

DIHYDRO-OR TETRAHYDROPYRAN DERIVATIVES USEFUL AS ANTI-CANCER COMPOUNDS

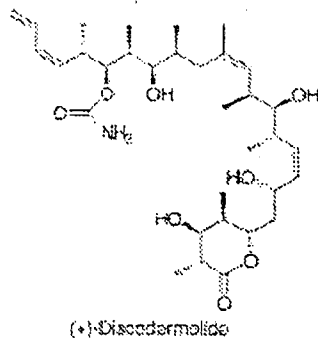
FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

10

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

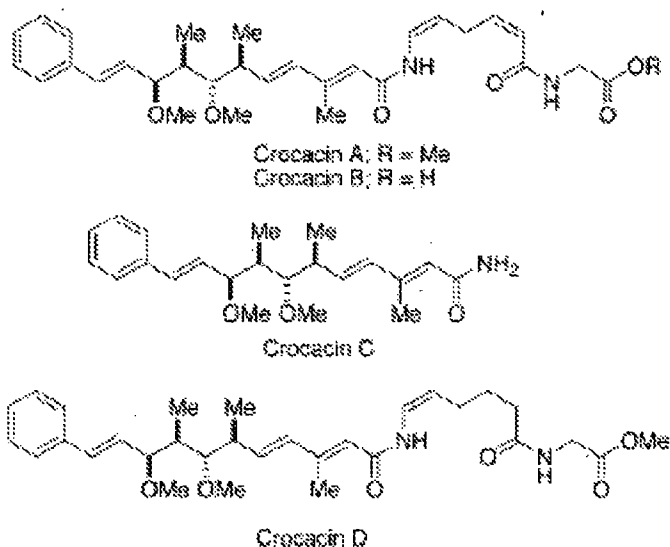


15

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

25

2 On the other hand, some unusual linear dipeptides containing a
 N-acyl enamide functionality have been isolated from a myxobacteria
 belonging to the *Chondromyces* genus (Kunze B et al. J. Antibiot. 1994, 47,
 881-886 and Jansen R et al. J. Org. Chem. 1999, 1085-1089). 5 Specifically,
 these compounds are crocacin A, B, C and D and are a group of electron
 transport inhibitors. [err[[err] Crocacin A-D moderately inhibit the
 growth of a few Gram- 10 positive bacteria and are potent inhibitors of
 animal cell cultures and several yeasts and fungi. The most active is
 crocacin D which showed a MIC of 1.4 ng/mL against the fungus *Saccharomyces*
cerevisiae and cytotoxicity (IC₅₀ of 0.06 mg/L) toward L929 mouse fibroblast
 cell culture. 15 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
 20 this regard, it is disclosed that L-thryptophan derivatives exhibited
 anxiolytic properties and the D-thryptophan derivatives, anxiogenic 3
 group of electron transport inhibitors.

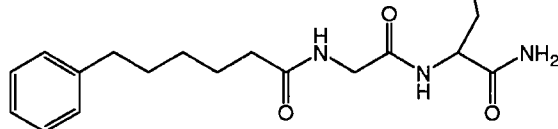


Crocacins A-D moderately inhibit the growth of a few Gram-
 10 positive bacteria and are potent inhibitors of animal cell cultures and
 several yeasts and fungi. The most active is crocacin D which showed a
 MIC of 1.4 ng/mL against the fungus *Saccharomyces cerevisiae* and
 strong toxicity (IC₅₀ of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

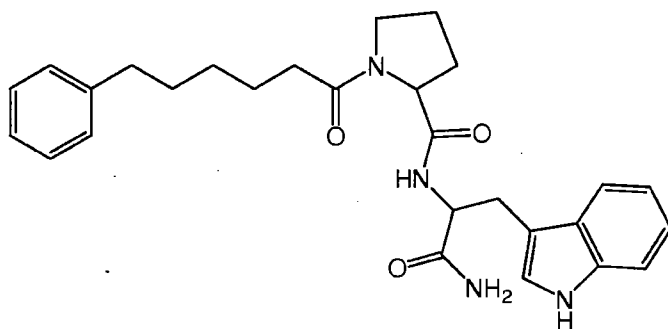
15

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
 20 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: and the following compounds were disclosed as intermediates in the synthesis of compounds R and U: 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 10 provide compounds that are useful in the treatment of cancer. SUMMARY OF THE INVENTION In one aspect, the present invention is directed to compounds of 15 general formula I or pharmaceutically acceptable salts, tautomers, prodrugs or stereoisomers thereof 5 (I) wherein Y is selected from -CHRay-, -CHRay-CHRby-, -CRay=CRby-, -CHRay-CHRby-CHRcy-, -CHIRay-CRby=CIRcy-, and -CHRay-CC-; 5 each Ray, Rby, and Rcy is independently selected from hydrogen, substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, and substituted or unsubstituted C2-C12 alkynyl;

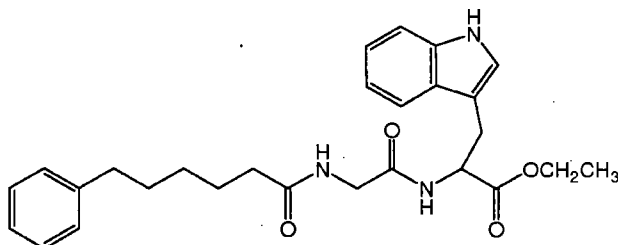


Compound R

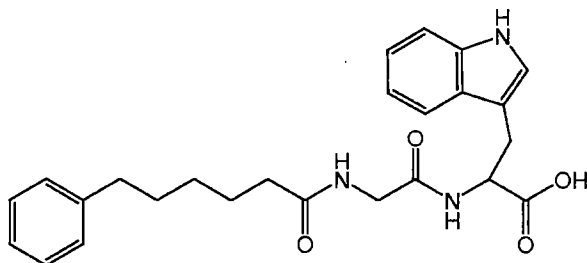


Compound U

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



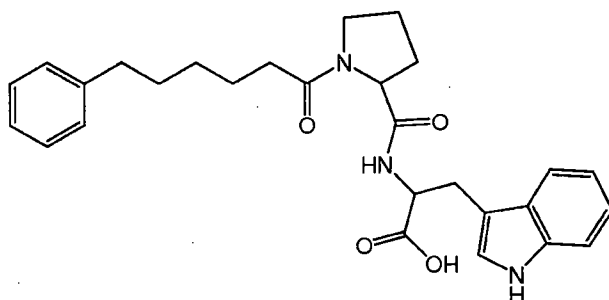
Compound S



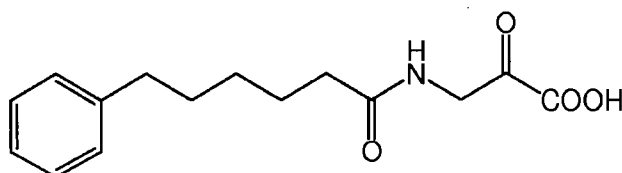
Compound T

10 each R₁, R₂, R₃, R₄, and R₅ is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; R₆ is selected from NR₈R₉, and OR₁₀; 15 A is selected from R₁₈ and 20 W is selected from 0 and NR₇; R₇ is selected from hydrogen, COR., COOR., substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅ together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group; R₈ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl; R₁₀ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, each dotted line represents an optional additional bond, but when a

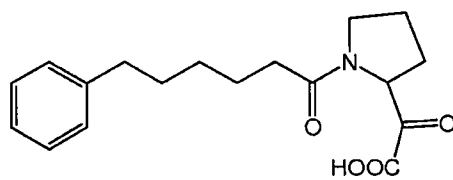
Compound V



Compound W



Compound Y



Compound Z.

5

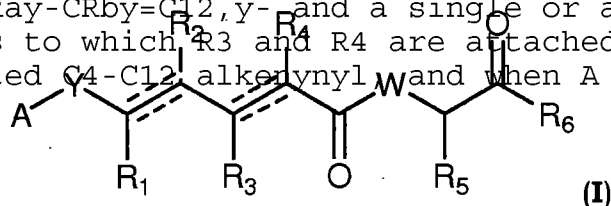
Cancer is a leading cause of death in animals and humans. Huge efforts have been and are still being undertaken in order to obtain an antitumor agent active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that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

SUMMARY OF THE INVENTION

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

15

triple bond exists between the C atoms to which R₁ and R₂ are attached, 15 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; and 20 when A is R₁₈, then R₉ is selected from hydrogen, COR_a, COOR., substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl, with the proviso that when Y is -CHRay-CHRby-CHRCy- or -CHRay-CRby=C₁₂, y- and a single or a double bond exists between the C atoms to which R₃ and R₄ are attached then R₉ is substituted or unsubstituted C₄-C₁₂ alkenynyl and when A is R₁₈



wherein Y is selected from -CHRay-, -CHRay-CHRby-, -CRay=CRby-, -C≡C-, -CHRay-CHRby-CHRCy-, -CHRay-CRby=CRcy-, and -CHRay-C≡C-;

5

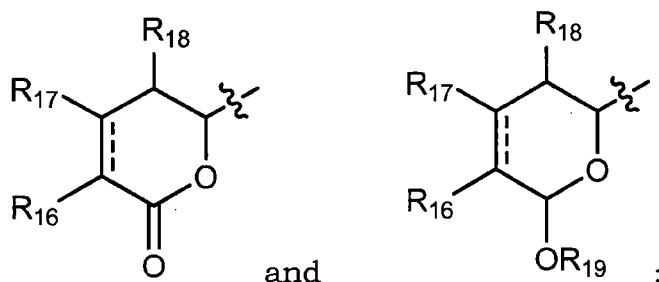
each Ray, Rby, and Rcy is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

10 each R₁, R₂, R₃, R₄, and R₅ is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

R₆ is selected from NR₈R₉, and OR₁₀;

15

A is selected from



20 W is selected from O and NR₇;

R₇ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅

OR19, then R9 is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl; each R₁₆, R₁₇ and R₁₈ are independently selected from hydrogen, OR_a, OCOR_a, OCOOR_a, NR_aR_b, NR_aCOR_b, and NR_aC(=NR_a)NR_aR_b, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; R₁₉ is selected from hydrogen, COR_a, COOR_a, CONR_aR_b, S(0)R_a, SO₂R_a, P(0)(R_a)OR_b, S(0)R_aOR_b, S(0)R_aR_bR_c, substituted or unsubstituted C₁-C₁₂ alkyl, 20 substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; and 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 C₁-C₁₂ heterocycloalkyl, substituted or unsubstituted C₂-C₁₂

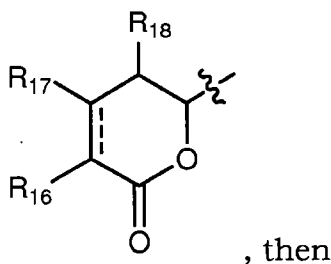
alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

R₁₀ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each dotted line represents an optional additional bond, but when a triple bond 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;

and

when A is



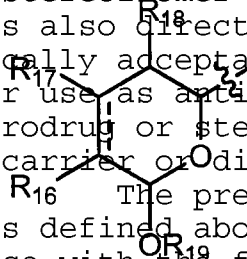
R₉ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl, with the proviso that when Y is -CHR_{ay}-CHR_{by}-CHR_{cy}- or -CHR_{ay}-CR_{by}=CR_{cy}- and a single or a double

In another aspect, the present invention is also directed to a compound of formula I, or a pharmaceutically acceptable salt, 5 tautomer, prodrug or stereoisomer thereof, for use as medicament. In another aspect, the present invention is also directed to a compound of formula I, or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof, for use as medicament for 10 treating cancer. In a further aspect, the present invention is also directed to the use of compounds of formula I, or pharmaceutically acceptable salts, tautomers, prodrugs or stereoisomers thereof, in the treatment of 15 cancer, or in the preparation of a medicament for the treatment of cancer. 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 20 individual a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof. In a yet further aspect, the present invention is also directed to a 25 compound of formula I, or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof, for use as anticancer agent. 9 pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof, together with a pharmaceutically acceptable carrier or diluent. 5 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to compounds of general formula I as defined above. 10 In these compounds the groups can be selected in accordance with the following guidance: Alkyl groups may be branched or unbranched, and preferably have from 1 to about 12 carbon atoms. One more preferred class of 15 alkyl groups has from 1 to about 6 carbon atoms. Even more preferred are alkyl groups selected from hydrogen, 1, COR_a, COOR_a, substituted methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl, sec-butyl and isobutyl are

unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl; when A is



10 alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl; each R₁₆, R₁₇ and R₁₈ are independently selected from hydrogen, OR_a, OCOR_a, OCOOR_a, NR_aR_b, NR_aC(=NR_a)NR_aR_b, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; R₁₉ is selected from hydrogen, COR_a, COOR_a, CONR_aR_b, S(O)R_a, SO₂R_a, P(O)(R_a)OR_b, SiR_aR_bR_c, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; and 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.

