over
10 anhydrous Na₂SO₄, filtrated and concentrated in vacuo to afford the
primary amine **11a** (510 mg, yield: 95 %) as a yellow oil which was used
without further purification.

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),
15 2.14 (m, 4H), 1.97 (s, 3H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 6H).

¹³C NMR (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.

Synthesis of intermediate 11b

20

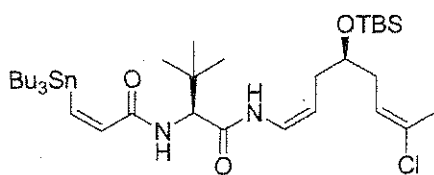


A solution of amino protected derivative **10b** (255 mg, 0.52 mmol) in
ethylenglycol (15 mL) was heated at 200 °C for 15 min. The reaction
25 mixture was then cooled at room temperature, diluted with DCM,
quenched with brine and poured into water. A few drops of 3M NaOH
were added until the solution reached pH 14 and then was extracted

thoroughly with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 , filtrated and concentrated in vacuo to afford the primary amine **11b** (170 mg, yield: 85%) as a yellow oil which was used without further purification.

- 5 ^1H NMR (CDCl_3 , 300 MHz) δ : 9.27 (d, 1H, J = 10.2 Hz), 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).
- 10 ^{13}C NMR (CDCl_3 , 75 MHz) δ : 172.1, 131.1, 124.1, 122.5, 107.4, 71.5, 60.2, 36.2, 33.7, 30.8, 26.0, 21.3, 20.0, 18.3, 16.1, -4.3, -4.4.

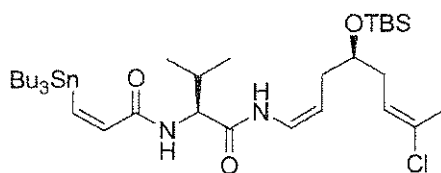
Synthesis of intermediate 12a



- To a solution of amine **11a** (918 mg, 2.27 mmol) in anhydrous DCM/DMF (10:1, 39.6 mL), a solution of (Z)-3-tributylstannylpropenoic acid (1028 mg, 2.84 mmol) in anhydrous DCM was added, under N_2 atmosphere, and then was cooled at 0 °C. Diisopropylethylamine (DIPEA) (0.6 mL, 3.4 mmol), 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 saturated aqueous solution of NH_4Cl , poured into water and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **12a** (1.11 g; yield: 66%) as an oil.
- 20
- 25
- 30

¹H NMR (CDCl₃, 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),
5 1.25 (m, 8H), 1.0 (s, 9H), 0.88 (s, 9H), 0.84 (m, 13H), 0.06 (s, 6H).

Synthesis of intermediate 12b

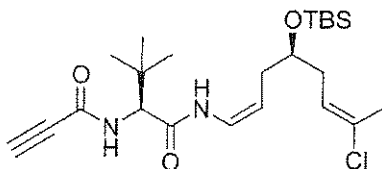


10

To a solution of amine **11b** (170 mg, 0.437 mmol) in anhydrous DCM/DMF (10:1, 7.7 mL), a solution of (Z)-3-tributylstannylpropenoic acid (197.2 mg, 0.546 mmol) in anhydrous DCM was added, under N₂ atmosphere, and then was cooled at 0 °C. DIPEA (0.11 mL, 0.655
15 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
20 anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **12b** (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
25 (m, 8H), 0.88 (s, 9H), 0.84 (m, 19H), 0.06 (s, 6H).

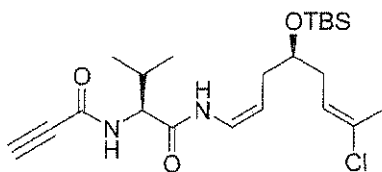
¹³C NMR (CDCl₃, 75 MHz) δ: 169.2, 166.8, 153.8, 136.2, 131.1, 123.9, 122.6, 108.7, 71.6, 59.2, 36.5, 33.7, 31.4, 29.5, 27.6, 26.1, 21.3, 19.5,
30 18.5, 14.0, 11.8, -4.3, -4.4.

Synthesis of intermediate 13a

To a solution of **11a** (120 mg, 0.30 mmol) and propiolic acid (23 μ L, 0.37 mmol) in anhydrous DCM/DMF 10:1 (4.2 mL) at 0 °C, HATU (113 mg, 0.30 mmol), HOAt (40 mg, 0.30 mmol) and DIPEA (0.78 μ L, 0.44 mmol) were added. The reaction was stirred at 0 °C for 30 min and 2 hours at room temperature. Then, the crude mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 . The combined filtrates were washed with H_2O . After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes mixture) to afford pure compound **13a** (50 mg, yield: 40 %).

^1H NMR (CDCl_3 , 300 MHz) δ : 8.20 (d, 1H, J = 10.2 Hz), 6.83 (d, 1H, J = 9.6 Hz), 6.72 (t, 1H, J = 9.3 Hz), 5.55 (t, 1H, J = 6.9 Hz), 4.88 (q, 1H, J = 8.7 Hz), 4.58 (d, 1H, J = 9.6 Hz), 3.75 (m, 1H), 2.90 (s, 1H), 2.17 (m, 4H), 2.00 (s, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 167.5, 152.1, 131.0, 124.1, 122.3, 109.4, 77.1, 74.8, 71.7, 60.9, 36.5, 35.7, 33.8, 26.7, 26.1, 21.2, 18.3, -4.3, -4.4.

Synthesis of intermediate 13b

To a solution of **11b** (200 mg, 0.51 mmol) and propiolic acid (39 μ L, 0.64 mmol) in anhydrous DCM/DMF 10:1 (8 mL) at 0 °C, HATU (194 mg, 0.51 mmol), HOAt (69 mg, 0.51 mmol) and DIPEA (133 μ L, 0.76

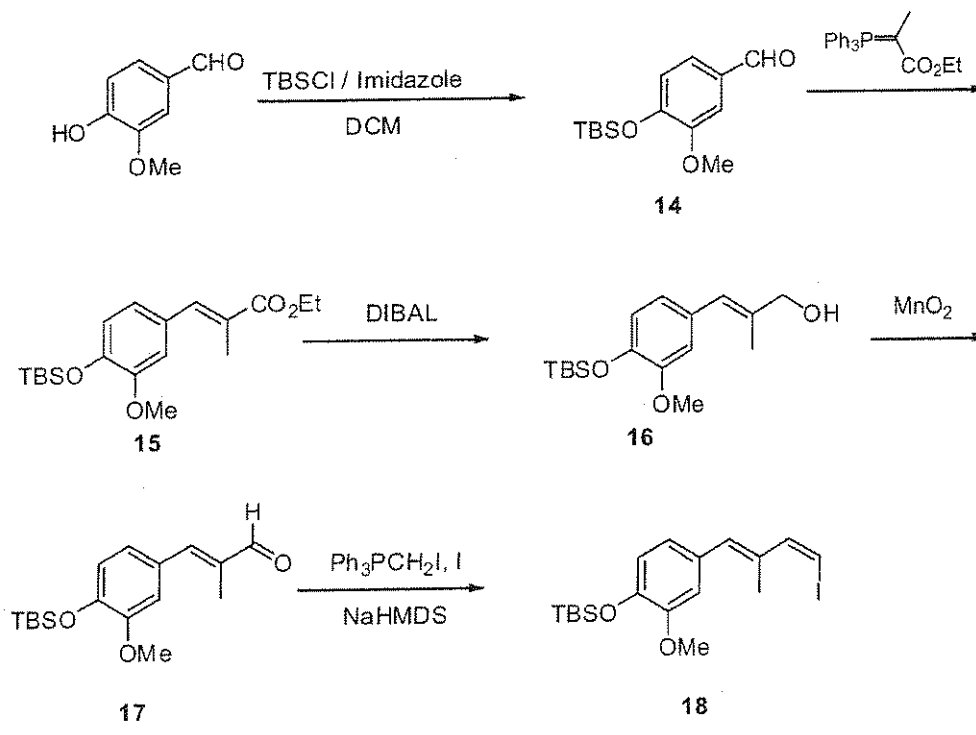
mmol) were added. The reaction was stirred at 0 °C for 30 min and 2 hours at room temperature. Then, the crude mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 . The combined filtrates were washed with H_2O . After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes mixture) to afford pure compound **13b** (150 mg, yield: 67%).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.02 (d, 1H, $J = 11.4$ Hz), 6.75 (dd, 1H, $J = 10.8, 9.0$ Hz), 6.53 (d, 1H, $J = 10.2$ Hz), 5.58 (dd, 1H, $J = 9.0, 7.8$ Hz), 4.87 (q, 1H, $J = 7.8$ Hz), 4.33 (dd, 1H, $J = 8.7, 6.3$ Hz), 3.84-3.76 (m, 1H), 2.83 (s, 1H), 2.23-2.11 (m, 5H), 2.05-2.03 (m, 3H), 0.99 (d, 6H, $J = 6.9$ Hz), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

15

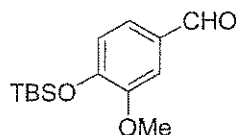
EXAMPLE 2: SYNTHESIS OF FRAGMENT 18

Scheme 2 provides an example of the synthesis of fragment 18.



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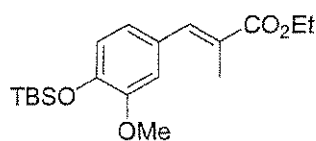
Scheme 2

Synthesis of intermediate 14

5

To a solution of 4-hydroxy-3-methoxybenzaldehyde (1 g, 6.57 mmol) in anhydrous DCM (14 mL), under N₂ atmosphere and at 0 °C, imidazole (1.118 g, 8.21 mmol) and *tert*-Butyldimethylsilylchloride (1.084 g, 7.22 mmol) were added. After 3 hours at room temperature the reaction was
10 quenched with a solution of HCl 0.5N and diluted with CH₂Cl₂ (100 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 1.71 g (yield: 98%) of aldehyde **14**.

15 ¹H NMR (CDCl₃, 300 MHz) δ: 9.84 (s, 1H), 7.40-7.36 (m, 2H), 6.96 (d, 1H, *J* = 7.8 Hz), 3.87 (s, 3H), 1.00 (s, 9H), 0.19 (s, 6H).

Synthesis of intermediate 15

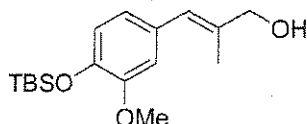
20

Over a solution of aldehyde **14** (1 g, 3.75 mmol) in toluene (20 mL) Carboethoxyethylidene-triphenylphosphorane (3.4 g, 9.38 mmol) was added and the mixture was heated at 60 °C over 2.5 h. Then, the
25 solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 12:1) affording 1.1 g (yield: 81%) of ester compound **15**.

50

^1H NMR (CDCl_3 , 300 MHz) δ : 7.62 (s, 1H), 6.96-6.85 (m, 3H), 4.26 (q, 2H, $J = 7.2$ Hz), 3.82 (s, 3H), 2.14 (s, 3H), 1.34 (t, 3H, $J = 7.2$ Hz), 1.00 (s, 9H), 0.18 (s, 6H).

5 Synthesis of intermediate 16

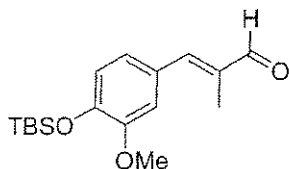


Over a -78°C cooled solution of ester **15** (640 mg, 1.746 mmol) in
10 anhydrous THF (8.7 mL) under N_2 atmosphere, Diisobutylaluminum
hydride (DIBAL) 1M in toluene (3.84 mL, 3.84 mmol) was added over a
period of 10 min and the mixture was stirred at -78°C . After 4 hours
the reaction was quenched with MeOH (0.16 mL) and a saturated
aqueous solution of sodium potassium tartrate was added (15 mL) and
15 diluted with EtOAc. This mixture was stirred for 1 h and then the
organic layer was decanted. The aqueous residue was extracted with
additional EtOAc and the combined organic layers were dried over
anhydrous Na_2SO_4 and the solvent was evaporated. The resulting oil
was purified by column chromatography (hexane/EtOAc 9:1 to 6:4)
20 affording 360 mg (yield: 68%) of alcohol **16**.

^1H NMR (CDCl_3 , 300 MHz) δ : 6.80-6.76 (m, 3H), 6.43 (br s, 1H), 4.16 (d, 2H, $J = 3.3$ Hz), 3.79 (s, 3H), 1.91 (s, 3H), 1.00 (s, 9H), 0.16 (s, 6H).

Synthesis of intermediate 17

25



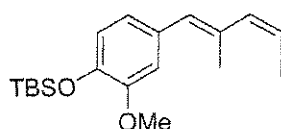
51

Over a solution of alcohol **16** (270 mg, 0.875 mmol) in ethyl ether (4.4 mL) under N₂ atmosphere, MnO₂ (1.141 g, 13.12 mmol) was added and the mixture was stirred at room temperature for 2 hours. This mixture was filtrated over a silica gel column eluting with EtOAc and the
5 resulting solution was dried under reduced pressure to afford 256 mg (yield: 96%) of aldehyde **17**.

¹HNMR (CDCl₃, 300 MHz) δ: 9.54 (s, 1H), 7.18 (br s, 1H), 7.109-7.081 (m, 2H), 6.92 (d, 1H, *J* = 8.1 Hz), 3.86 (s, 3H), 2.10 (s, 3H), 1.00 (s, 9H), 0.19 (s, 6H).

10

Synthesis of intermediate 18



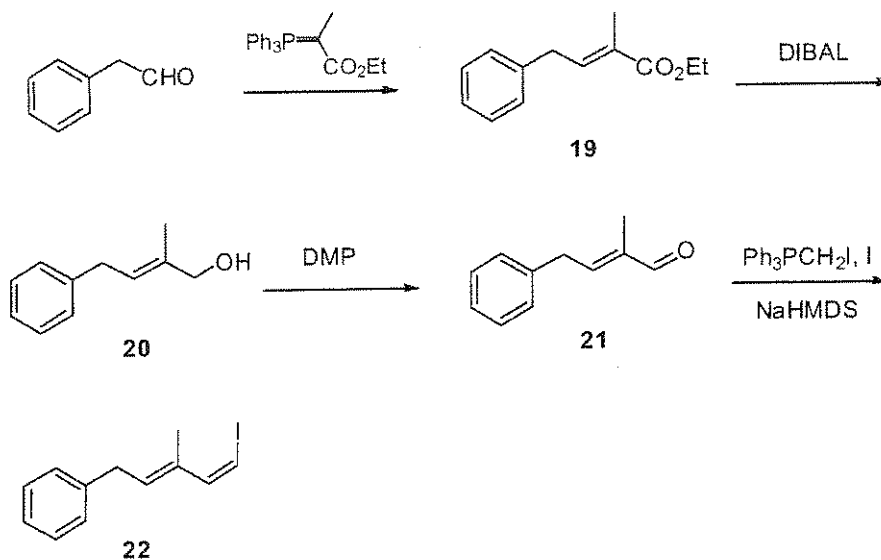
15 To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert Stork, KZ. *Tetrahedron letters* 1989, 30 (17), 2173) (605 mg, 1.142 mmol) in THF (4.6 mL) at room temperature, a 1M solution of sodium hexamethyldisilazane (NaHMDS) (1.142 mL, 1.142 mmol) was slowly added. After stirring for an additional 2 min, the solution was cooled to
20 -78 °C and a solution of aldehyde **17** (250 mg, 0.815 mmol) in THF (3 mL) was added. The temperature was kept at -78 °C while the reaction mixture was stirred for 2 hours. Hexane was added and the resulting slurry was filtrated over Celite® and washed with additional hexane. The filtrate was evaporated under reduced pressure and the resulting oil
25 was purified by column chromatography (hexane/EtOAc 100:0 to 20:1) affording 250 mg (yield: 71%) of iodide **18**.

¹HNMR (CDCl₃, 300 MHz) δ: 6.92 (d, 1H, *J* = 8.1 Hz), 6.83 (br s, 3H), 6.66 (s, 1H), 6.25 (d, 1H, *J* = 8.1 Hz) 3.82 (s, 3H), 2.18 (s, 3H), 1.00 (s,
30 9H), 0.18 (s, 6H).

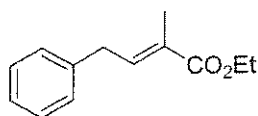
EXAMPLE 3: SYNTHESIS OF FRAGMENT 22

Scheme 3 provides an example of the synthesis of fragment 22.

5



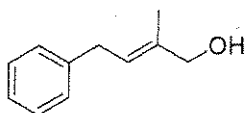
Scheme 3

10 Synthesis of intermediate 19

Over a solution of Phenylacetaldehyde (100 mg, 0.83 mmol) in toluene
 15 (5.0 mL) Carboethoxyethylidene-triphenylphosphorane (754 mg, 2.08
 mmol) was added and the mixture was stirred at room temperature over
 18 h. Then, the solvent was removed under reduced pressure and the
 resulting oil was purified by column chromatography (Ethyl
 acetate/hexanes mixture) affording pure 150 mg (90% yield) of ester
 20 compound **19**.

^1H NMR (CDCl_3 , 300MHz) δ : 7.35-7.18 (m, 5H), 6.94 (t, 1H, $J = 7.5$ Hz), 4.20 (q, 2H, $J = 7.2$ Hz), 3.54 (d, 2H, $J = 7.8$ Hz), 1.97 (s, 3H), 1.29 (t, 3H, $J = 7.2$ Hz).

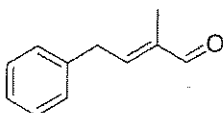
5 Synthesis of intermediate 20



Over a -78 °C cooled solution of ester **19** (150 mg, 0.73 mmol) in
10 anhydrous THF (3.6 mL) under N_2 atmosphere, Diisobutylaluminum
hydride (DIBAL) 1M in toluene (1.62 mL, 1.62 mol) was added over a
period of 5 min and the mixture was stirred at -78 °C. After 4 hours the
reaction was quenched with MeOH (0.7 mL) and a saturated aqueous
solution of sodium potassium tartrate was added (4 mL) and diluted
15 with EtOAc (10 mL). This mixture was stirred for 2 h and then the
organic layer was decanted. The aqueous residue was extracted with
additional EtOAc (2 x 15 mL) and the combined organic layers were
dried (anhydrous Na_2SO_4) and the solvent was evaporated affording 110
mg (yield: 92%) of alcohol **20**, which was used without further
20 purification.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.32 (m, 3H), 7.23 (m, 2H), 5.64 (t, 1H, $J = 6.3$ Hz), 4.04 (s, 2H), 3.43 (d, 2H, $J = 7.2$ Hz), 2.19 (bs, 1H), 1.80 (s, 3H).

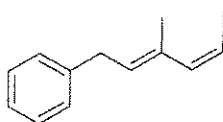
25 Synthesis of intermediate 21



Over a solution of alcohol **20** (96 mg, 0.59 mmol) in Dichloromethane (3.8 mL) under N₂ atmosphere, Dess Martin periodinane (DMP) (502 mg, 1.18 mol) was added and the mixture was stirred at room temperature for 2 hours. This mixture was quenched with a saturated aqueous solution of NH₄Cl (3 mL) and diluted with Dichloromethane (5 mL). The organic phase was dried over anhydrous Na₂SO₄, and evaporated at reduced pressure. Purification by column chromatography (hexane/Ethyl acetate 10:1) afforded pure aldehyde **21** (75 mg, yield: 80%)

¹H NMR (CDCl₃, 300 MHz) δ : 9.43 (s, 1H), 7.35-7.18 (m, 5H), 6.64 (t, 1H, J = 7.2 Hz), 3.43 (d, 2H, J = 7.2 Hz), 1.88 (s, 3H).
¹³C NMR (CDCl₃, 75 MHz) δ : 195.3, 152.4, 139.8, 138.4, 129.1, 128.7, 127.0, 62.2, 35.4.

15 Synthesis of intermediate 22



To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (347 mg, 0.66 mmol) in THF (2.7 mL) at room temperature, a 1M solution in THF of sodium hexamethyldisilazane (NaHMDS) (0.66 mL, 0.66 mmol) was slowly added. After stirring for an additional 2 min, the solution was cooled to -78 °C and a solution of aldehyde **21** (75 mg, 0.47 mmol) dissolved in THF (1.75 mL) was added.