15 or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl;

20 substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; and

25 C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic group.

particularly preferred alkyl groups in the compounds of the present invention. Another preferred class of alkyl groups has from 6 to about 20 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. Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more 25 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. We define an 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. 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. Specifically preferred aryl groups include substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted 15 phenanthryl and substituted or unsubstituted anthryl. 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 compounds of the present invention contain from 6 to about 10 ring atoms, most preferably 6, 7 or 8 ring atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, 25 isquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, cancer, or in the preparation of a medicament for the treatment of cancer. 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

20 individual a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof.

25 In a yet further aspect, the present invention is also directed to a compound of formula I, or a pharmaceutically acceptable salt, tautomer, prodrug 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

11 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, oxepanyl, thiopanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6- tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 3H-pyranyl, 4Hpyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-10

azabicyclo[4.1.0]hept-7-yl, 2H-indolyl and allyl. 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(CO₂)₂, NHSO₂R', 15 NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, substituted

5 **DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS** substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic 20 group, wherein each of the R groups is independently selected from a group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, CO₂H, substituted as defined above, C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or 25 unsubstituted heterocyclic group.

10 In these compounds the groups can be selected in accordance with the foregoing list. Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I. 30 12 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, 1st Ed. George Thieme Verlag. These references provide sections on protecting groups for OH. All these 5 references are incorporated by reference in their entirety. Examples of such protected OH include 15 alkyl groups having 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 20 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.

Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more 25 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 30 preferably 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms.

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, 14 benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trichloroacetamidate, trifluoroacetate, methoxyacetate, tetrahydrothienyl, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, phenylacetate, tetrahydrothienopyranyl, piperidyl, morpholinyl, thiomorpholinyl, 5-propanoyl, 4-pentenoate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, 5p-bis(4-methoxyphenyl)hydroxymethylphenoxyllevulinate, pivaloate, 1-adamantosteoxepanyl, thiopanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-pyranyl, 4,6-trimethylbenzoate, 4-bromobenzoate, 2,5-difluorobenzoate, p-nitrobenzoate, tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 4-azidobutyrate, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, (2-azidomethyl)phenylacetate, 2-(tritylthio)oxymethylbenzoate, 24[(4-methoxytrityl)dihydropyranylmethyl]benzoate, 2-dihydrofuranyl, pyrazolidinyl, 2-methoxytritylthiomethylamino-methylbenzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxy)cyclo[4.1.0]hept-1-en-1-yl, 3H-indolyl, and quinolizinyl.

6-(levulinylloxymethyl)-3-methoxy-2-nitrobenzoate, 15 6-(levulinylloxymethyl)-3-methoxy-4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsilyloxybutyrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, or 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',
- 15 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
- 20 group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, CO₂H, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or
- 25 unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

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

30

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 references provide sections on protecting groups for OH. 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, 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-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *o*-bis(2-acetoxyethoxy)methyl, tetrahydropyranyl, fluorous 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-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-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*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-

[illegible]

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 geometrical isomers, tautomers, atropisomers, hydrates, solvates, polymorphs, and isotopically labelled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.¹⁻¹⁵

To provide a more concise description, some of the quantitative expressions given herein are not quantified by numbers, whether the term "about" is used explicitly or not; every quantity given herein is meant to refer to the actual value; 20 and it is also meant to refer to the approximate value based on the ordinary skill in the art, including equivalents and approximations due to experimental and/or measurement conditions for such given value.²⁵

In compounds of general formula I, particularly preferred Y is -CHRay-, -CRay-CRby-, and -CHRay-CRby=CREy-, wherein Ray, Rby,³⁰ and Rey are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred Ray, Rby, and Re y are hydrogen and substituted or unsubstituted Ci-Cb alkyl, and even more preferred Ray is hydrogen, substituted or unsubstituted methyl,³⁵ 19 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 pentyl.⁴⁰

The groups OR', SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'', ON, halogen, COR', COOR', OCOR', OCONHR', CONR''R', CONHR', CONP(R''), protected OH, substituted or unsubstituted aryl,⁴⁵ 01-012 alkyl, substituted or unsubstituted 02-012 alkenyl, substituted or unsubstituted 02-012 alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R'⁵⁰ groups is independently selected from the group consisting of hydrogen, OH, NO₂, NHCOAcetoxyethyl]benzoate, alkyl 2-[2-chloroacetoxyethyl]benzoate, unsubstituted 01-012 alkyl, substituted (benzyloxy)ethyl]benzoate,

(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 4-(methoxyethoxymethyl)butyrate, 2-methylphenoxymethyl]benzoate, 2-trichloroacetoxymethyl]benzoate, alkyl 2-[2-chloroacetoxyethyl]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-

butoenoate, o-(methoxycarbonyl)]benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphordiamidate, and 2-chlorobenzoate. In the case of sulfonates, sulfenates and sulfinates the protecting group for the OH can be selected from sulfate, allylsulfonate, methanesulfonate, benzysulfonate, tosylate, 2-[(4-nitrophenyl)ethyl)sulfonate, 2-trifluoromethylbenzenesulfonate, 4-monomethoxytritlysulfenate, alkyl 2,4-

dinitrophenylsulfenate, 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate, borate, and dimethylphosphinothiolyl. In the case of carbonates the

5 butyl. 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. 15 Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. 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 and prodrugs can be carried out by methods known in the art. 25 In compounds wherein A is R18 22 When Y is a) -CHRay-, -CHRay-CHRby-, -CRay=CRby-, or -CHRay-CC-; or b) -CHRay-CHRby-CHRey- or -CHRay-CRby=ClRcy-, and a triple bond exists between the C atoms to which R9 and R10 are attached, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety, by conventional chemical methods. 10 Generally such salts are, for example, prepared by reacting the free

- acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of 15 the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and *p*-toluenesulfonate. 20 Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkyl ethanolamine, triethanolamine and basic amino acids salts.

25

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

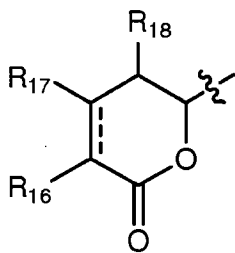
30

Any compound that is a prodrug of a compound of formula I is within the scope and spirit of the invention. The term "prodrug" as

5 3- [2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are the most preferred substituents for these alkenynyl groups. Particularly preferred R₁₆ is hydrogen, OR, and OCOR, wherein R, is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ 10 alkyl. Particularly preferred R, 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, OH and methoxy are the most preferred R₁₆ groups. 15 Particularly preferred R₁₇ and R₁₈ are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₁₇ and R₁₈ are hydrogen and substituted or unsubstituted C₁-C₆ alkyl. More preferred R₁₇ and R₁₈ are hydrogen and even more preferred are hydrogen. 20 On the other hand, in compounds wherein A is 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, 27 substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl. The preferred substituted alkyl, substituted alkenyl, substituted alkenyl, and substituted alkenynyl may present not only one 5 but two or more substituents. More preferred alkyl groups are those having from 9 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are preferred heterocyclic 6 group is a heterocyclic group even more preferably 7, 8 10 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 15 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, 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 20 alkenynyl 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 atoms. Oct-1-en-7-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, hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said alkyl, alkenyl, alkynyl and alkenynyl groups are OR, =O, SR, SO₂R', NO₂, NHR', NR', R', N(R')₂, NHCOR', N(COR')₂, NHSO₂R', NR'(C(=NR')N(R')₂), CN, halogen, COR', COOR', OCOR', invention.

25

In compounds wherein A is



5 butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1, 1, 3,3-tetraisopropyl- [2 - (triphenylmethoxy)ethoxy] disiloxane- 1 -yl, and
 fluorosilyl, are the most preferred substituents for these alkyl,
 alkenyl, alkynyl and alkenynyl groups. 10 Particular preferred R₁₆ is
 hydrogen, OR_a and OCOR_a, wherein R_a is selected from hydrogen and
 substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is
 hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more
 preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl,
 including *tert*-butyl. 15 Hydrogen, OH and methoxy are the most preferred
 R₁₆ groups. Particularly preferred R₁₇ and R₁₈ are hydrogen and substituted
 or unsubstituted C₁-C₁₂ alkyl and particularly preferred R₁₉ is hydrogen,
 substituted or unsubstituted C₁-C₁₂ alkyl, and COR_a, wherein R_a is
 substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₁₇ and R₁₈ are
 hydrogen and substituted or unsubstituted C₁-C₆ alkyl and more preferred
 R₁₉ are hydrogen, substituted or unsubstituted C₁-C₆ alkyl, protected OH, substituted or
 wherein R_a is a substituted or unsubstituted C₁-C₆ alkyl. Particularly
 preferred R_a is methyl, ethyl, propyl, isopropyl and butyl, 25 including
tert-butyl. Even more preferred R₁₇, R₁₈ and R₁₉ are hydrogen, substituted or
 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
 and R₄ are groups 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
 15 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
 20 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂
 alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or
 unsubstituted aryl. Even more preferred substituents for these alkyl,
 alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCONHR',
 OCONR'R', CONHR', CONR'R', and protected OH wherein the protecting
 25 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-
 30 pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-
 hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-
 butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-

30 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. 5 More particularly, preferred compounds of general formula I are those also having general formula IA or pharmaceutically acceptable salts, tautomers, prodrugs or stereoisomers thereof 10 R₁ (IA) wherein Y is selected from -CHRay- -CHRay- CHRby- -CRay=CRby-, -C H Ray- CHRby- -CHRCy- -CHRay- CRby, = C Rey-, and -CHRay-C-C-; each Ray, Rby, and Rcy is independently selected from hydrogen, 15 substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein each of the R' groups is more preferably selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, R₆ is selected from NR₈R₉ and R₁₀, W is selected from 0 and NR₇, 25 31 alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅ together with the corresponding protecting group for the OH is preferably selected from a substituted or unsubstituted heterocyclic group.

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-
 10 pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are the most preferred substituents for these alkyl, alkenyl, alkynyl and
 15 alkenynyl groups.

When Y is -CHRay-CHRby-CHRCy- or -CHRay-CRby=CRcy- and a single or a double bond exists between the C atoms to which R₃ and R₄ are attached, then R₉ is substituted or unsubstituted C₄-C₁₂ alkenynyl.
 20 The preferred substituted alkenynyl may present not only one but two or more substituents. More preferred alkenynyl groups are those having from 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-
 25 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 alkenynyl groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NRR', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR',
 30 COOR', OCOR', OCONHR', OCONRR', CONHR', CONRR', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted

5 each R8 and R9 are independently selected from hydrogen, CORa, COORa, substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, substituted or unsubstituted C2-C12 alkynyl, and substituted or unsubstituted C4-C12 alkenynyl, with the proviso that when Y is -CHRay-CHRby-CHRCy- or -CHRay-CRby=CRey- and 10 a single or a double bond exists between C3 and C4, then R9 is substituted or unsubstituted C4-C12 alkenynyl; R10 is selected from hydrogen, substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, and substituted or unsubstituted C2-C12 alkynyl; R16 is selected from hydrogen, ORa, OCORa, OCONHRa, OCONR'R', CONHR', CONR'R', 15 or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R groups is independently selected from the substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, and substituted or unsubstituted C2-C12 alkynyl, and each Ra and Rb 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. 20 In compounds of general formula I, each R group is independently selected from hydrogen, substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, and substituted or unsubstituted C2-C12 alkynyl, and each Ra and Rb 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. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. Particularly preferred Ray, Rby, and Rcy are hydrogen and substituted or unsubstituted C1-C12 alkyl. More preferred Ray, Rby, and Rcy are hydrogen and substituted or unsubstituted C1-C6 alkyl, and

10 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

15 substituents for these 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,

20 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- 25 3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and wherein each of the R' groups is more preferably selected from hydrogen, unsubstituted C1-C6 alkyl, and substituted or unsubstituted aryl. Cl, OH, =O, OCONH2, OCONHPhenyl, and protected OH wherein

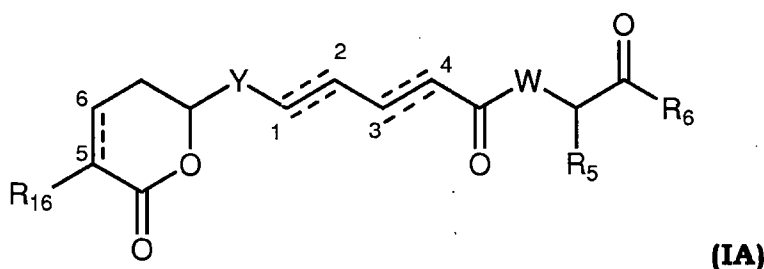
the protecting group for the OH is preferably selected from 30 trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, t-butylldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl,

5 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 10 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 15 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 20 or unsubstituted C₂-C₁₂ alkenyl, 5,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220,1221,1222,1223,1224,1225,1226,1227,1228,1229,1230,1231,1232,1233,1234,1235,1236,1237,1238,1239,1240,1241,1242,1243,1244,1245,1246,1247,1248,1249,1250,1251,1252,1253,1254,1255,1256,1257,1258,1259,1260,1261,1262,1263,1264,1265,1266,1267,1268,1269,1270,1271,1272,1273,1274,1275,1276,1277,1278,1279,1280,1281,1282,1283,1284,1285,1286,1287,1288,1289,1290,1291,1292,1293,1294,1295,1296,1297,1298,1299,1300,1301,1302,1303,1304,1305,1306,1307,1308,1309,1310,1311,1312,1313,1314,1315,1316,1317,1318,1319,1320,1321,1322,1323,1324,1325,1326,1327,1328,1329,1330,1331,1332,1333,1334,1335,1336,1337,1338,1339,1340,1341,1342,1343,1344,1345,1346,1347,1348,1349,1350,1351,1352,1353,1354,1355,1356,1357,1358,1359,1360,1361,1362,1363,1364,1365,1366,1367,1368,1369,1370,1371,1372,1373,1374,1375,1376,1377,1378,1379,1380,1381,1382,1383,1384,1385,1386,1387,1388,1389,1390,1391,1392,1393,1394,1395,1396,1397,1398,1399,1400,1401,1402,1403,1404,1405,1406,1407,1408,1409,1410,1411,1412,1413,1414,1415,1416,1417,1418,1419,1420,1421,1422,1423,1424,1425,1426,1427,1428,1429,1430,1431,1432,1433,1434,1435,1436,1437,1438,1439,1440,1441,1442,1443,1444,1445,1446,1447,1448,1449,1450,1451,1452,1453,1454,1455,1456,1457,1458,1459,1460,1461,1462,1463,1464,1465,1466,1467,1468,1469,1470,1471,1472,1473,1474,1475,1476,1477,1478,1479,1480,1481,1482,1483,1484,1485,1486,1487,1488,1489,1490,1491,1492,1493,1494,1495,1496,1497,1498,1499,1500,1501,1502,1503,1504,1505,1506,1507,1508,1509,1510,1511,1512,1513,1514,1515,1516,1517,1518,1519,1520,1521,1522,1523,1524,1525,1526,1527,1528,1529,1530,1531,1532,1533,1534,1535,1536,1537,1538,1539,1540,1541,1542,1543,1544,1545,1546,1547,1548,1549,1550,1551,1552,1553,1554,1555,1556,1557,1558,1559,1560,1561,1562,1563,1564,1565,1566,1567,1568,1569,1570,1571,1572,1573,1574,1575,1576,1577,1578,1579,1580,1581,1582,1583,1584,1585,1586,1587,1588,1589,1590,1591,1592,1593,1594,1595,1596,1597,1598,1599,1600,1601,1602,1603,1604,1605,1606,1607,1608,1609,1610,1611,1612,1613,1614,1615,1616,1617,1618,1619,1620,1621,1622,1623,1624,1625,1626,1627,1628,1629,1630,1631,1632,1633,1634,1635,1636,1637,1638,1639,1640,1641,1642,1643,1644,1645,1646,1647,1648,1649,1650,1651,1652,1653,1654,1655,1656,1657,1658,1659,1660,1661,1662,1663,1664,1665,1666,1667,1668,1669,1670,1671,1672,1673,1674,1675,1676,1677,1678,1679,1680,1681,1682,1683,1684,1685,1686,1687,1688,1689,1690,1691,1692,1693,1694,1695,1696,1697,1698,1699,1700,1701,1702,1703,1704,1705,1706,1707,1708,1709,1710,1711,1712,1713,1714,1715,1716,1717,1718,1719,1720,1721,1722,1723,1724,1725,1726,1727,1728,1729,1730,1731,1732,1733,1734,1735,1736,1737,1738,1739,1740,1741,1742,1743,1744,1745,1746,1747,1748,1749,1750,1751,1752,1753,1754,1755,1756,1757,1758,1759,1760,1761,1762,1763,1764,1765,1766,1767,1768,1769,1770,1771,1772,1773,1774,1775,1776,1777,1778,1779,1780,1781,1782,1783,1784,1785,1786,1787,1788,1789,1790,1791,1792,1793,1794,1795,1796,1797,1798,1799,1800,1801,1802,1803,1804,1805,1806,1807,1808,1809,1810,1811,1812,1813,1814,1815,1816,1817,1818,1819,1820,1821,1822,1823,1824,1825,1826,1827,1828,1829,1830,1831,1832,1833,1834,1835,1836,1837,1838,1839,1840,1841,1842,1843,1844,1845,1846,1847,1848,1849,1850,1851,1852,1853,1854,1855,1856,1857,1858,1859,1860,1861,1862,1863,1864,1865,1866,1867,1868,1869,1870,1871,1872,1873,1874,1875,1876,1877,1878,1879,1880,1881,1882,1883,1884,1885,1886,1887,1888,1889,1890,1891,1892,1893,1894,1895,1896,1897,1898,1899,1900,1901,1902,1903,1904,1905,1906,1907,1908,1909,1910,1911,1912,1913,1914,1915,1916,1917,1918,1919,1920,1921,1922,1923,1924,1925,1926,1927,1928,1929,1930,1931,1932,1933,1934,1935,1936,1937,1938,1939,1940,1941,1942,1943,1944,1945,1946,1947,1948,1949,1950,1951,1952,1953,1954,1955,1956,1957,1958,1959,1960,1961,1962,1963,1964,1965,1966,1967,1968,1969,1970,1971,1972,1973,1974,1975,1976,1977,1978,1979,1980,1981,1982,1983,1984,1985,1986,1987,1988,1989,1990,1991,1992,1993,1994,1995,1996,1997,1998,1999,2000,2001,2002,2003,2004,2005,2006,2007,2008,2009,2010,2011,2012,2013,2014,2015,2016,2017,2018,2019,2020,2021,2022,2023,2024,2025,2026,2027,2028,2029,2030,2031,2032,2033,2034,2035,2036,2037,2038,2039,2040,2041,2042,2043,2044,2045,2046,2047,2048,2049,2050,2051,2052,2053,2054,2055,2056,2057,2058,2059,2060,2061,2062,2063,2064,2065,2066,2067,2068,2069,2070,2071,2072,2073,2074,2075,2076,2077,2078,2079,2080,2081,2082,2083,2084,2085,2086,2087,2088,2089,2090,2091,2092,2093,2094,2095,2096,2097,2098,2099,2100,2101,2102,2103,2104,2105,2106,2107,2108,2109,2110,2111,2112,2113,2114,2115,2116,2117,2118,2119,2120,2121,2122,2123,2124,2125,2126,2127,2128,2129,2130,2131,2132,2133,2134,2135,2136,2137,2138,2139,2140,2141,2142,2143,2144,2145,2146,2147,2148,2149,2150,2151,2152,2153,2154,2155,2156,2157,2158,2159,2160,2161,2162,2163,2164,2165,2166,2167,2168,2169,2170,2171,2172,2173,2174,2175,2176,2177,2178,2179,2180,2181,2182,2183,2184,2185,2186,2187,2188,2189,2190,2191,2192,2193,2194,2195,2196,2197,2198,2199,2200,2201,2202,2203,2204,2205,2206,2207,2208,2209,2210,2211,2212,2213,2214,2215,2216,2217,2218,2219,2220,2221,2222,2223,2224,2225,2226,2227,2228,2229,2230,2231,2232,2233,2234,2235,2236,2237,2238,2239,2240,2241,2242,2243,2244,2245,2246,2247,2248,2249,2250,2251,2252,2253,2254,2255,2256,2257,2258,2259,2260,2261,2262,2263,2264,2265,2266,2267,2268,2269,2270,2271,2272,2273,2274,2275,2276,2277,2278,2279,2280,2281,2282,2283,2284,2285,2286,2287,2288,2289,2290,2291,2292,2293,2294,2295,2296,2297,2298,2299,2300,2301,2302,2303,2304,2305,2306,2307,2308,2309,2310,2311,2312,2313,2314,2315,2316,2317,2318,2319,2320,2321,2322,2323,2324,2325,2326,2327,2328,2329,2330,2331,2332,2333,2334,2335,2336,2337,2338,2339,2340,2341,2342,2343,2344,2345,2346,2347,2348,2349,2350,2351,2352,2353,2354,2355,2356,2357,2358,2359,2360,2361,2362,2363,2364,2365,2366,2367,2368,2369,2370,2371,2372,2373,2374,2375,2376,2377,2378,2379,2380,2381,2382,2383,2384,2385,2386,2387,2388,2389,2390,2391,2392,2393,2394,2395,2396,2397,2398,2399,2400,2401,2402,2403,2404,2405,2406,2407,2408,2409,2410,2411,2412,2413,2414,2415,2416,2417,2418,2419,2420,2421,2422,2423,2424,2425,2426,2427,2428,2429,2430,2431,2432,2433,2434,2435,2436,2437,2438,2439,2440,2441,2442,2443,2444,2445,2446,2447,2448,2449,2450,2451,2452,2453,2454,2455,2456,2457,2458,2459,2460,2461,2462,2463,2464,2465,2466,2467,2468,2469,2470,2471,2472,2473,2474,2475,2476,2477,2478,2479,2480,2481,2482,2483,2484,2485,2486,2487,2488,2489,2490,2491,2492,2493,2494,2495,2496,2497,2498,2499,2500,2501,2502,2503,2504,2505,2506,2507,2508,2509,2510,2511,2512,2513,2514,2515,2516,2517,2518,2519,2520,2521,2522,2523,2524,2525,2526,2527,2528,2529,2530,2531,2532,2533,2534,2535,2536,2537,2538,2539,2540,2541,2542,2543,2544,2545,2546,2547,2548,2549,2550,2551,2552,2553,2554,2555,2556,2557,2558,2559,2560,2561,2562,2563,2564,2565,2566,2567,2568,2569,2570,2571,2572,2573,2574,2575,2576,2577,2578,2579,2580,2581,2582,2583,2584,2585,2586,2587,2588,2589,2590,2591,2592,2593,2594,2595,2596,2597,2598,2599,2600,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2611,2612,2613,2614,2615,2616,2617,261

34 Particularly preferred W is NR7 wherein R7 is as defined before. Particularly preferred R6 is NR8R9, wherein R8 and R9 are as defined before. 5 Particularly preferred R7 and R8 are hydrogen and substituted or unsubstituted C1-C12 alkyl. More preferred R7 and R8 are hydrogen and substituted or unsubstituted C1-C6 alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen is the most preferred. In another embodiment, 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 group, wherein each of the R groups is independently selected from the 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. 20 When Y is a) -CHRay-, 5-CHRay-CRby-CHRy-, substituted or unsubstituted C2-C12 alkenyl, substituted or unsubstituted C2-C12 alkynyl, substituted or unsubstituted C2-C12 alkenyl, substituted or unsubstituted C2-C12 alkynyl, and a triple bond exists between C3 and C4, then particularly preferred R9 is hydrogen, substituted or unsubstituted C1-C12 alkyl, substituted or unsubstituted C2-C12 alkenyl, substituted or unsubstituted C2-C12 alkynyl, 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, 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 heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. 10 and alkenynyl groups are halogen, OR', =O, 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 heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. 15