The temperature was kept at -78 °C while the reaction mixture was stirred for 2 hours. Hexane (25 mL) was added and the resulting slurry was filtrated over Celite® and washed with additional hexane (50 mL). The filtrate was evaporated under reduced pressure and the resulting

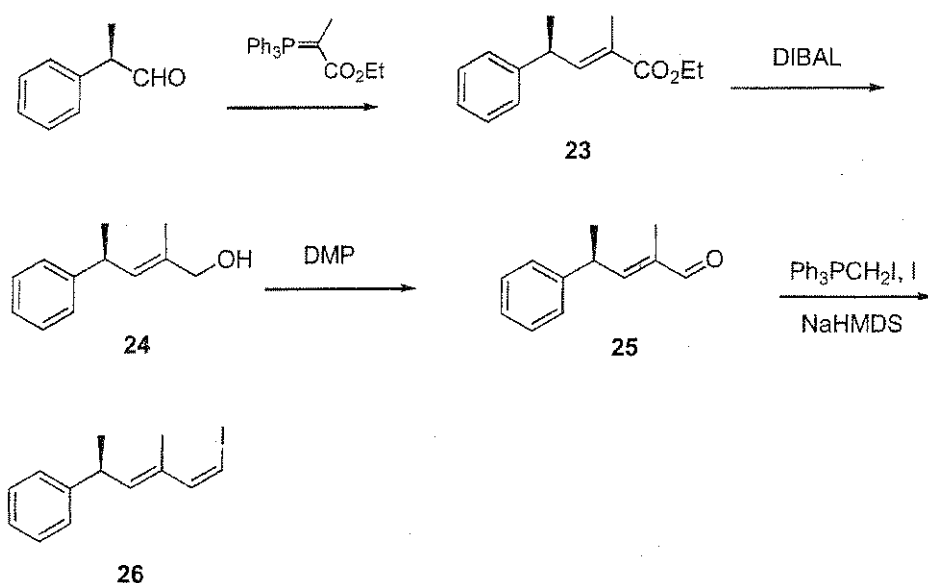
55

oil was purified by column chromatography (hexane/EtOAc 20:1 to 15:1) affording 82 mg (yield: 62%) of iodide **22**.

¹H NMR (CDCl₃, 300 MHz) δ: 7.35-7.18 (m, 5H), 6.82 (d, 1H, *J* = 8.4 Hz), 6.17 (dd, 1H, *J* = 8.4 Hz), 5.90 (tt, 1H, *J* = 7.5, 1.2 Hz), 3.50 (d, 2H, *J* = 7.5 Hz), 2.03 (s, 3H).

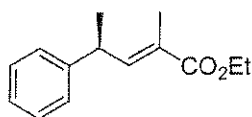
EXAMPLE 4: SYNTHESIS OF FRAGMENT 26

Scheme 4 provides an example of the synthesis of fragment 26.



Scheme 4

Synthesis of intermediate 23



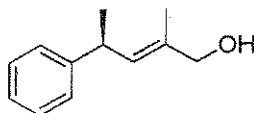
Over a solution of (*R*)-2-Phenylpropanal (prepared following the procedure described in *Tetrahedron Asymmetry* 1998, 1929-1931) (80 mg, 0.59 mmol) in toluene (2.8 mL) Carboethoxyethylidene-triphenylphosphorane (540 mg, 1.49 mmol) was added and the mixture

was stirred at room temperature over 4 h. Then, the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 10:1) affording 70 mg (55 % yield) of ester compound **23**.

- 5 ^1H NMR (CDCl_3 , 300 MHz) δ : 7.34-7.19 (m, 5H), 6.87 (dq, 1H, $J = 9.9$, 1.4 Hz), 4.18 (q, 2H, $J = 7.1$ Hz), 3.80 (m, 1H), 1.92 (d, 3H, $J = 1.4$ Hz), 1.41 (d, 3H, $J = 7.0$ Hz), 1.29 (t, 3H, $J = 7.1$ Hz).

Synthesis of intermediate 24

10



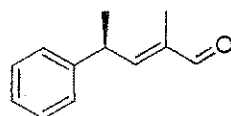
- Over a $-78\text{ }^\circ\text{C}$ cooled solution of ester **23** (70 mg, 0.321 mmol) in anhydrous THF (1.6 mL) under N_2 atmosphere, diisobutylaluminum hydride (DIBAL) 1M in toluene (0.71 mL, 0.71 mmol) was added and the mixture was stirred at $-78\text{ }^\circ\text{C}$. After 4 hours the reaction was quenched with MeOH (0.4 mL) and a saturated aqueous solution of sodium potassium tartrate was added (1.5 mL) and diluted with EtOAc (6 mL).
- 20 This mixture was stirred for 1 h and then the organic layer was decanted. The aqueous residue was extracted with additional EtOAc (2 x 6 mL) and the combined organic layers were dried (anhydrous Na_2SO_4) and the solvent was evaporated. The resulting oil was purified by column chromatography (hexane/EtOAc 6:1) affording 40 mg (75% yield) of alcohol **24** as a colourless oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.34-7.16 (m, 5H), 5.57 (dq, 1H, $J = 9.4$, 1.2 Hz), 4.00 (s, 2H), 3.71 (m, 1H), 1.75 (d, 3H, $J = 1.2$ Hz), 1.35 (d, 3H, $J = 7.0$ Hz).

- ^{13}C NMR (CDCl_3 , 75 MHz) δ : 146.7, 133.9, 131.4, 128.7, 127.1, 126.2, 68.9, 37.9, 22.3, 14.1.
- 30

Synthesis of intermediate 25

57

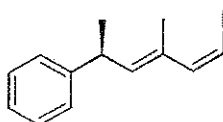


Over a solution of alcohol **24** (40 mg, 0.226 mmol) in dichloromethane
5 (1.5 mL) under N₂ atmosphere, Dess Martin periodinane (DMP) (193 mg,
0.454 mol) was added and the mixture was stirred at room temperature
for 2 hours. This mixture was quenched with a saturated aqueous
solution of NaHCO₃ (2 mL) and diluted with dichloromethane (5 mL).
The organic phase was dried over anhydrous Na₂SO₄ and evaporated
10 under reduced pressure. Purification by column chromatography
(hexane/ EtOAc 10:1) afforded pure aldehyde **25** (18 mg, 50% yield) as
a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ : 9.42 (s, 1H), 7.39-7.23 (m, 5H), 6.56 (dq,
1H, J = 9.7, 0.9 Hz), 4.00 (m, 1H), 1.83 (s, 3H), 1.47 (d, 3H, J = 7.0 Hz).

15 ¹³C NMR (CDCl₃, 75 MHz) δ : 195.6, 158.2, 143.8, 137.9, 129.1, 127.2,
127.1, 39.1, 21.1, 9.6.

Synthesis of intermediate 26



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To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert
Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (77 mg, 0.144 mmol)
in THF (0.6 mL) at room temperature, a 1M solution of sodium
25 hexamethyldisilazane (NaHMDS) in THF (0.144 mL, 0.144 mmol) was
slowly added. After stirring for an additional 2 min, the solution was
cooled to -78 °C and a solution of aldehyde **25** (18 mg, 0.103 mmol)
dissolved in THF (0.5 mL) was added.

The temperature was kept at -78 °C while the reaction mixture was
30 stirred for 2 hours. Hexane (15 mL) was added and the resulting slurry
was filtrated over Celite® and washed with additional hexane (30 mL).

The filtrate was evaporated under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 10:1) affording 22 mg (72% yield) of iodide **26** as a colourless oil.

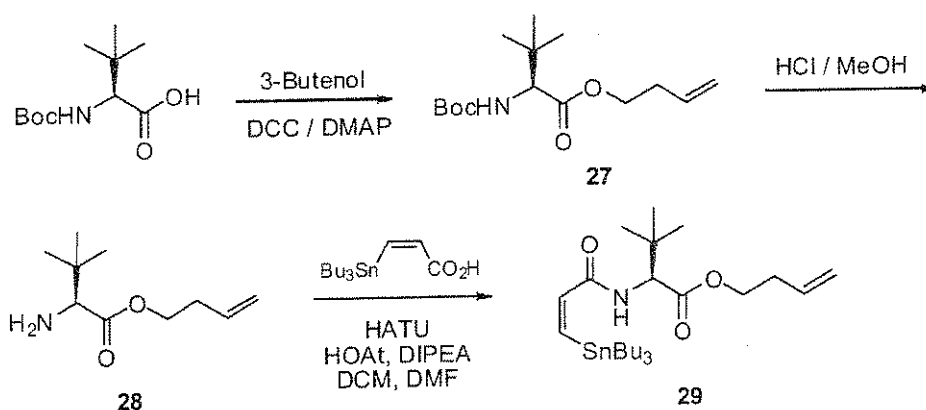
^1H NMR (CDCl_3 , 300 MHz) δ : 7.34-7.17 (m, 5H), 6.73 (d, 1H, $J = 8.4$ Hz), 6.14 (d, 1H, $J = 8.4$ Hz), 5.83 (d, 1H, $J = 9.5$ Hz), 3.79 (m, 1H), 1.95 (s, 3H), 1.40 (d, 3H, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 145.9, 142.3, 139.1, 131.9, 128.7, 127.3, 127.2, 126.3, 38.4, 22.1, 16.0

10

EXAMPLE 5: SYNTHESIS OF FRAGMENT 29

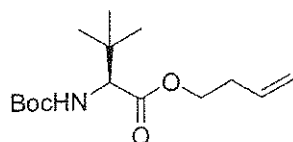
Scheme 5 provides an example of the synthesis of fragment 29.



15

Scheme 5

20 Synthesis of intermediate 27



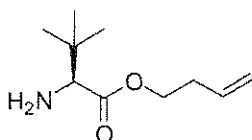
To a mixture of L-Boc-tert-leucine (300 mg, 1.3 mmol) in DCM anhydrous (13 mL) and Dicyclohexylcarbodiimide (DCC) (295 mg, 1.43 mmol) at 0°C, under N_2 , the 3-butenol (0.3 mL, 3.9 mmol) and the

25

Dimethylaminopyridine (DMAP) (15.9 mg, 0.13 mmol) were added. The reaction mixture was stirred for 5 minutes at 0°C and 4 hours at room temperature. The organic solvent was evaporated under reduced pressure and the resulting solid was purified by column chromatography (hexane/EtOAc 10:1) affording 300 mg (yield: 81%) of ester **27**.