- unsubstituted aryl. Even more preferred substituents for these alkyl, 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 the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-
- 20
- 25
- 30

pyrenylmethoxysilyl, tris (trimethylsilyl) silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and wherein each of the R' groups is more preferably selected from hydrogen, unsubstituted C1-C6 alkyl, and substituted or unsubstituted aryl, Cl, OH, =O, OCONH2, OCONHPhenyl, and protected OH wherein the protecting group for the OH is preferably selected from 25 trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, and 2 mixtures of the isomers fall within the scope of the present invention. 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. Most particularly, preferred compounds of general formula I are those also having general formula IA or pharmaceutically acceptable salts, tautomers, prodrugs or stereoisomers thereof



10

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 C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

R_5 is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

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

W is selected from O and NR_7 ;

25

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂

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 alkenynyl groups are halogen, OR', =O, OCOR'', OCONHR', OCONR'R', CONHR', CONR'R', 30 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 alkenynyl groups are halogen, OR', =O, OCOR'', OCONR'R', CONHR', CONR'R', and protected OH, wherein the protecting group for the OH is preferably selected from trimethylsilyl, 5 triethylsilyl, triisopropylsilyl, even more preferred is hydrogen, substituted or unsubstituted methyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, tbutyldimethylsilyl, substituted or unsubstituted ethyl, substituted or unsubstituted t-butylsilyl, triphenylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, substituted or unsubstituted isopropyl, and substituted or pyrenylmethoxysilyl, tri s (trime thylsilyl) s fly' (2- 10 hydroxystyryl)dimethylsilyl, (2 -hydroxystyryl)diisopropylsilyl, tbutylmethoxyphenylsilyl, 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 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, and 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

3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are 25 the most preferred substituents for these alkenynyl groups. Particular preferred R₁₆ is hydrogen, OR, and OCOR, wherein R is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R is hydrogen and substituted or 30 unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R₁₆ groups. 39 Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. More preferred is the presence of one additional bond between C₁ and C₂, and/or the presence of one or two additional bonds between C₃ and C₄, and/or the presence of one additional bond between C₅ and C₆. 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. 5 10 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 15OR19 (IB) wherein Y is selected from -CH₂Ray, -CH₂Rby, -CH₂Ray-CH₂Rby-, -CH₂Ray-CH₂Rby-, -CH₂Ray-CH₂Rby=CRcy-, and -CH₂Ray-C≡C-; 20 each Ray, Rby, and Rcy is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; R₅ is selected from hydrogen, 10 substituted or unsubstituted tert-butyl, 25 substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; R₆ is selected from NR₈R₉, and R₁₀;

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', 15 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, 20 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 25 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 30 preferred R₅ groups, and even most preferred methyl, isopropyl, and tert-butyl.

40 W is selected from 0 and NR₇; R₇ is selected from hydrogen, CORa, COORa, substituted or 5 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅ together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group; 10 each R₈ and R₉ are independently selected from hydrogen, CORa, COORa, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl; 15 R₁₀ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; R₁₆ is selected from hydrogen, CORa, COORa, NRa, NRaCORb, 20 and NRaC(=NRa)NRaRb, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl; R₁₉ is selected from hydrogen, CORa, COORa, CONRaRb, S(O)Ra, SO₂R₃, 25 P(O)(Ra)ORb, SiRaRbRc, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl. More preferred R₇ and R₈ are hydrogen and independently selected from hydrogen, 30 substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₄-C₁₂ alkenynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic group; and each dotted line represents 40 butyl. Hydrogen is the most preferred. In compounds of general formula IB, particularly preferred Y is -CHRay-, -CRay=CRby-, and -CHRay-CRby=CIRcy-, wherein Ray, Rby, and Rcy are as defined before.

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.

20

When Y is a) -CHRay-, -CHRay-CHRby-, -CRay=CRby-, -C≡C-, or -CHRay-C≡C-; or b) -CHRay-CHRby-CHRcy- or -CHRay-CRby=CRcy- and a triple bond exists between C₃ and C₄, then particularly preferred R₉ is hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or 25 unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl. More preferably is hydrogen, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl. The preferred substituted alkyl, 30 substituted alkenyl, substituted alkynyl and substituted alkenynyl may present not only one but two or more substituents. More preferred alkyl groups are those having from 6 to about 10 carbon atoms; and

alkynyl, substituted or unsubstituted aryl, and substituted or 30 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 42 OH, SCH₃, SH, NH₂, NHC(=NH)NH₂, CONH₂, COOH, phenyl, p-, m- or ohydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen and methyl are the most preferred Ray, Rby, and Ray groups. Specifically, when Y is -CHRay- then 5 particularly preferred Ray is methyl, when Y is -CRay=CRoy- then particularly preferred Ray is hydrogen and particularly preferred Rby is methyl, and when Y is -CHRay-CRby=CRcy- then particularly preferred Ray is hydrogen or methyl, particular preferred Rby is hydrogen, and particularly preferred Rcy is methyl. 10 More preferred substituents for the above mentioned alkenyl, alkynyl and alkenynyl groups are halogen, OR', =O, OCONR', OCONHR', OCONR'R', CONHR', CONR'R', and protected OH, wherein each of the R' substituted or unsubstituted methyl, substituted or 15 unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl and substituted or unsubstituted butyl, including substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₂-C₁₂ alkenynyl and substituted or unsubstituted aryl. Even more preferred substituents for said groups are OR', =O, SR', SOR', SO₂R', 20 NO₂, NHR', NR'R', N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R',

- 10 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 the protecting group for the OH is preferably selected from
- 25 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

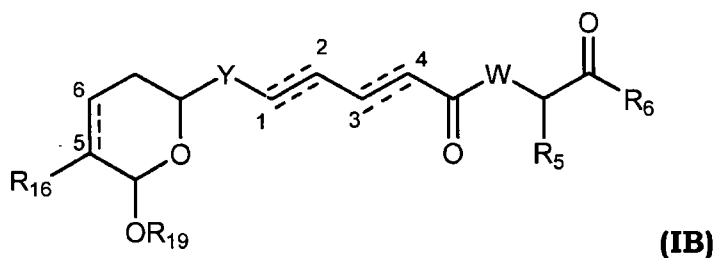
Particularly preferred R7 and R8 are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R7 and R8 are hydrogen and 15 substituted or unsubstituted C₁-C₆ alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tertbutyl. Hydrogen is the most preferred. In another embodiment, it is particularly preferred that R7 and R5 20 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, 25 most preferably 5, 6 or 7 ring atoms. A pyrrolidine group is the most preferred. Particularly preferred R₉ is hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ 30 alkenyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkenynyl, and dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, triphenylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethoxysilyl, di-*t*-butylmethoxysilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and wherein each of the R' groups is more preferably selected from hydrogen, unsubstituted C₁-C₆ alkyl, and substituted or unsubstituted aryl, Cl, OH, =O, OCONH₂, OCONHPhenyl, and protected OH wherein the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethoxysilyl, di-*t*-butylmethoxysilyl, 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 alkenynyl groups.

Particular preferred R₁₆ is hydrogen, OR_a and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a 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, OH and methoxy are the most preferred R₁₆ groups.

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, 10 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. 15 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 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, oct-1-en-2-ynyl, oct-1-en-1-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, non-1-en-2-ynyl, non-1-en-1-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, hept-1-en-3-ynyl, hept-1-en-2-ynyl, and hept-1-en-1-ynyl are the most preferred alkenynyl groups. Particularly preferred is the presence of one or more additional bands in the places indicated with a dotted line. More 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, and/or the presence of one additional bond between C₅ and C₆. In addition, the stereochemistry of each double bond may exist as (E) or (Z). The single substituents for said alkyl, alkenyl, alkynyl and alkenynyl groups are isomers and mixtures of the isomers fall within the scope of the present invention.

10

Another particular preferred compounds of general formula I are those having general formula **IB** or pharmaceutically acceptable salts, tautomers, prodrugs or stereoisomers thereof



15

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 $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$;

20 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, 25 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} ;

OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR)₁₂,
 NHSO₂R', NR'C(=NR)NR'R', CN, halogen, COR', COOR', OCOR', OCONHR',
 OCONR'R', CONHR', CONR'R', protected OH, substituted or 30 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 40 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
 C_i-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', 10 OCONR'R',
 CONHR', CONR'R', unsubstituted C_i-C₆ alkyl, substituted or unsubstituted C₂-C₁₂
 alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅
 together with the corresponding N atom and C atom to which they are
 attached may form a substituted or unsubstituted heterocyclic group; CONR'R',
 and protected OH wherein the protecting group for the OH is preferably
 selected from trimethylsilyl, triethylsilyl, triisopropylsilyl,
 dimethylisopropylsilyl, and R_d are independently selected from hydrogen, 15 COR_a,
 2-norbornyldimethylsilyl, t-butyltrimethylsilyl, t- 20
 butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl,
 diphenylmethylsilyl, di-t-butylmethylsilyl, substituted (or unsubstituted C₂-C₁₂
 pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-
 hydroxystyryl)methylsilyl, (2-oxystyryl)silyl, triisopropylsilyl, t-
 butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl- 25
 3[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, and
 wherein each R_i is selected from hydrogen, substituted or unsubstituted C_i-C₆
 unsubstituted C_i-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: 30 trimethylsilyl, triethylsilyl,
 triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl,
 dimethylhexylsilyl, 2-norbornyldimethylsilyl, tbutyldimethylsilyl,
 t-butyl-diphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl

R₁₆ is selected from hydrogen, OR_a, OCOR_a, OCOOR_a, NR_aR_b, NR_aCOR_b,
 20 and NR_aC(=NR_a)NR_aR_b, substituted or unsubstituted C₁-C₁₂ alkyl,
 substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or
 unsubstituted C₂-C₁₂ alkynyl;

R₁₉ is selected from hydrogen, COR_a, COOR_a, CONR_aR_b, S(O)R_a, SO₂R_a,
 25 P(O)(R_a)OR_b, SiR_aR_bR_c, substituted or unsubstituted C₁-C₁₂ alkyl,
 substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or
 unsubstituted C₂-C₁₂ alkynyl; and

each R_a, R_b and R_c are independently selected from hydrogen,
 30 substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted
 C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted

46 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- 5 3- [2- (triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are the most preferred substituents for these alkyl, alkenyl, alkynyl and alkenynyl groups. Particular preferred R₁₆ is hydrogen, OR_a and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted Ci-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted Ci-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R₁₆ groups. 15 Particularly preferred R₁₉ is hydrogen, substituted or unsubstituted Ci-C₁₂ alkyl and COR_a, wherein R_a is a substituted or unsubstituted Ci-C₁₂ alkyl. More preferred R₁₉ is hydrogen, substituted or unsubstituted C₁-C₆ alkyl and COR_a, wherein R_a is a substituted or unsubstituted Ci-C₆ alkyl. Particularly preferred R_a is methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Even more preferred R₁₉ is hydrogen, COR_{ay}, CR_{ay}-CR_{by}, and CHR_{ay}-CR_{by}-CR_{cy}, wherein R_{ay}, R_{by}, and R_{cy} are as defined before. 20 In compounds of general formula IB, particularly preferred Y is each dotted line represents an optional additional bond. Particularly preferred R_{ay} and R_{by} are 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. 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

- 15 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',
- 20 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
- 25 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
- 30 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

\./ R2 Fragment C - Fragment D Scheme A where R₁, R₂, R₃, R₄, R₅, R₆, A, Y and W are the desired groups or an 10 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: 15 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). 20 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, New York, 1994).

OH, SCH₃, SH, NH₂, NHCl=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

- 5 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.

10

- Particularly preferred R₅ is hydrogen and substituted or 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
- 15 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',
- 20 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
- 25 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
- 30 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

48 Fragments A, B, C and D can be independently prepared following standard procedures in organic synthesis. 5 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). 10 When necessary, appropriate protecting groups can be used on the substituents to ensure that reactive groups are not affected. The synthesis can be designed to employ precursor substituents which can be converted as the appropriate hydroxyphenyl, indolyl, including 1, 15 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 synthesis, and even more preferred methyl, isopropyl, and 5 preferred R₅ groups, and even more preferred methyl, isopropyl, and tert-butyl. 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 25 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 stereoisomers. 40 Particularly preferred R₆ is NR₆, wherein R₆ is as defined before. Particularly preferred R₇ and R₈ are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₇ and R₈ are hydrogen and 15 substituted or unsubstituted C₁-C₆ alkyl, and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl, and butyl, including tert-butyl. Hydrogen is the most preferred. 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.