¹H NMR (CDCl₃, 300 MHz) δ: 5.82-5.71 (m, 1H), 5.14-5.06 (m, 2H), 4.24-4.12 (m, 2H), 4.08 (d, 1H, *J* = 9.8 Hz), 2.41 (q, 2H, *J* = 6.7 Hz), 1.43 (s, 9H), 0.96 (s, 9H).

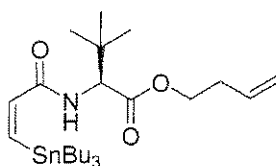
Synthesis of intermediate 28



The solution of the ester **27** (180 mg, 0.63mmol) in HCl·MeOH 1M (3.6mL) was stirred at room temperature for 24 hours. The organic solvent was evaporated under reduced pressure and the resulting solid was diluted in DCM and washed with H₂O. The resulting organic phase was dried over anhydrous Na₂SO₄, filtered, and the solvent was evaporated to afford 116 mg (yield: 100%) of **28**.

¹H NMR (CDCl₃, 300 MHz) δ: 5.85-5.72 (m, 1H), 5.15-5.06 (m, 2H), 4.16 (t, 2H, *J* = 6.7 Hz), 3.15 (s, 1H), 4.44-4.37 (m, 2H), 0.96 (s, 9H).

Synthesis of intermediate 29

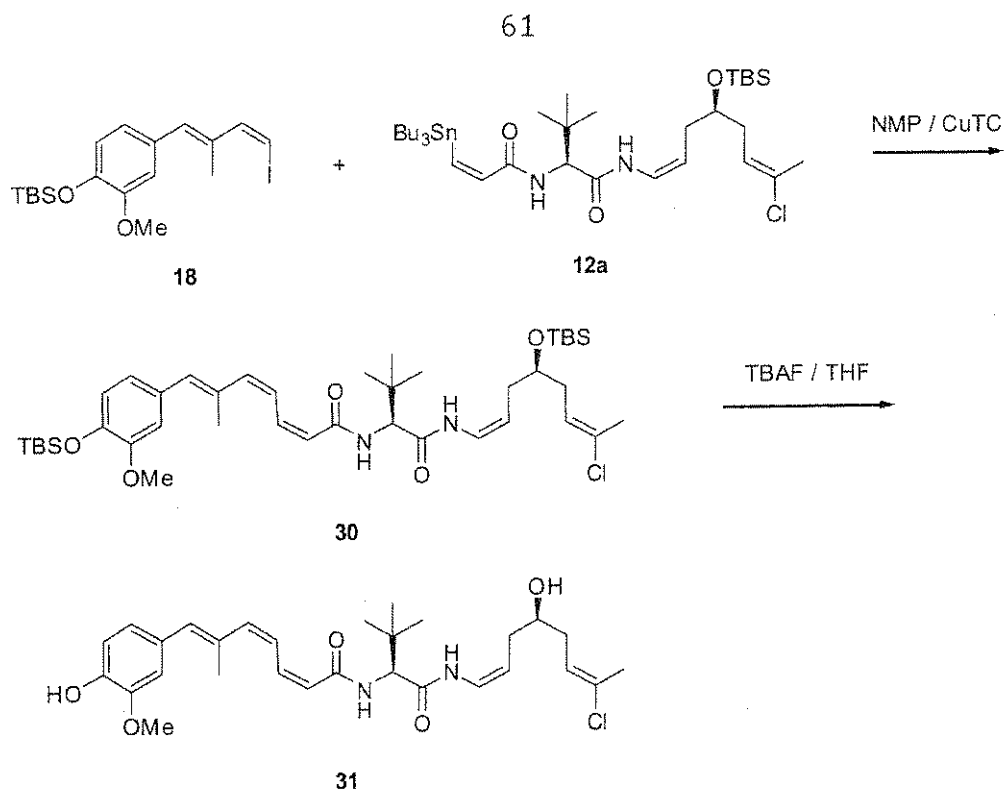


DIPEA (0.24mL, 1.4 mmol), HOAt (123.3 mg, 0.9 mmol), and HATU (345 mg, 0.9 mmol) were added to a solution of **28** (168 mg, 0.9 mmol), and (Z)-3-tributylstannylpropenoic acid (393mg, 1.2 mmol) in
5 DCM/DMF (10:1, 14 mL) at 0 °C under N₂ atmosphere. After 2 hours, the cold bath was removed and the reaction mixture was stirred at room temperature for 1 h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined
10 organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 15:1 to 10:1) to give **29** (340 mg; yield: 72%).

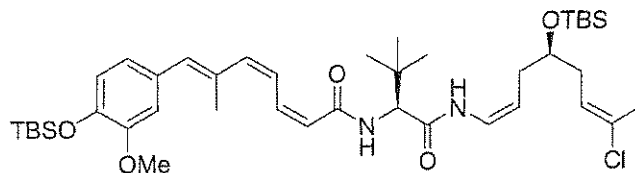
¹H NMR (CDCl₃, 300 MHz) δ: 7.01 (d, 1H, *J* = 12.3 Hz), 6.75 (d, 1H, *J* = 12.3), 6.03 (d, NH, *J* = 9.73 Hz), 5.84-5.69 (m, 1H), 5.14-5.05 (m, 15
2H), 4.60 (d, 1H, *J* = 9.76 Hz), 4.19-4.14 (m, 2H), 2.40 (q, 2H, *J* = 6.70 Hz), 1.48-1.40 (m, 6H), 1.31-1.19 (m, 6H), 0.96 (s, 9H), 0.93-0.83 (m, 15H)

20 EXAMPLE 6

Scheme 6 provides the synthesis of several compounds of the invention.



Scheme 6

Synthesis of compound 30

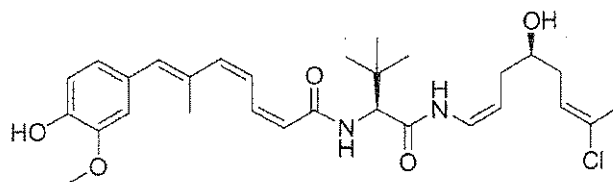
5

- To a solution of alkenylstannane **12a** (130mg, 0.174 mmol) and **18** (90 mg, 0.209 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1.75 mL) at 0 °C, Copper thiophenecarboxylate (CuTC) (49.6 mg, 0.261 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 8:1 to 1:1) to give triene **30** (65 mg, yield: 49%) as an oil.

62

^1H NMR (CDCl_3 , 300 MHz) δ : 7.64 (d, 1H, $J = 11.1$ Hz), 7.33 (dd, 1H, $J = 11.7, 11.4$ Hz), 7.04 (dd, 1H, $J = 12.0, 11.1$ Hz), 6.83-6.81 (m, 3H), 6.77-6.70 (m, 1H), 6.45 (br s, 1H), 6.33 (d, 1H, $J = 11.7$ Hz), 6.22 (d, 1H, $J = 9.0$ Hz), 5.64 (d, 1H, $J = 11.4$ Hz), 5.62-5.56 (m, 1H), 4.89-4.80 (m, 1H), 4.36 (d, 1H, $J = 9.3$ Hz), 3.81 (s, 3H), 3.80-3.78 (m, 1H), 2.23-2.14 (m, 4H), 2.08 (s, 3H), 2.03 (s, 3H), 1.05 (s, 9H), 1.00 (s, 9H), 0.89 (s, 9H), 0.17 (s, 6H), 0.08 (s, 3H), 0.06 (s, 3H).

Synthesis of compound 31

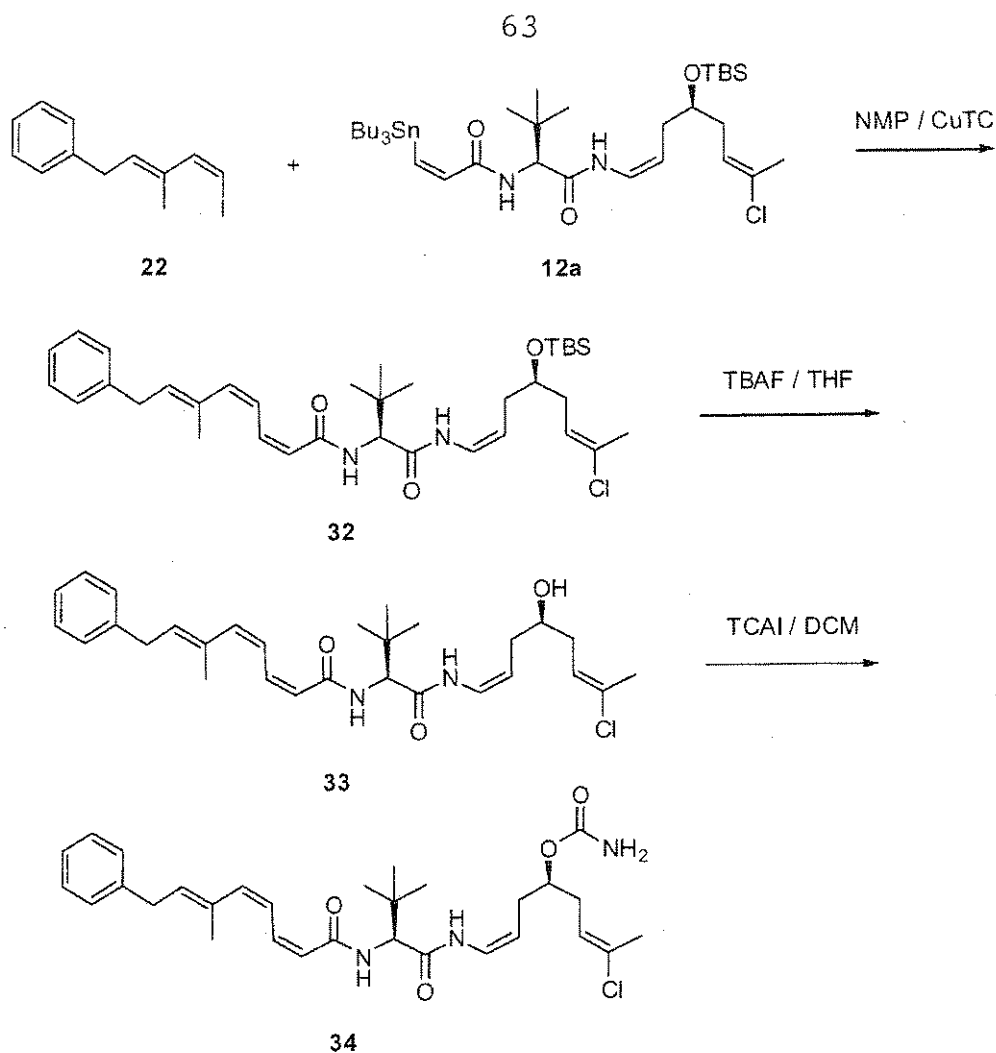


To a solution of **30** (60 mg, 0.08 mmol) in THF (1.5 mL) under N_2 and at room temperature, Tetrabutylammonium fluoride (TBAF) 1M in THF (0.23 mL, 0.23 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 5:1 to 1:1) to give alcohol **31** (25.4 mg; yield: 60 %) as a white solid.