In another embodiment, it is particularly preferred that R₇ and R₈ 20 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, 25 most preferably 5, 6 or 7 ring atoms. A pyrrolidine group is the most preferred.

Particularly preferred R₉ is hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ 30 alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl, and more preferably is hydrogen, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or

15 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. 20 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 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.

- 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms.
- 15 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
- 20 those having from 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
- 25 hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said alkyl, 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
- 30 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 alkyl, 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 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,

TBSO 10 To a 0 C solution of (2S,3,9-3,5-Bis([(tert-butyl)dimethylsilyl]oxy}-2- methylpentan-1-ol (P. Phukan, S. Sasmal and M.E. Maier Eur. J. Org. Chem. 2003, 1733-1740) (50 g, 0.14 mol) in a mixture of 52 Dichloromethane/DMSO (331mL/149 mL), Et₃N (96.1 mL, 0.69 mol) was added via addition funnel. After 10 min, S03.Pyr (54.8 g, 0.34 mol) was added portionwise and the solution was stirred for another 2h at 0 C. Then, it was diluted with dichloromethane (800 ml) and quenched 5 with HCl (0.5N, 800 mL). The organic layer was decanted, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 100:0 to 10:1) afforded 45.6 g (yield: 96%) of aldehyde 1. ¹H NMR (CDCl₃, 300 MHz) δ: 9.79 (s, 1H), 4.30 (m, 1H), 3.65 (m, 2H), 2.51 (m, 1H), 1.65 (m, 2H), 1.10 (d, 3H, J = 6.9 Hz), 0.99 (m, 1H), 0.03-0.07 (m, 12H). ¹³C NMR (CDCl₃, 75 MHz) δ: 205.4, 169.4, 59.6, 51.7, 37.5, 26.1, 26.0, 18.4, 18.2, 8.0, -4.3, -4.5, -5.2. 15 Synthesis of intermediates 3-12 (triphenylmethoxy)ethoxydisiloxane allyl and fluorous silyl, and the most preferred substituents for these alkyl, alkenyl, alkynyl and arkenyl groups.

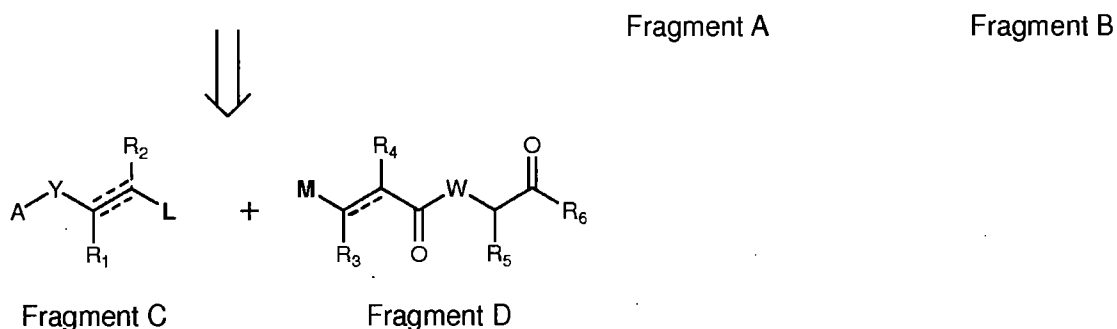
53.3 g (yield: 96%) of ester compound 2. ¹H NMR (CDCl₃, 300 MHz) δ: 6.71 (dd, 1H, J = 1.5, 10.2 Hz), 4.19 (m, 2H), 3.77 (m, 1H), 3.66 (m, 2H), 2.61 (m, 1H), 1.85 (d, 3H, J = 1.5 Hz), 1.68 (m, 2H), 1.30 (t, 3H, J = 7.2 Hz), 0.98 (d, 3H, J = 6.9 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ: 168.3, 145.4, 126.7, 72.2, 60.4, 59.7, 38.4, 30.3, 25.9, 18.2, 18.1, 14.3, 14.3, 12.6, -4.4, -4.6, -5.4. 15 This is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R₁₆ is hydrogen, OR_a and OCOR_a, wherein R_a is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R₁₆ groups.

15

Particularly preferred R₁₉ is hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl and COR_a, wherein R_a is a substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₁₉ is hydrogen, substituted or unsubstituted C₁-C₆ alkyl and COR_a, wherein R_a is a substituted or unsubstituted C₁-C₆ alkyl. Particularly preferred R_a is methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Even more preferred R₁₉ is hydrogen.

Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. More preferred is the presence of one additional bond between C₁ and C₂, and/or the presence of one or two additional bonds between C₃ and C₄, and/or the presence of one additional bond between C₅ and C₆. 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.

53 Synthesis of intermediate 3 TBSO 5 Over a -78 C cooled solution of ester 2 (46.7 g, 0.105 mol) in anhydrous THF (525 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (231 mL, 0.231 mol) was added over a period of 10 min and the mixture was stirred at -78 C. After 4 hours the reaction 10 was quenched with MeOH (10 mL) and a saturated solution of sodium potassium tartrate was added (800 mL) and diluted with EtOAc (1000 mL). This mixture was stirred for 2 h and then the organic layer was decanted. The aqueous residue was extracted with additional EtOAc (2 x 400 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was evaporated. The resulting oil was purified by column chromatography (hexane/EtOAc 20:1 to 10:1) affording 32.5 g (yield: 77%) of alcohol 3. ¹H NMR (CDCl₃, 300 MHz): 5.31 (d, 1H, J= 9.6 Hz), 3.98 (m, 2H), 3.66 (m, 3H), 2.49 (m, 1H), 1.67 (s, 3H), 1.70-1.62 (m, 2H), 0.91 (d, 3H, J= 20.6.9 Hz), 0.88 (m, 18H), 0.03 (m, 12H). ¹³C NMR (CDCl₃, 75 MHz): 133.9, 129.8, 73.2, 69.1, 59.9, 37.5, 25.9, 18.3, 18.1, 15.9, 13.9, -4.4, -4.4, -5.3. Synthesis of intermediate 4 25 TBSO TBSO



5

Scheme A

where R₁, R₂, R₃, R₄, R₅, R₆, A, Y and W are the 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:

15

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).

20

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).

37.9, 26.0, 18.3, 18.2, 15.7, 15.7, -4.4, -5.2, -5.2. Synthesis of intermediate 6 TBSO To a solution of iodide 5 (12 g, 22.9 mmol) in EtOH (114 mL) pyridinium p-toluenesulfonate (PPTS) (2.01 g, 8.0 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then 15 the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 10:1) affording 8.7 g (yield: 93%) of alcohol 6. ¹H NMR (CDCl₃, 300 MHz) 5: 6.69 (d, 1H, J= 8.4 Hz), 6.12 (d, 1H, J= 8.4 Hz), 5.47 (d, 1H, J= 9.9 Hz), 3.67-3.87 (m, 4H), 2.71 (m, 1H), 1.89-2.01 (s, 3H), 1.73-1.86 (m, 2H), 1.01 (d, 3H, J= 6.9 Hz), 0.91 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) 142.4, 136.4, 132.6, 75.8, 75.2, 60.0, 38.1, 36.4, 26.1, 18.2, 17.1, 16.0, -4.1, -4.2. 25
 Synthesis of intermediate 7 TBSO 56

With this invention we provide novel pharmaceutical compositions

- 5 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.

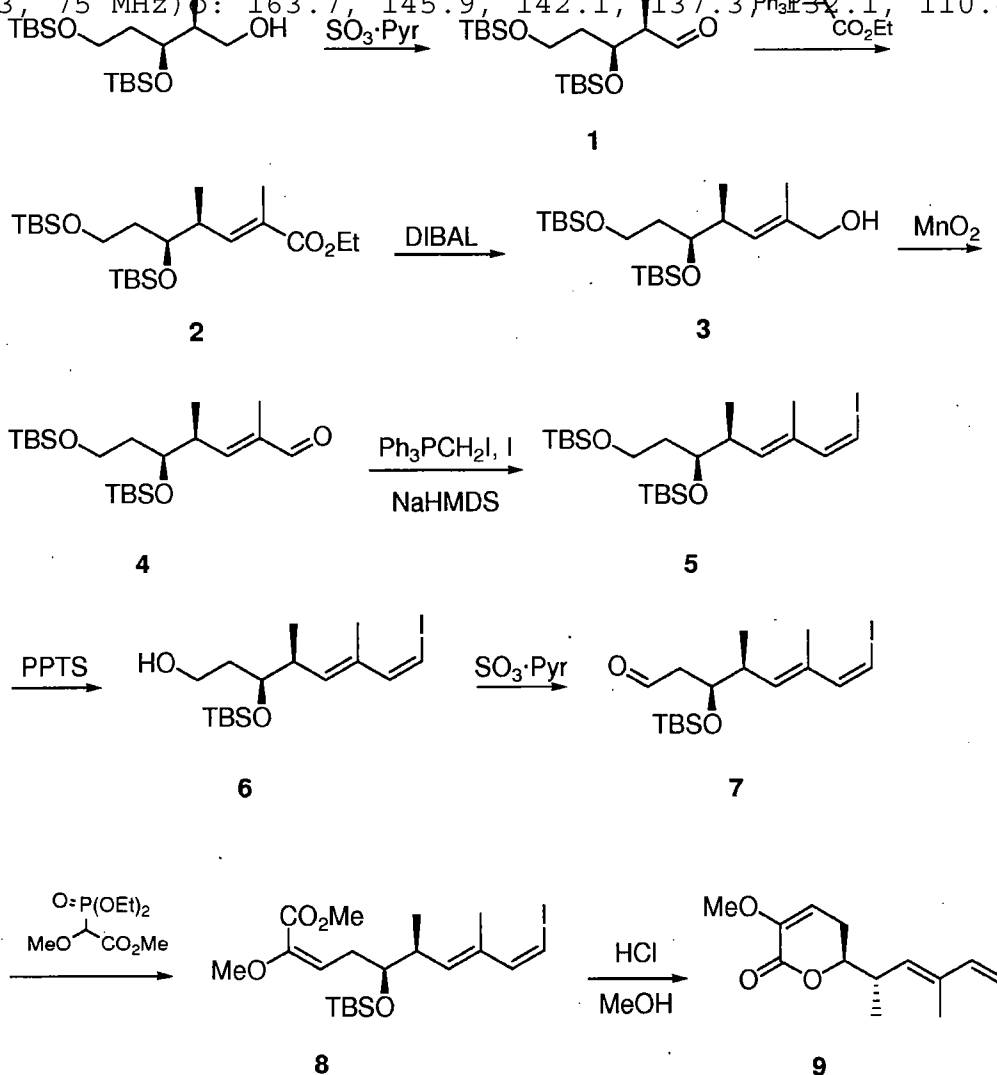
10

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.

- 15 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.