^1H NMR (CDCl_3 , 300 MHz) δ : 8.74 (d, 1H, $J = 10.2$ Hz), 7.77-7.68 (m, 1H), 6.90-6.50 (m, 4H), 6.61-6.57 (m, 3H), 6.36 (d, 1H, $J = 9.0$ Hz), 5.62 (m, 2H), 4.86 (q, 1H, $J = 8.5$ Hz), 4.37 (d, 1H, $J = 9.0$ Hz), 3.90 (s, 3H), 3.77 (m, 1H), 2.67 (bs, 1H), 2.20 (m, 4H), 2.09 (s, 3H), 2.07 (s, 3H), 1.05 (s, 9H).

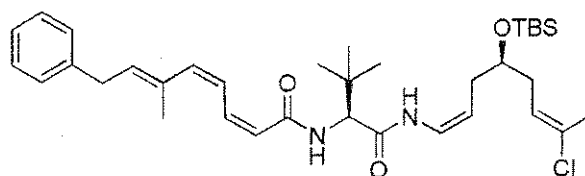
EXAMPLE 7

Scheme 7 provides the synthesis of several compounds of the invention.



Scheme 7

5 Synthesis of compound 32



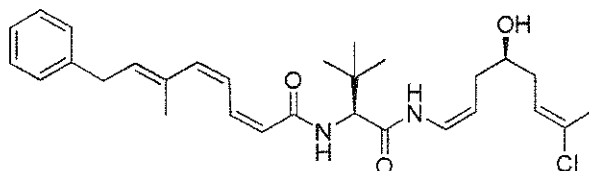
10

To a solution of alkenylstannane **12a** (42 mg, 0.056 mmol) and iodide **22** (20 mg, 0.067 mmol) in 1-methyl-2-pyrrolidinone (NMP) (0.6 mL) at

0 °C, Copper thiophenecarboxylate (CuTC) (16 mg, 0.084 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
5 filtrates were washed with HCl 0.5N (3x5 mL). The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 12:1 to 6:1) to give triene **32** (15 mg, yield: 45%) as an oil.

10 ¹H NMR (CDCl₃, 300 MHz) δ: 7.67 (d, 1H, *J* = 10.8 Hz), 7.35-7.18 (m, 6H), 6.92 (t, 1H, *J* = 11.4 Hz), 6.72 (t, 1H, *J* = 10.8 Hz), 6.22 (m, 2H), 5.69 (t, 1H, *J* = 7.5 Hz), 5.58 (m, 2H), 4.82 (q, 1H, *J* = 8.7 Hz), 4.35 (d, 1H, *J* = 9.3 Hz), 3.75 (m, 1H), 3.49 (d, 2H, *J* = 7.5 Hz), 2.15 (m, 4H), 2.02 (s, 3H), 1.91 (s, 3H), 1.02 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s,
15 3H).

Synthesis of compound 33



20

To a solution of **32** (15 mg, 0.024 mmol) in THF (0.5 mL) under N₂ and at room temperature, TBAF 1M in anhydrous THF (0.05 mL, 0.05 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and
25 extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **33** (4 mg, yield: 35%).

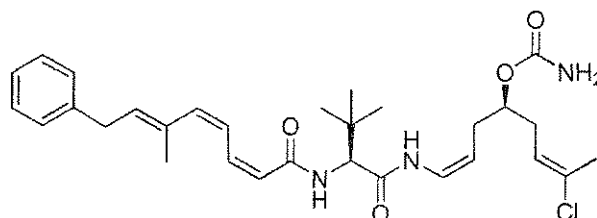
65

¹H NMR (CDCl₃, 300 MHz) δ: 8.76 (d, 1H, *J* = 9.6 Hz), 7.35-7.17 (m, 6H), 6.96 (t, 1H, *J* = 11.4 Hz), 6.76 (t, 1H, *J* = 8.4 Hz), 6.21 (m, 2H), 5.69 (t, 1H, *J* = 7.5 Hz), 5.61 (m, 2H), 4.87 (q, 1H, *J* = 8.1 Hz), 4.29 (d, 1H, *J* = 9.3 Hz), 3.77 (m, 1H), 3.49 (d, 2H, *J* = 7.2 Hz), 2.2 (m, 4H), 2.06 (s, 3H),
5 1.91 (s, 3H), 1.02 (s, 9H).

MS (ES) *m/z* 499 (M+1)⁺, 521 (M+Na)⁺.

Synthesis of compound 34

10



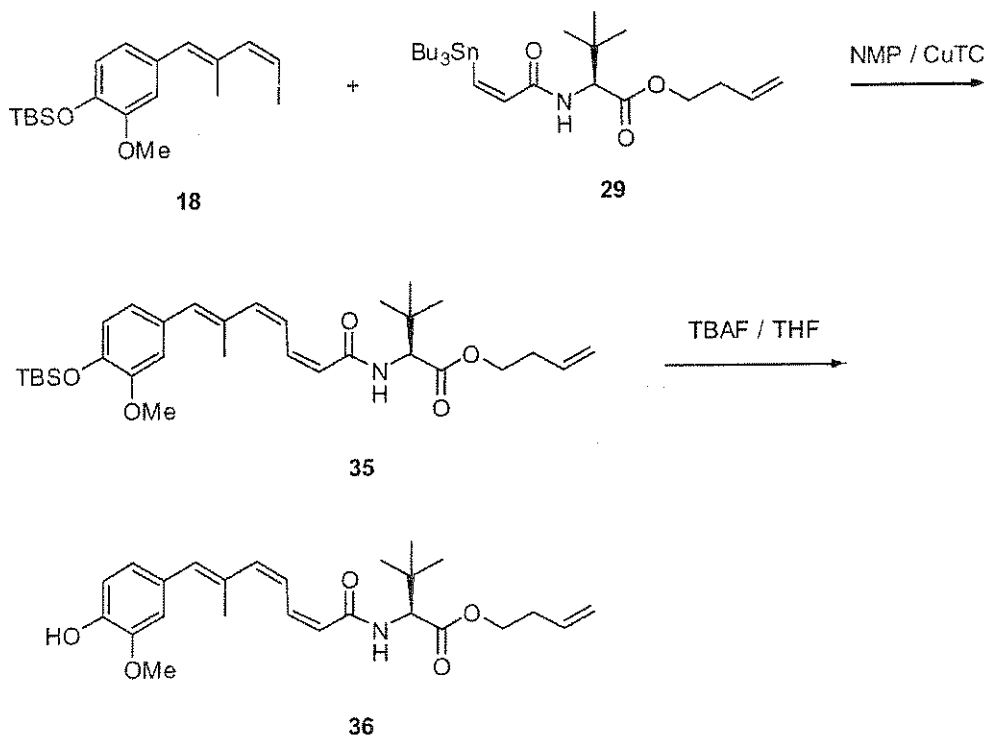
To a solution of **33** (3 mg, 0.006 mmol) in Dichloromethane (0.4 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (1 μL, 0.0072 mmol) was added. The reaction was stirred at room temperature for 30
15 min and then neutral aluminium oxide was added. The mixture was stirred for 30 min and then 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 2:1) to give
20 compound **34** (2 mg, yield: 63%).

¹H NMR (CDCl₃, 300 MHz) δ: 8.55 (d, 1H, *J* = 11.4 Hz), 7.35-7.17 (m, 6H), 6.96 (t, 1H, *J* = 11.1 Hz), 6.82 (t, 1H, *J* = 8.4 Hz), 6.32 (d, 1H, *J* = 9.3 Hz), 6.22 (d, 1H, *J* = 10.5 Hz), 5.68 (t, 1H, *J* = 7.5 Hz), 5.62 (m, 2H), 4.81 (q, 1H, *J* = 8.1 Hz), 4.46 (m, 1H), 4.42 (d, 1H, *J* = 9.3 Hz), 3.50 (d,
25 2H, *J* = 7.2 Hz), 2.34 (m, 4H), 2.06 (s, 3H), 1.91 (s, 3H), 1.03 (s, 9H).

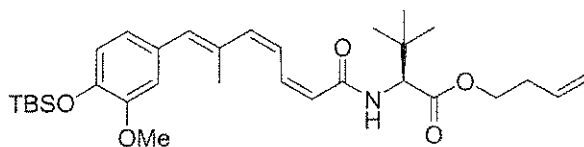
EXAMPLE 8

Scheme 8 provides the synthesis of several compounds of the invention.

5



Scheme 8

10 Synthesis of compound 35

To a solution of **29** (25mg, 0.05 mmol) and **18** (31 mg, 0.06 mmol) in
 15 NMP (0.5 mL) at 0 °C, Copper thiophenecarboxylate (CuTc, 13.5 mg, 1.5
 mmol) was added. The reaction was stirred at 0°C for 45 min and at
 room temperature for an hour. Then, the crude mixture was filtered
 through a plug of neutral alumina, washed with EtOAc/Ether 50:50 (20
 mL) and the combined filtrates were washed with HCl 0.5N (3x10 mL).

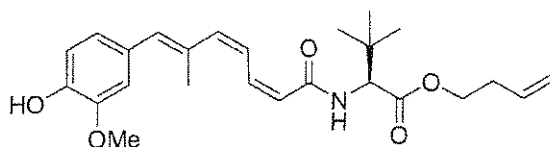
67

After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (EtOAc/hexane, from 10:1 to 5:1) to afford pure **35** (5 mg, yield:18%).

- 5 ¹H NMR (CDCl₃, 300 MHz) δ: 7.38 (m, 1H), 7.04 (m, 1H), 6.83-6.81 (m, 3H), 6.46 (s, 1H), 6.32 (d, 1H, *J* = 11.1 Hz), 6.03 (d, 1H, *J* = 9.3 Hz), 5.77 (m, 1H), 5.64 (d, 1H, *J* = 11.4 Hz), 5.16-5.07 (m, 2H), 4.55 (d, 1H, *J* = 9.6 Hz), 4.18 (m, 2H), 3.81 (s, 3H), 2.42 (m, 2H), 2.08 (s, 3H), 1.00 (m, 18H), 0.16 (s, 3H), 0.06 (s, 3H).

10

Synthesis of compound 36



- 15 A solution of **35** (4mg, 0.007 mmol) in HCl·MeOH 1M (1.2 mL) was stirred at room temperature for 2 hours and 30 min. The organic solvent was evaporated under reduced pressure and the resulting crude was purified by column chromatography (Ethyl acetate/hexane 10:1-1:10) to afford pure **36** (1.8mg, yield: 60%).

20

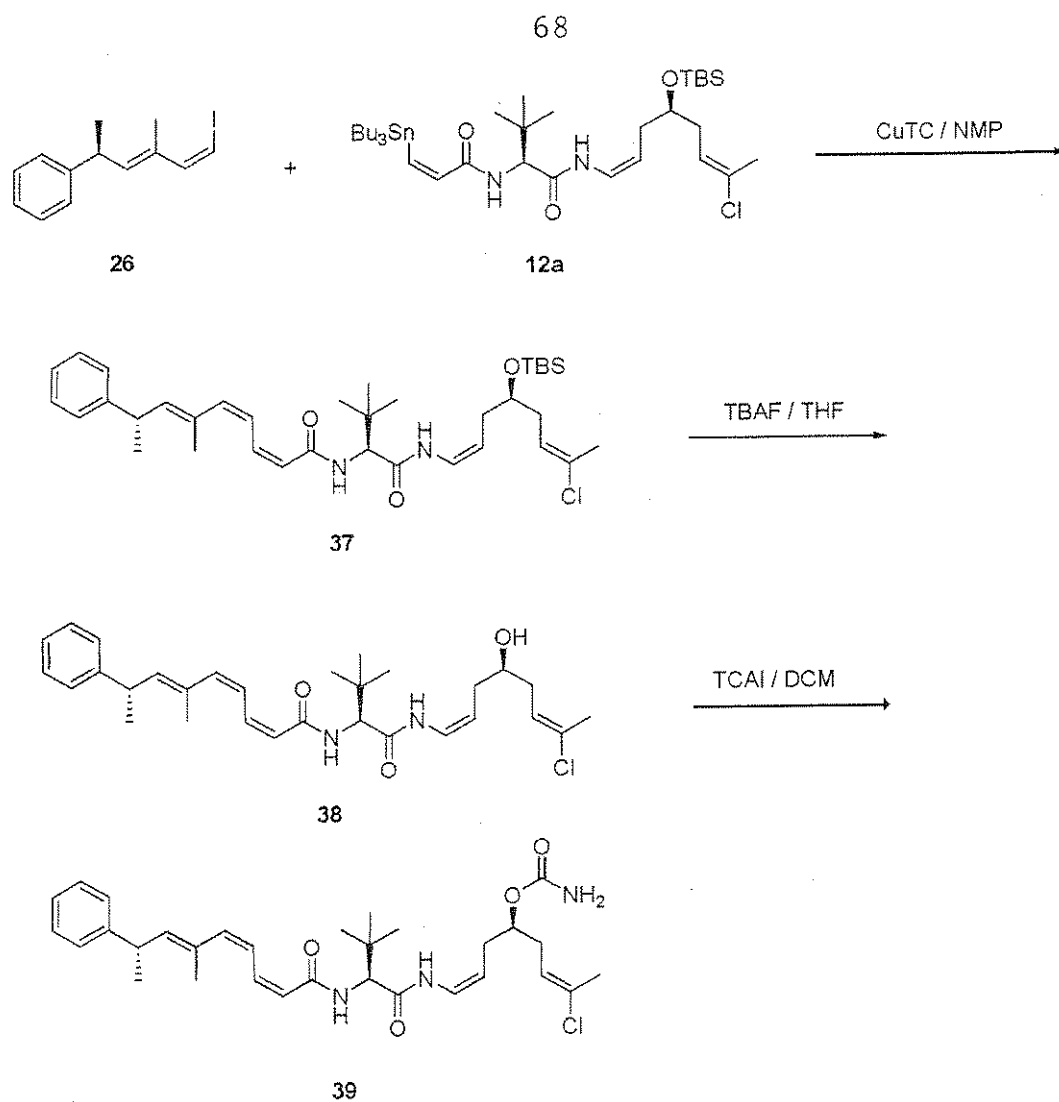
¹H NMR (CDCl₃, 300 MHz) δ: 7.31-7.26 (m, 1H), 7.00-6.92 (m, 4H), 6.60-6.55 (m, 2H), 6.03 (d, 1H, *J* = 9.0 Hz), 5.82-5.71 (m, 1H), 5.65 (d, 1H, *J* = 10.5 Hz), 5.14-5.06 (m, 2H), 4.58 (d, 1H, *J* = 9.5 Hz), 4.17-4.08 (m, 2H), 3.90 (s, 3H), 2.54-2.39 (m, 2H), 2.01 (s, 3H), 1.03 (s, 9H).

25

EXAMPLE 9:

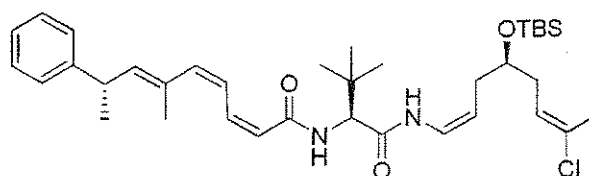
Scheme 9 provides the synthesis of several compounds of the invention.

30



Scheme 9

5

Synthesis of compound 37

10

To a solution of **12a** (42 mg, 0.056 mmol) and iodide **26** (20 mg, 0.067 mmol) in 1-methyl-2-pyrrolidinone (NMP) (0.6 mL) at 0 °C, Copper thiophenecarboxylate (CuTC) (16 mg, 0.084 mmol) was added. The

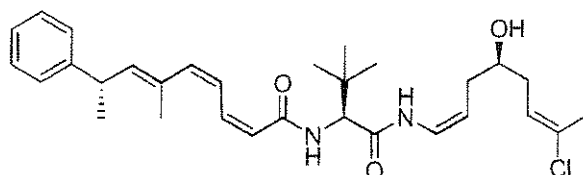
reaction was stirred at 0 °C for 45 min and at room temperature for 20 minutes. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Et₂O 50:50 and the combined filtrates were washed with HCl 0.5N (3x5 mL). The organic solution was dried
5 and evaporated to give the crude product which was purified by column chromatography (hexane/EtOAc 7:1 to 5:1) to give triene **37** (9 mg, 26 % yield) as an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 7.63 (d, 1H, *J* = 10.5 Hz), 7.33-7.15 (m, 6 H), 6.90 (t, 1H, *J* = 11.6 Hz), 6.73 (t, 1H, *J* = 10.1 Hz), 6.19 (m, 2H),
10 5.61 (m, 3H), 4.82 (q, 1H, *J* = 8.8 Hz), 4.34 (d, 1H, *J* = 9.3 Hz), 3.76 (m, 2H), 2.16 (m, 4H), 2.02 (s, 3H), 1.85 (s, 3H), 1.37 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz) δ: 168.4, 166.4, 146.2, 141.2, 139.9, 137.9, 131.6, 131.2, 128.7, 127.1, 126.3, 124.0, 123.7, 122.5, 120.3, 108.6,
15 71.6, 60.6, 38.8, 36.5, 35.1, 33.8, 29.9, 26.8, 26.1, 22.4, 21.3, 17.1, -4.3, -4.4.

Synthesis of compound 38

20

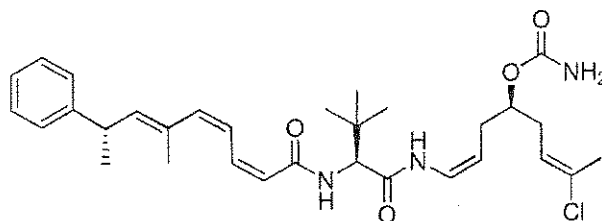


To a solution of **37** (9 mg, 0.014 mmol) in THF (0.3 mL) under N₂ and at room temperature, TBAF 1M in THF (0.028 mL, 0.028 mmol) was
25 added. The reaction was stirred at room temperature for 7 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:1 to 1:1) to give alcohol **38**
30 (4.5 mg, 62.5 % yield) as a colourless oil.

70

¹H NMR (CDCl₃, 300 MHz) δ: 8.80 (d, 1H, *J* = 10.2 Hz), 7.34-7.19 (m, 6H), 6.91 (t, 1H, *J* = 11.7 Hz), 6.76 (t, 1H, *J* = 9.2 Hz), 6.34 (d, 1H, *J* = 8.8 Hz), 6.19 (d, 1H, *J* = 11.6 Hz), 5.62 (m, 3H), 4.85 (q, 1H, *J* = 8.2 Hz), 4.33 (d, 1H, *J* = 9.2 Hz), 3.75 (m, 2H), 2.77 (bs, 1H) 2.18 (m, 4H), 2.06 (s, 3H), 1.85 (s, 3H), 1.36 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 9H).