- 20 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
 25 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
 30 nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

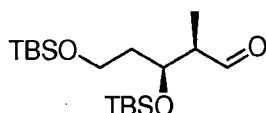
a saturated NH_4Cl solution (200 mL), warmed to room temperature and diluted with Dichloromethane (1000 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. 57 Purification by column chromatography (hexane/ Et_2O 20:1) afforded pure 4.2 g (59%) of (E)-8. ^1H NMR (CDCl_3 , 300 MHz): δ : 6.70 (d, 1H, $J = 8.4$ Hz), 6.08 (d, 1H, $J = 8.4$ Hz), 5.47 (d, 1H, $J = 9.9$ Hz), 5.37 (t, 1H, $J = 7.2$ Hz), 3.78 (s, 3H), 3.60 (s, 3H), 3.60 (m, 1H), 2.79 (m, 1H), 2.52-2.67 (m, 2H), 1.83 (s, 3H), 0.99 (d, 3H, $J = 6.6$ Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ : 163.7, 145.9, 142.1, 137.3, 135.1, 110.4,



Scheme 1

5

Synthesis of intermediate 1

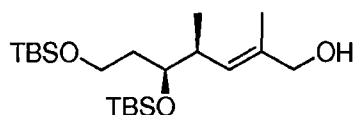


- 10 To a 0 °C solution of (2S,3S)-3,5-Bis[[(*tert*-butyl)dimethylsilyl]oxy]-2-methylpentan-1-ol (P. Phukan, S. Sasmal and M.E. Maier *Eur. J. Org. Chem.* 2003, 1733-1740) (50 g, 0.14 mol) in a mixture of

81.7, 77.4, 55.4, 37.1, 26.6, 16.5, 16.1. 58 EXAMPLE 2: SYNTHESIS OF FRAGMENTS 21 AND 22 Scheme 2 provides an example of the synthesis of fragments 21 and 22. i) mC PBA, DCM ii) (R,R)Co-salenBuLi, BF₃OEt₂, THF 10AcOH, H₂O 11 1 ==CO₂H HATU HOAt, DIP EA DCM, DM F OTBS 0 R Air H

53

Synthesis of intermediate 3



5

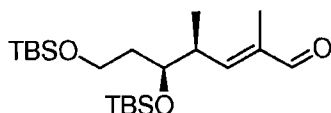
Over a -78 °C cooled solution of ester **2** (46.7 g, 0.105 mol) in anhydrous THF (525 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (231 mL, 0.231 mol) was added over a period of 10 min and the mixture was stirred at -78 °C. After 4 hours the reaction was quenched with MeOH (10 mL) and a saturated solution of sodium potassium tartrate was added (800 mL) and diluted with EtOAc (1000 mL). This mixture was stirred for 2 h and then the organic layer was decanted. The aqueous residue was extracted with additional EtOAc (2 x 400 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was evaporated. The resulting oil was purified by column chromatography (hexane/EtOAc 20:1 to 10:1) affording 32.5 g (yield: 77%) of alcohol **3**.

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

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

Synthesis of intermediate 4

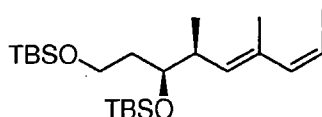
25



Over a solution of alcohol **3** (31.2 g, 77.5 mmol) in ethyl ether (387 mL) under argon atmosphere, MnO₂ (101 g, 1.16 mol) was added and the

N H 0 22a R=tBu 22b R= 'Pr 59 Scheme 2 Synthesis of intermediate 11 10TBS
 5 To a solution of intermediate 10 (72.3 g, 0.39 mol) in anhydrous
 dichloromethane (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. 10 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 compound 11 as a colourless oil (46.45 g,
 82%). To a solution of racemic epoxide (30 g, 0.15 mol) in anhydrous THF
 (7.5 mL) (R,R) (+)-1,1'-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. The solution was stirred at 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 10:1) as
 eluent, provided chiral epoxide (+)-11 (13.6 g, yield: 46%) as a 25
 colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 9.37 (s, 1H), 6.44 (d, 1H, J = 9.6 Hz), 3.82
 (dd, 1H, J = 6.3, 10.8 Hz), 3.65 (m, 2H), 2.82 (m, 1H), 1.74 (s, 3H), 1.67
 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 195.4, 157.3, 138.3, 72.1, 59.5, 38.7, 37.5, 30.0
 25.8, 18.2, 18.0, 14.3, 9.4, 4.4, 4.5, 5.4. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 9.37 (s, 1H), 6.44 (d, 1H, J = 9.6 Hz), 3.82
 (dd, 1H, J = 6.3, 10.8 Hz), 3.65 (m, 2H), 2.82 (m, 1H), 1.74 (s, 3H), 1.67
 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 195.4, 157.3, 138.3, 72.1, 59.5, 38.7, 37.5, 30.0
 25.8, 18.2, 18.0, 14.3, 9.4, 4.4, 4.5, 5.4. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 9.37 (s, 1H), 6.44 (d, 1H, J = 9.6 Hz), 3.82
 (dd, 1H, J = 6.3, 10.8 Hz), 3.65 (m, 2H), 2.82 (m, 1H), 1.74 (s, 3H), 1.67
 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 60.2, 50.2, 47.3, 36.1, 26.1, 18.4, -5.2.

Synthesis of intermediate 5

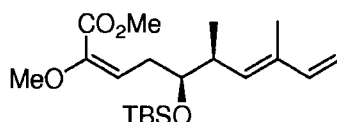


- 15 To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert
 Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (96.3 g, 181.7 mmol)
 in anhydrous THF (727 mL) at 0 °C, a 1M solution of sodium
 hexamethyldisilazane (NaHMDS) (181.7 mL, 181.7 mmol) was slowly
 added, via addition funnel,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

Over a solution of 12 (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 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 exhaustively extracted with 10 EtOAc (3 x 500 mL). The combined organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 13 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 = 15.8 Hz), 4.45 (m, 2H), 3.80 (s, 3H), 3.65 (m, 3H), 2.40 (m, 2H), 1.82 (m, 52H). Then, it was diluted with Dichloromethane (800 mL) and quenched with HCl (0.5N, 50 mL). The organic layer was decanted, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 10:1) afforded 6.9 g (yield: 80%) of aldehyde 7.

¹H-NMR (CDCl₃, 300 MHz) δ: 9.84 (d, 1H, J = 15.8 Hz), 6.67 (d, 1H, J = 15.8 Hz), 6.13 (d, 1H, J = 8.4 Hz), 5.43 (d, 1H, J = 10.2 Hz), 3.98 (m, 1H), 2.59-2.69 (m, 3H), 1.85 (s, 3H), 1.01 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).
¹³C NMR (CDCl₃, 75 MHz) δ: 201.8, 141.9, 135.2, 133.3, 76.3, 71.9, 49.3, 39.3, 25.8, 18.0, 16.7, 15.9, -4.4, -4.5.

Synthesis of intermediate 8



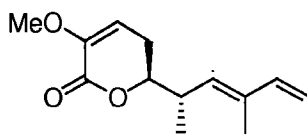
20

To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (5.51 g, 14.45 mmol) and 18-crown-6 (11.5 g, 43.34 mmol) in anhydrous THF (390 mL) stirred under argon atmosphere at -78 °C, a 0.5 M Potassium bis(trimethylsilyl)amide solution (KHMDS) (43.34 mL, 21.67 mmol) was added dropwise. After 15 min aldehyde 7 (5.9 g, 14.45 mmol) in anhydrous THF was added dropwise over a period of 30 min and stirred at -78 °C for 90 min. Then, the reaction was quenched with a saturated NH₄Cl solution (200 mL), warmed to room temperature and diluted with Dichloromethane (1000 mL). The organic phase was dried over anhydrous Na₂SO₄ and evaporated at reduced pressure.

30

62 reaction was diluted with Hexane/EtOAc (95:5; 500 mL). Removing of the solid by filtration and evaporation of volatiles provided 14 as yellow oil which was used without further purification (15.1 g, yield: 86 %). $[\alpha]_D^{20} = +20.5$ (c 1, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ : 7.25 (d, 2H, $J = 8.7$ Hz), 6.87 (d, 2H, $J = 8.7$ Hz), 5.64 (td, 1H, $J = 7.8, 0.9$ Hz), 4.45 (q, 2H, $J = 11.1$ Hz), 3.80 (s, 3H), 3.70 (m, 2H), 3.62 (m, 1H), 2.27 (t, 2H, $J = 6.9$ Hz), 2.03 (s, 3H), 1.70 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ : 159.4, 130.9, 130.7, 129.6, 124.2, 114.0, 107.5, 71.4, 59.8, 55.5, 37.7, 33.8, 26.1, 21.2, 18.5, 15.1. Synthesis of intermediate 15 OPMB OH 15 To a solution of 14 (23 g, 0.058 mol) in anhydrous THF (288 mL) under N₂ 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 solution of NH₄Cl (200 mL). The mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (hexane /EtOAc 4:1 to 1:1) provided 15 as a colourless oil (11.9 g, yield: 73%). ¹H NMR (CDCl₃, 300 MHz) δ : 7.25 (d, 2H, $J = 8.7$ Hz), 6.86 (d, 2H, $J = 8.7$ Hz), 5.47 (d, 1H, $J = 9.9$ Hz), 5.37 (t, 1H, $J = 7.2$ Hz), 3.78 (s, 3H), 3.60 (s, 3H), 3.60 (m, 1H), 2.79 (m, 1H), 2.52 (m, 2H), 1.83 (s, 3H), 0.99 (d, 3H, $J = 6.6$ Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ : 163.7, 145.9, 142.1, 137.3, 132.1, 110.4, 75.4, 74.8, 55.4, 51.9, 38.1, 32.3, 25.9, 41.5, 16.5, 15.7, 34.8, 4.5. 3H), 3.70 (m, 3H), 2.35 (m, 2H), 2.03 (s, 3H), 1.75 (m, 2H). 63 OPMB (Diacetoxyiodo)benzene (BAIB) (11.5 g, 35.7 mmol) was added to a

10 Synthesis of intermediate 9



To a solution of ester **8** (4.15 g, 8.39 mmol) in MeOH (125 mL) at room temperature, HCl 37% (1.04 mL) was added and the reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with Dichloromethane (3 x 200 mL), dried and evaporated.

Filtration by column chromatography (hexane/EtOAc 10:1 to 2:1) afforded 2.76 g (yield: 94%) of lactone **9**.

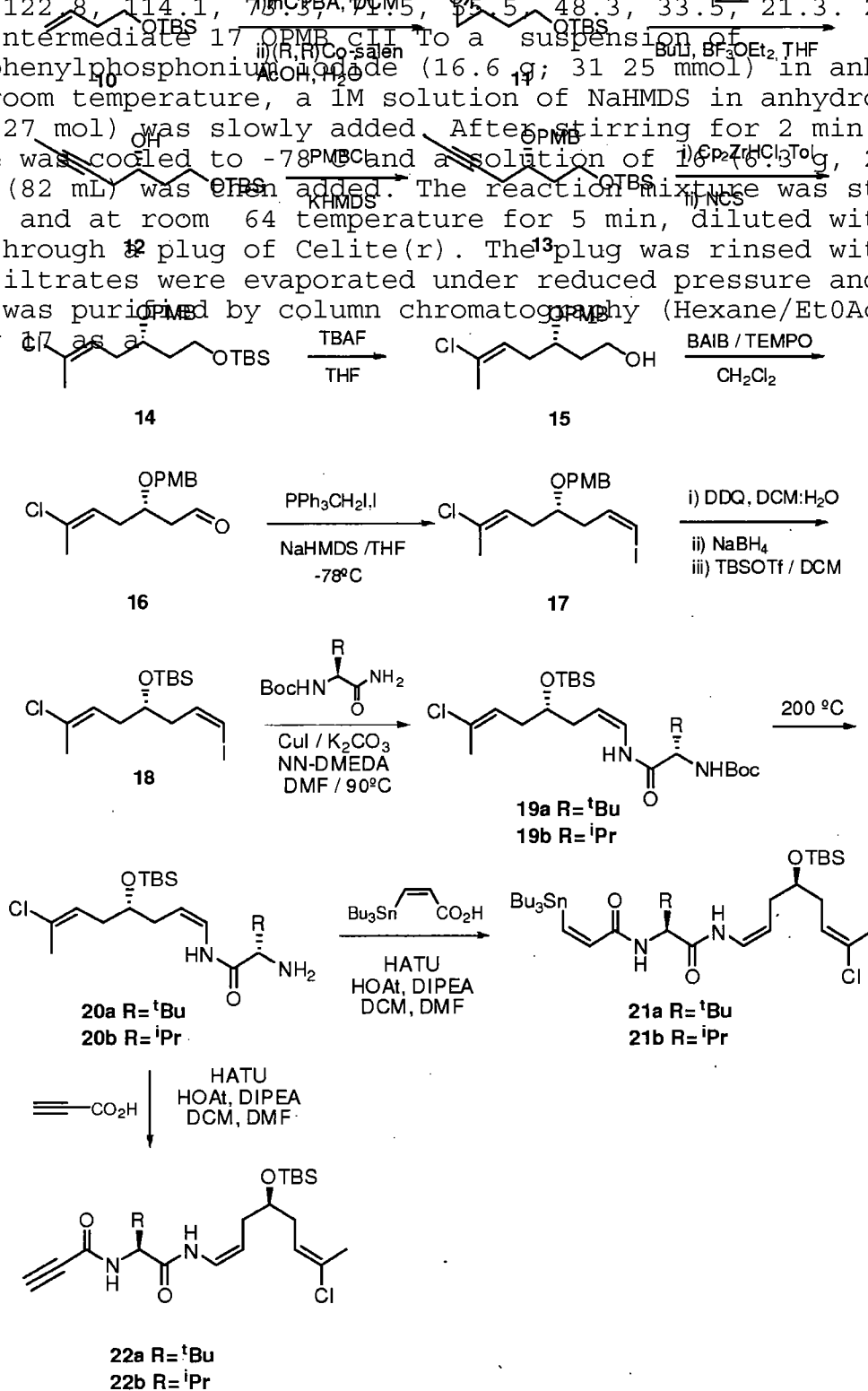
¹H NMR (500 MHz, CDCl₃) δ : 6.68 (d, 1H, $J = 9.0$ Hz), 6.20 (d, 1H, $J = 8.5$ Hz), 5.63 (dd, 1H, $J = 2.5, 6.5$ Hz), 5.43 (d, 1H, $J = 10.0$ Hz), 4.19 (m, 1H), 3.65 (s, 3H), 2.84 (m, 1H), 2.55 (m, 1H), 2.43 (dc, 1H, $J = 3.0, 12.0, 15.0, 18.0$ Hz), 1.87 (s, 3H), 1.16 (d, 3H, $J = 6.5$ Hz).

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

5 solution of alcohol 15 (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 10 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 16 as

colourless oil (6.3 g, yield: 69%). In 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, 70.3, 71.5, 65.5, 48.3, 33.5, 21.3, 20.

Scheme 2 provides an example of the synthesis of fragments 21 and 22. Synthesis of intermediate 17. To a suspension of iodomethyltriphenylphosphonium salt (16.6 g; 31.25 mmol) in anhydrous THF (126 mL), at room temperature, a 1M solution of NaHMDS in anhydrous THF (31.27 mL, 31.27 mmol) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78°C and a solution of 16 (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(r). 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 17 as a



200CI 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. 25 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 **18** (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 **19a** (670 mg, yield:53%) was obtained as an oil.

Synthesis of intermediate 12
¹H NMR (CDCl₃, 300 MHz) δ: 7.72 (d, 1H, J = 9.9 Hz), 6.70 (t, 1H, J = 9.6 Hz), 5.54 (t, 1H, J = 7.8 Hz), 5.35 (d, 1H, J = 9.0 Hz), 4.76 (q, 1H, J = 7.8 Hz), 3.89 (d, 1H, J = 9.0 Hz), 3.73-3.68 (m, 1H), 2.12 (m, 4H), 1.98 (s, 3H), 1.40 (s, 59H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ: 168.9, 156.0, 131.1, 123.9, 122.6, 108.2, 79.9, 71.6, 62.5, 36.5, 34.8, 33.8, 28.1, 26.7, 25.9, 21.2, 18.3, -4.3, -4.4.

Synthesis of intermediate 19b
 Propyne (10 mL, 0.176 mol) was condensed at -78 °C and dissolved in anhydrous THF (155 mL). n-Butyllithium (75.1 mL, 0.188 mol) was

added dropwise under N₂ over 30 min, and the resultant white suspension was stirred for an additional 30 min at -78 °C. A solution of (+) (R)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxirane **11** (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 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 **12** (22.7 g, yield: 80%) as a colourless oil.

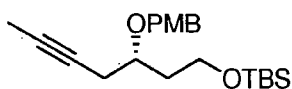
[α]_D = +5.6 (c 0.1, CHCl₃).

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, 18.3, 3.7, -5.3, -5.4.

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

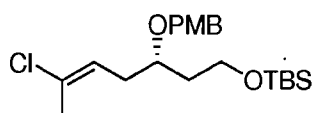
Synthesis of intermediate 13



OCI 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), evacuated and filled with N₂. N,N-Dimethylethylenediamine (45.11 g, 0.426 mmol), vinyl iodide **18** (283 mg, 0.71 mmol) and anhydrous DMF (35 mL) were added under N₂. The Schlenk tube was sealed, heated at 90 °C for 18 h 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 67 flash chromatography on silica gel (Hexane/EtOAc, 7:1 to 3:1). Intermediate **19** (27.0 g, 0.190 mol) in anhydrous THF (100 mL) at -78 °C under N₂ atmosphere, a 0.5N solution of KHMDS in toluene (380 mL, 0.190 mol) was added 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 exhaustively extracted 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 **13** 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 14



20

- To a solution of **13** (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

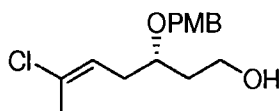
30

10 OTBS)1\ H2NThrN. OCI A solution of amino protected derivative 19a (670 mg, 1.33 mmol) in 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 anhydrous Na2SO4, filtered and concentrated in vacuo to afford the 20 primary amine 20a (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), 3.14 (s, 1H), 2.14 (m, 4H), 1.97 (s, 3H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 6H). 25 ¹³C NMR (CDCl₃, 75 MHz)δ: 171.2, 151.0, 124.1, 122.9, 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 20b 68 OTBS N CI

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

¹³C NMR (CDCl₃, 75 MHz)δ: 159.4, 130.9, 130.7, 129.6, 124.2, 114.0, 10 75.2, 71.4, 59.8, 55.5, 37.7, 33.8, 26.1, 21.2, 18.5, -5.1.

Synthesis of intermediate 15



15

To a solution of **14** (23 g, 0.058 mol) in anhydrous THF (288 mL) under N₂ 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 solution of NH₄Cl (200 mL). The layers were separated and the aqueous phase was exhaustively extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (hexane /EtOAc 4:1 to 1:1) 20 provided **15** as a colourless oil (11.9 g, yield: 73%).

¹H NMR (CDCl₃, 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).

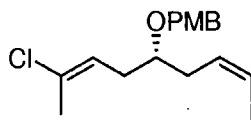
30 Synthesis of intermediate 16

0 A solution of amino protected derivative 19b (255 mg, 0.52 mmol) in ethylenglycol (15 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 anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the primary amine 20b (170 mg, yield 85%) as a yellow oil which was used without further purification. ¹H NMR (CDCl₃, 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, 4H), 2.20-2.16 (m, 4H), 2.03 (s, 3H), 1.59 (br s, 2H), 1.00 (d, 3H, J = 6.9 Hz), 0.99 (s, 9H), 0.82 (d, 3H, J = 6.9 Hz), 0.05 (s, 6H). ¹³C NMR (CDCl₃, 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. 20 Synthesis of intermediate 21a OTBS To a solution of amine 20a (918 mg, 2.20 mmol) in anhydrous DCM (10 mL), a solution of (Z)-3-tributylstannylpropene (11.5 g, 35.7 mmol) was added to a solution of alcohol **15** (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 NH₄Cl and extracted with DCM (3 x 100 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 4:1 to 1:1) to afford **16** as colourless oil (6.3 g, yield: 69%)

¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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.

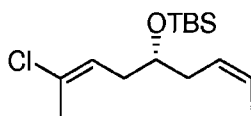
20 Synthesis of intermediate 17



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 mmol) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78 °C and a solution of **16** (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

acid (1028 mg, 2.84 mmol) in anhydrous DCM was added, under N₂ atmosphere, and then was cooled at 0 °C. Diisopropylethylamine 69 (DIPEA) (0.6 mL, 3.4 mmol), 1-Hydroxy-7-azabenzotriazole (HOAt) (310 mg, 2.27 mmol), and N,N,N',N'-Tetramethyl-0-(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 5 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 anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide 21a (1.11 g; yield: 66%) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.45 (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), 2.15 (yellow oil (3.6 g, yield: 62%)). ¹H NMR (CDCl₃, 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).

10 Synthesis of intermediate 18

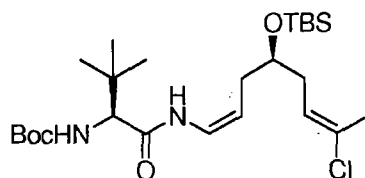


2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (3.6g, 16 mmol) was added to a solution of **17** (5 g, 12 mmol) in DCM-H₂O (20:1, 98 mL) under N₂ atmosphere at room temperature. After 1.5 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et₂O (200 mL) and washing with 1M NaOH (3 x 50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na₂SO₄, 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 NaBH₄ (0.60g, 16 mmol) under N₂ atmosphere was maintained at room temperature for 1 h. The reaction mixture was then quenched by pouring into Et₂O (100 mL) and washing with 1 M HCl (40 mL) and brine (40 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting oil was purified on silica gel (Hexane/EtOAc 10:1 to 4:1) to provide the secondary alcohol as colourless oil. (2.8 g, yield: 80%).

atmosphere, and then was cooled at 0 °C. DIPEA (0.11 mL, 0.655 mmol), HOAt (59.4 mg, 0.437 mmol), and HATU (166 mg, 0.437 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide 21b (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 = 5.1 Hz), 6.75 (d, 1H, J = 12.3 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, 1H), 2.01 (s, 3H), 1.45 (m, 7H), 1.25 (m, 8H), 0.88 (s, 9H), 0.84 (m, 19H), 0.06 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ: 169.2, 166.8, 153.8, 136.2, 131.1, 123.9, 10.122.6, 108.7, 71.6, 59.2, 36.55, 33.07. 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 18 as a colorless oil (3.14 g, yield: 89%). ¹H NMR (CDCl₃, 300 MHz) δ: 8.20 (d, 1H, J = 10.2 Hz), 6.83 (d, 1H, J = 8.6 Hz), 6.25 (m, 2H), 5.84 (t, 1H, J = 5.8 Hz), 3.82 (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), 2.38 (t, 2H, J = 6.0 Hz), 2.20 (t, 2H, J = 6.3 Hz), 2.03 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H).

- 15 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.

Synthesis of intermediate 19a

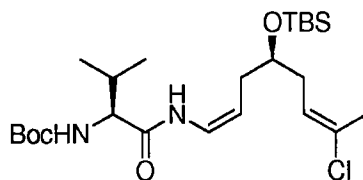


20

- 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 **18** (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

71 ¹³C NMR (CDCl₃, 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. 5 Synthesis of intermediate 22b OTBS To a solution of 20b (200 mg, 0.51 mmol) and propiolic acid (39 μL, 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 μL, 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 NH₄Cl and extracted with CH₂Cl₂. The resultant mixture was diluted with EtOAc and quenched with water. The combined filtrates were washed with H₂O. After drying and evaporating 15 the solvent, 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, 20:18 to 15:1) to afford pure compound 22b (150 mg, yield: 67%). ¹H NMR (CDCl₃, 300 MHz) δ: 7.02 (d, 1H, J = 11.4 Hz), 6.75 (dd, 1H, J = 20.1, 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), 3.84-3.75 (m, 2H), 2.18 (s, 1H). Intermediate 19a (670 mg, yield 53%), was obtained as an oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.72 (d, 1H, J = 9.9 Hz), 6.70 (t, 1H, J = 9.6 Hz), 5.54 (t, 1H, J = 7.8 Hz), 5.35 (d, 1H, J = 9.0 Hz), 4.76 (q, 1H, J = 7.8 Hz), 3.89 (d, 1H, J = 9.0 Hz), 3.73-3.68 (m, 1H), 2.12 (m, 4H), 1.98 (s, 3H), 1.40 (s, 9H), 0.97 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ: 168.9, 156.0, 131.1, 123.9, 122.6, 108.2, 79.9, 71.6, 62.5, 36.5, 34.8, 33.8, 28.1, 26.7, 25.9, 21.2, 18.3, -4.3, -4.4.