Synthesis of compound 39



10

To a solution of **38** (3 mg, 0.006 mmol) in dichloromethane (0.5 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (1 μL, 0.0069 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide (44 mg) was added. The mixture was stirred for 30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of dichloromethane /MeOH 50:1. The filtrate was evaporated under reduced pressure to give the crude product which was purified by column chromatography (hexane/EtOAc 3:1 to 1:1) to give compound **39** (1.6 mg, 50% yield) as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 8.58 (d, 1H, *J* = 10.8 Hz), 7.32-7.19 (m, 6H), 6.91 (t, 1H, *J* = 11.6 Hz), 6.84 (t, 1H, *J* = 9.0 Hz), 6.33 (d, 1H, *J* = 9.8 Hz), 6.18 (d, 1H, *J* = 10.7 Hz), 5.61 (m, 3H), 4.80 (q, 1H, *J* = 8.9 Hz), 4.45 (m, 1H), 4.40 (d, 1H, *J* = 9.5 Hz), 3.77 (m, 1H), 2.34 (m, 4H), 2.07 (s, 3H), 1.86 (s, 3H), 1.36 (d, 3H, *J* = 7.0 Hz), 1.04 (s, 9H).

MS (ES) *m/z* 578.2 [M+Na]⁺.

30

EXAMPLE 10: 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

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

10

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).

15

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), 55-63). All the cell lines used in this study, derived from different types of human cancer, were obtained from the American Type Culture Collection (ATCC).

20

Cells were maintained in Dulbecco's Modified Eagle Medium (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

25

from subconfluent cultures using trypsinization and resuspended in fresh medium before counting and plating.

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 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% 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 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).

20

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).

25

Table 1 illustrates data on the biological activity of compounds of the present invention.

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Table 1. Cytotoxicity assay - Activity Data (Molar)

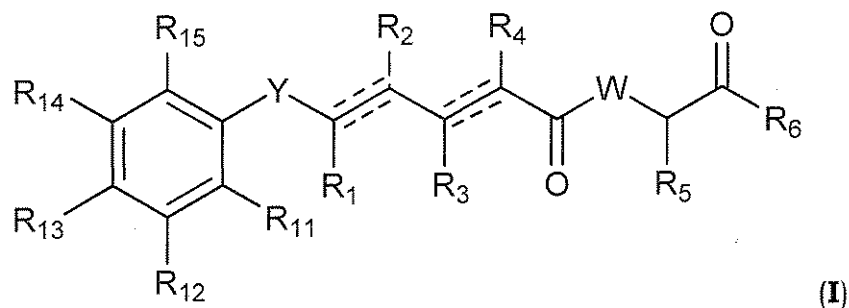
		Compound 30	Compound 32	Compound 33	Compound 34
MDA- MB-231	GI ₅₀	7.64E-07	8.33E-07	3.01E-06	1.03E-06
	TGI	9.74E-07	1.11E-06	4.81E-06	4.43E-06
	LC ₅₀	1.26E-06	1.50E-06	8.01E-06	> 1.84E-05
A549	GI ₅₀	6.71E-07	4.90E-07	1.58E-06	7.01E-07
	TGI	7.64E-07	6.86E-07	3.41E-06	2.77E-06
	LC ₅₀	9.08E-07	1.06E-06	7.41E-06	> 1.84E-05
HT29	GI ₅₀	7.77E-07	4.90E-07	1.10E-06	4.43E-07
	TGI	8.16E-07	6.21E-07	1.82E-06	5.72E-07
	LC ₅₀	8.69E-07	8.49E-07	3.81E-06	9.04E-07

5

		Compound 36	Compound 37	Compound 38	Compound 39
MDA- MB-231	GI ₅₀	1.15E-06	5.26E-6	2.14E-6	9.17E-8
	TGI	2.57E-06	7.01E-6	4.48E-6	2.70E-7
	LC ₅₀	1.92E-05	9.40E-6	>1.95E-5	>1.80E-5
A549	GI ₅₀	3.27E-06	2.87E-6	1.81E-6	5.57E-8
	TGI	> 2.34E-05	5.90E-6	4.87E-6	>1.80E-5
	LC ₅₀	> 2.34E-05	1.08E-5	>1.95E-5	>1.80E-5
HT29	GI ₅₀	1.96E-06	3.67E-6	1.09E-6	3.60E-8
	TGI	7.95E-06	4.46E-6	1.52E-6	5.93E-8
	LC ₅₀	> 2.34E-05	5.90E-6	4.68E-6	3.60E-7

CLAIMS

1. A compound of general formula I



5

wherein Y is selected from $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$, $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, and $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$;

each R_{ay} , R_{by} , and R_{cy} is independently selected from hydrogen,
 10 substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

each R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from hydrogen,
 substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted
 15 $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

R_6 is selected from NR_8R_9 , and OR_{10} ;

W is selected from O and NR_7 ;

20

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, or R_7 and R_5 together with the corresponding N atom and C atom to which they are
 25 attached may form a substituted or unsubstituted heterocyclic group;

R₈ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

- 5 R₁₀ is selected from hydrogen, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each dotted line represents an optional additional bond with the proviso that one or more additional bonds are present, but when a triple bond
10 exists between the C atoms to which R₁ and R₂ are attached, R₁ and R₂ are absent, and when a triple bond exists between the C atoms to which R₃ and R₄ are attached, R₃ and R₄ are absent;

R₉ is selected from hydrogen, COR_a, COOR_a, substituted or
15 unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

each R₁₁, R₁₂, R₁₃, R₁₄, and R₁₅ are independently selected from hydrogen, halogen, OR_a, COR_a, COOR_a, OCOR_a, OCOOR_a, OCONR_aR_b,
20 CONR_aR_b, OS(O)R_a, OSO₂R_a, OP(O)(R_a)OR_b, OSiR_aR_bR_c, NR_aR_b, NR_aCOR_b, NR_aCONR_aR_b, NR_aS(O)R_b, NR_aSO₂R_b, NR_aC(=NR_a)NR_aR_b, SR_a, S(O)R_a, SO₂R_a, S(O)NR_aR_b, SO₂NR_aR_b, S(O)OR_a, SO₂OR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; and

25 each R_a, R_b, and R_c 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
30 group; or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

2. A compound according to claim 1 wherein R_1 , R_2 , R_3 and R_4 are independently selected from hydrogen and a substituted or unsubstituted C_1 - C_6 alkyl.
- 5 3. A compound according to claim 2 wherein R_1 , R_2 , R_3 and R_4 are hydrogen.
4. A compound according to any preceding claim, wherein R_{11} , R_{14} and R_{15} are hydrogen.
- 10 5. A compound according to any preceding claim, wherein Y is selected from $-CHR_{ay}-$, $-CR_{ay}=CR_{by}-$ and $-CHR_{ay}-CR_{by}=CR_{cy}-$, and wherein R_{ay} , R_{by} and R_{cy} are independently selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.
- 15 6. A compound according to claim 5, wherein R_{ay} , R_{by} and R_{cy} are independently selected from hydrogen and methyl.
7. A compound according to any preceding claim, wherein R_{12} and R_{13} are independently selected from hydrogen, OR_a , $OCOR_a$ and $OSiR_aR_bR_c$, and wherein R_a , R_b and R_c are independently selected from hydrogen and a substituted or unsubstituted C_1 - C_6 alkyl.
- 20 8. A compound according to claim 7, wherein R_{12} is selected from hydrogen and OR_a .
- 25 9. A compound according to claim 7 or 8, wherein R_{13} is selected from hydrogen, OR_a and $OSiR_aR_bR_c$.
- 30 10. A compound according to any of claims 7 to 9, wherein R_a , R_b , and R_c are independently selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted

or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted tert-butyl.

11. A compound according to any preceding claim, wherein R_5 is
5 selected from hydrogen and a substituted or unsubstituted C_1 - C_6 alkyl.

12. A compound according to claim 11, wherein R_5 is selected from methyl, isopropyl and tert-butyl.

10 13. A compound according to any preceding claim, wherein W is NR_7 and wherein R_7 is as defined in claim 1.

14. A compound according to claim 13, wherein R_7 is hydrogen.

15 15. A compound according to any of claims 1 to 10, wherein W is NR_7 and wherein R_7 and R_5 together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted pyrrolidine group.

20 16. A compound according to any preceding claim, wherein R_6 is NR_8R_9 and wherein R_8 is hydrogen and R_9 is selected from hydrogen, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, and substituted or unsubstituted C_4 - C_{12} alkenynyl.

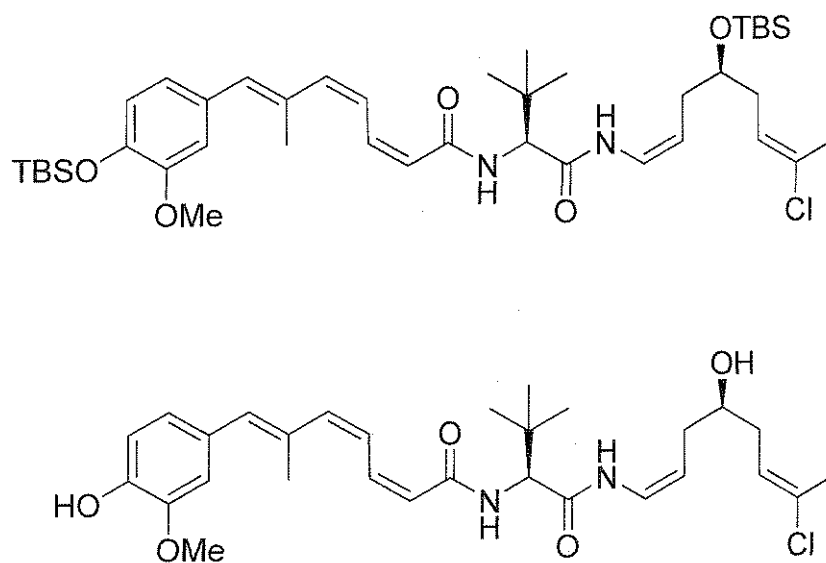
25

17. A compound according to claim 16, wherein R_9 is a substituted C_2 - C_{12} alkenyl that is substituted in one or more positions with halogen, OR' , $=O$, $OCOR'$, $OCONHR'$, $CONR'R'$, $CONHR'$, $CONR'R'$ and protected OH, wherein each of the R' groups is independently selected from
30 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 unsubstituted aryl.

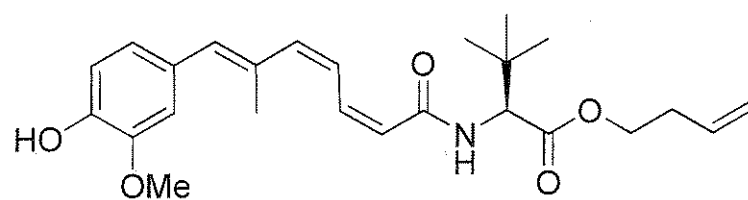
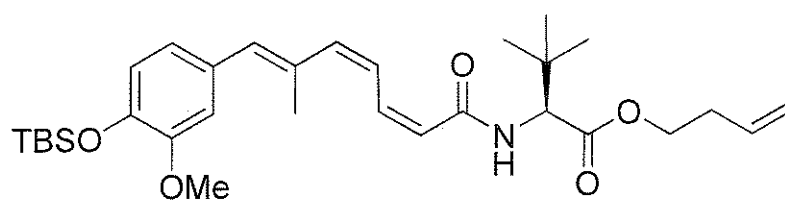
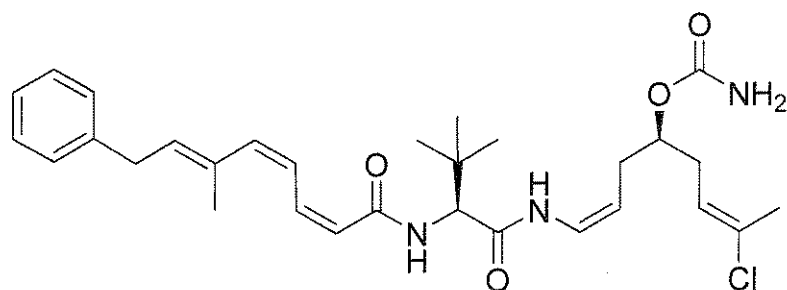
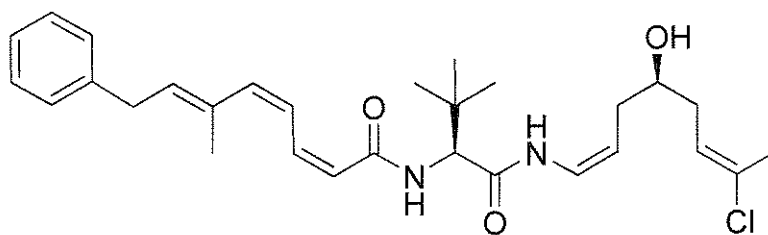
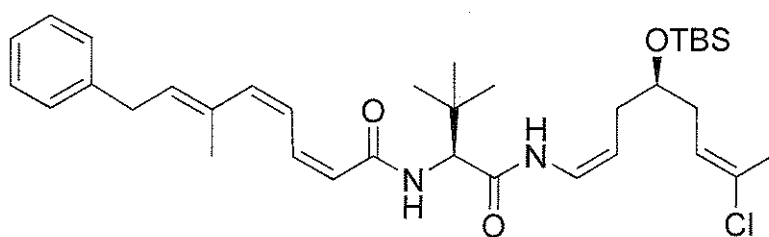
18. A compound according to any preceding claim, wherein one additional bond is present between the C atoms to which R₁ and R₂ are attached and another additional bond is present between the C atoms to which R₃ and R₄ are attached.

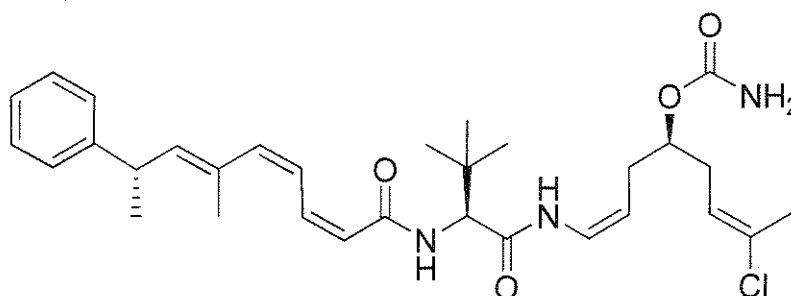
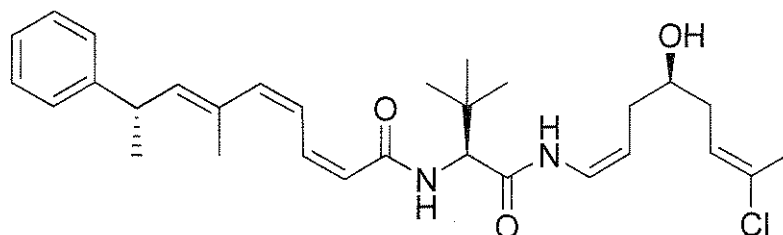
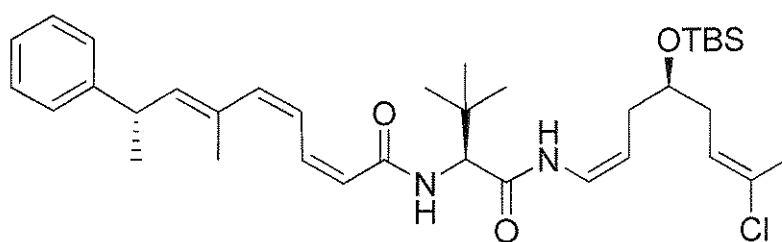
5

19. A compound according to claim 1, having the following formula



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

5

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

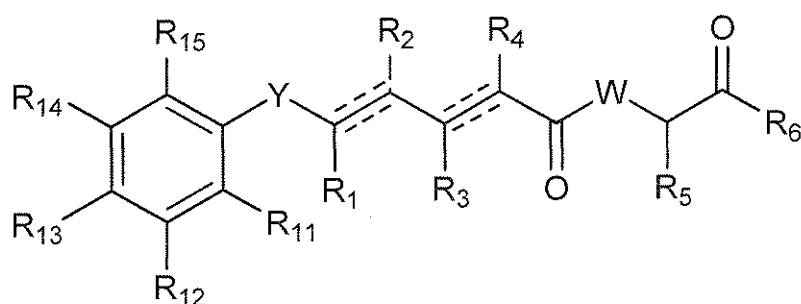
10

21. A compound or composition according to any of claims 1 to 20, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, for use as a medicament.

22. A compound or composition according to any of claims 1 to 20, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, for use in the treatment of cancer.

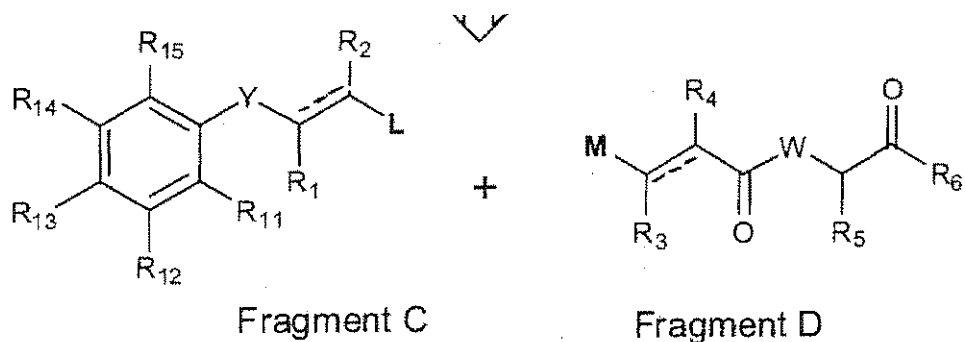
23. Use of a compound or composition according to any of claims 1 to 20, or pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer.

24. A process for the preparation of compounds according to formula I



as defined in any of claims 1 to 19 wherein Y, W and R₁, R₂, R₃, R₄, R₅, R₆, R₁₁, R₁₂, R₁₃, R₁₄ and R₁₅ are also as defined in any of claims 1 to 19

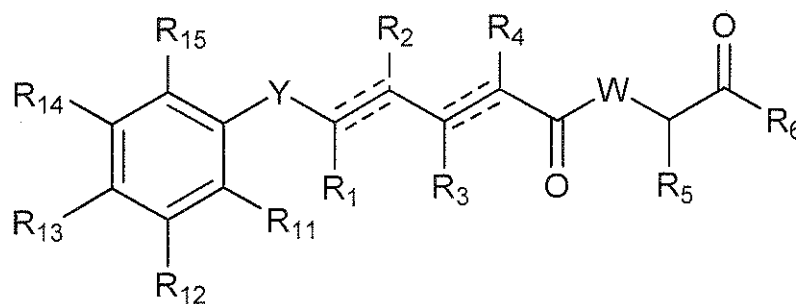
comprising the coupling of Fragments C and D



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , Y and W are the desired groups or an appropriate protecting group as needed, and L and M are the appropriate reacting or leaving groups.

- 5 25. A process according to claim 24, wherein the compound of formula I is any compound defined in claim 19.

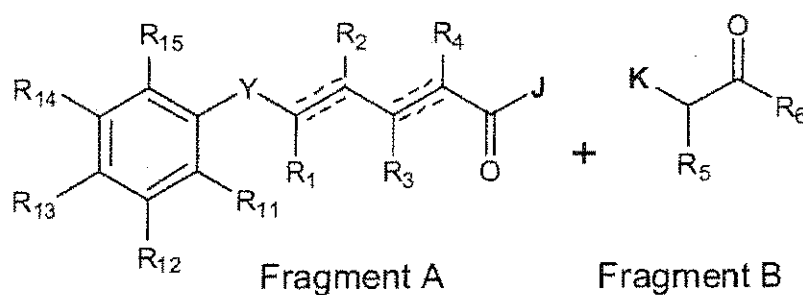
26. A process for the preparation of compounds according to formula I



10

as defined in any of claims 1 to 19 wherein Y , W and R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_{11} , R_{12} , R_{13} , R_{14} and R_{15} are also as defined in any of claims 1 to 19

- 15 comprising the coupling of Fragments A and B



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , and Y are the desired groups or an appropriate protecting group as needed, and J and K are the appropriate reacting or leaving groups.

20

27. A process according to claim 26, wherein the compound of formula I is any compound defined in claim 19.