15 Synthesis of intermediate 19b

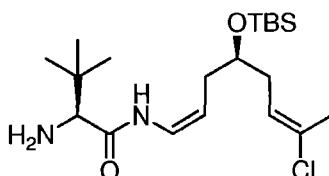


A resealable Schlenk tube was charged with copper (II) iodide (40.4 mg, 0.213 mmol), potassium carbonate (294 mg, 2.13 mmol) and Boc-Val-CONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (230 mg, 1.06 mmol), evacuated and filled with N₂. *N,N*-Dimethylethylenediamine (45 μL, 0.426 mmol), vinyl iodide **18** (283 mg, 0.71 mmol) and anhydrous DMF (35 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

TBSO To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert 10 Stork, KZ. Tetrahedron letters 1989, 30(17), 2173) (6.6 g, 12.47 mmol) in anhydrous THF (50 mL) at 0C, a 1M solution of sodium hexamethyldisilazane (NaHMDS) (12.5 mL, 12.47 mmol) was slowly added, via addition funnel, over a period of 10 min. After stirring for an additional 5 min, the solution was cooled to -78C and 1,3-Dimethyl- 15 3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (3.02 mL, 24.95 mmol) was then added via cannula, followed by the addition of aldehyde 1 (1.80 g, 4.99 mmol) dissolved in anhydrous THF (50 mL). The temperature was kept at -78C while the reaction mixture stirred for 2 hours. Hexane (200 mL) was added and the resulting slurry was 20 filtrated over Celite(r) and washed with additional Hexane (300 mL). The filtrate was evaporated under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 100:0 to 20:1) affording 1.64g (yield: 68%) of iodide 23. ¹H NMR (CDCl₃, 300 MHz)δ: 8.80 (d, 1H, J = 9.3 Hz), 6.79-6.73 (m, 1H), 5.58 (t, 1H, J = 7.5 Hz), 5.02 (br s, 1H), 4.85-4.76 (m, 1H), 3.93 (dd, 1H, J = 18.4, 6.0 Hz), 3.80-3.73 (m, 1H), 2.12-2.22 (m, 5H), 2.00 (s, 3H), 1.45 (s, 1H), 3.67 (m, 2H), 2.57 (m, 1H), 1.75-1.63 (m, 2H), 0.96 (d, 3H, J = 6.9 Hz), 0.89 (m, 18H), 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).

Synthesis of intermediate 20a

10



A solution of amino protected derivative **19a** (670 mg, 1.33 mmol) in 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 anhydrous Na₂SO₄, filtrated and concentrated in vacuo to afford the primary amine **20a** (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), 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 20b

HO TBSO To a solution of iodide **23** (520 mg, 1.07 mmol) in EtOH (5:3 mL) pyridinium p-toluenesulfonate (PPTS) (94.4 mg, 0.38 mmol) was added **15** and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 380 mg (yield: 87%) of alcohol **24**.

NMR (CDCl₃, 300 MHz) δ : 6.20 (d, 1H, J = 7.5 Hz), 6.08 (m, 1H), 3.87-3.72 (m, 3H), 2.69 (m, 1H), 1.85-1.80 (m, 1H), 1.71-1.65 (m, 1H), 0.99 (d, 3H, J = 6.6 Hz), 0.90 (m, 9H), 0.09 (m, 6H).

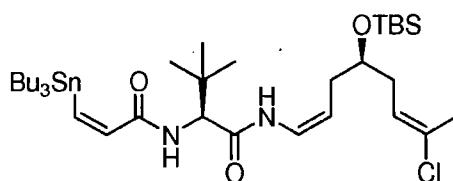
Synthesis of intermediate **25** TBSO **74** After 1 h, a saturated aqueous solution of NaHCO₃ (50 mL) was added and the organic layer was decanted, dried over anhydrous MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 4:1) afforded 350 mg (yield: 93%) of aldehyde **25**. ¹H NMR (CDCl₃, 300 MHz) δ : 9.82 (t, 1H, J = 2.1 Hz), 6.26 (dd, 1H, J = 0.6, 7.5 Hz), 6.05 (dd, 1H, J = 1.5, 9.0 Hz), 4.14 (m, 1H), 2.68 (m, 1H), 2.58 (m, 2H), 1.01 (d, 3H, J = 6.6 Hz), 0.87 (m, 9H), 0.07 (s, 3H), 0.03 (s, 3H). A solution of synthetic protected derivative **19b** (255 mg, 0.52 mmol) in Diethyl (methoxy[methoxycarbonyl]methyl)phosphonate ethyleneglycol (15 mL) was heated at 200 °C for 15 min. The reaction

5 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 Na₂SO₄, filtrated and concentrated in vacuo to afford the
10 primary amine **20b** (170 mg, yield 85%) as a yellow oil which was used without further purification.

¹H NMR (CDCl₃, 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
15 (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).

¹³C NMR (CDCl₃, 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.

20 Synthesis of intermediate **21a**

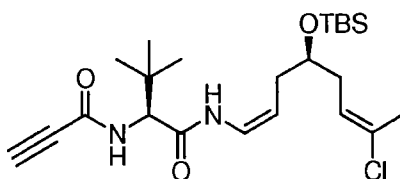


To a solution of amine **20a** (918 mg, 2.27 mmol) in anhydrous
25 DCM/DMF (10:1, 39.6 mL), a solution of (Z)-3-tributylstannylpropenoic acid (1028 mg, 2.84 mmol) in anhydrous DCM was added, under N₂ atmosphere, and then was cooled at 0 °C. Diisopropylethylamine

Synthesis of intermediate 28 0 5 To a mixture of L-Boc-tert-leucine (300 mg, 1.3 mmol) in anhydrous DCM (13 mL) and Dicyclohexylcarbodiimide (DCC) (295 mg, 1.43 mmol) at 0°C, under N₂, the 3-butenol (0.3 mL, 3.9 mmol) and the Dimethylaminopyridine (DMAP) (15.9 mg, 0.13 mmol) were added. The 10 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 ester 28 (300 mg, yield: 81%). 15 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), 2.11 (s, 3H). The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 9:1) to give amide 21b (250 mg, yield: 78%) as a white foam. 20 The solution of the ester 28 (180 mg, 0.63 mmol) in HCl-MeOH (3.6 mL) 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 25 ¹H NMR (CDCl₃, 300 MHz) δ: 7.94 (d, 1H, J = 10.8 Hz), 7.00 (d, 1H, J = 12.3 Hz), 6.55 (d, 1H, J = 12.3 Hz), 6.32 (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 (t, 1H, J = 6.7 Hz), 3.76 (m, 1H), 2.44 (m, 4H), 2.01 (s, 3H), 1.45 (m, 7H), 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, 10 122.6, 108.7, 71.6, 59.2, 36.5, 33.7, 31.4, 29.5, 27.6, 26.1, 21.3, 19.5, 18.5, 14.0, 11.8, -4.3, -4.4.

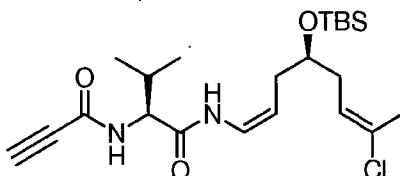
Synthesis of intermediate 22a



- 15 To a solution of **20a** (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 20 saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂. The combined filtrates were washed with H₂O. After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes mixture) to afford pure compound **22a** (50 mg, yield: 40%).
- 25 ¹H NMR (CDCl₃, 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).

10 DIPEA (0.24mL, 1.4mmol), HOAt (123.3 mg, 0.9 mmol), and HATU (345 mg, 0.9 mmol) were added to a solution of 29 (168 mg, 0.9 mmol), and (Z)-3-tributylstannylpropenoic acid (393mg, 1.2 mmol) in anhydrous DCM/DMF (10:1, 14 mL) at 0 °C under argon. After 2 hours, the cold 15 bath was removed and the reaction mixture was stirred at room temperature for 1 hour, quenched with saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined 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 30 (340 mg; yield: 72%).
¹H NMR (CDCl₃, 300 MHz) δ: 7.71 (d, 1H, J = 12.3 Hz), 6.75 (d, 1H, J = 12.3 Hz), 6.03 (d, 1H, J = 9.73 Hz), 5.84-5.69 (m, 1H), 5.14-5.05 (m, 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).
¹³C NMR (CDCl₃, 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, 14.3.
 EXAMPLE 5: SYNTHESIS OF FRAGMENT 37. Scheme 5 provides the synthesis of the fragment 37.

Synthesis of intermediate 22b



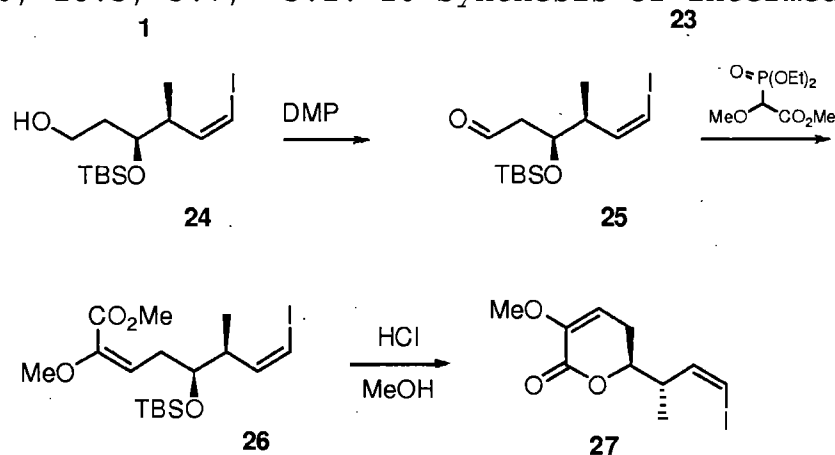
To a solution of **20b** (200 mg, 0.51 mmol) and propiolic acid (39 µL, 0.64 mmol) in anhydrous DCM/DMF 10:1 (8 mL) at 0 °C, HATU (194 mg, 0.51 mmol), HOAt (69 mg, 0.51 mmol) and DIPEA (133 µL, 0.76 mmol) were added. The reaction was stirred at 0 °C for 30 min and 2 hours at room temperature. Then, the crude mixture was treated with a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂. The combined filtrates were washed with H₂O. After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes mixture) to afford pure compound **22b** (150 mg, yield: 67%).

¹H NMR (CDCl₃, 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).

EXAMPLE 3: SYNTHESIS OF FRAGMENT 27

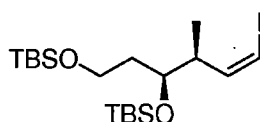
Scheme 3 provides an example of the synthesis of fragment 27.

OTBDPS = OTBS A solution of alcohol 12 (2.88 g, 11.9 mmol), tert-butyldiphenylsilyl chloride (4.39 mL, 16.89 mmol), and 4-(dimethylamino)pyridine (43.6 mg) in DMF (14 mL) was stirred overnight at room temperature. The mixture was diluted with water and extracted with Et₂O, and the organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether 31 (5.3 g, 93%) as a colourless liquid. ¹H NMR (300 MHz, CDCl₃) δ: 7.70-7.66 (m, 4H), 7.40-7.34 (m, 6H), 3.99-3.95 (m, 1H), 3.70-3.62 (m, 2H), 2.23-2.22 (s, 2H), 1.84-1.81 (m, 2H), 1.69 (t, 3H, J = 2.7 Hz), 1.05 (s, 9H), 0.84 (s, 9H), 0.01 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ: 136.1, 134.6, 129.7, 127.8, 127.8, 76.2, 69.9, 60.1, 39.6, 27.5, 27.2, 26.2, 19.6, 18.5, 3.7, -5.1. 10 Synthesis of intermediate 32 OTBDPS



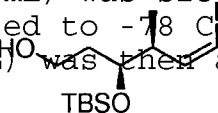
Scheme 3

5 Synthesis of intermediate 23



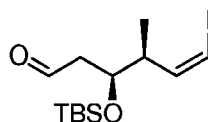
To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (6.6 g, 12.47 mmol) in anhydrous THF (50 mL) at 0°C, a 1M solution of sodium hexamethyldisilazane (NaHMDS) (12.5 mL, 12.47 mmol) was slowly added, via addition funnel, over a period of 10 min. After stirring for an additional 5 min, the solution was cooled to -78°C and 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (3.02 mL, 24.95 mmol) was then added via cannula, followed by the addition of aldehyde 1 (1.80 g, 4.99 mmol) dissolved in anhydrous THF (50 mL). The temperature was kept at -78°C while the reaction mixture was stirred for 2 hours. Hexane (200 mL) was added and the resulting slurry was filtrated over Celite® and washed with additional hexane (200 mL). The

OH PPTS (837.7 mg, 3.33 mmol) was added in one portion to a solution of 15 31 (4 g, 8.33 mmol) in ethanol (80 mL). The reaction mixture was stirred at room temperature for 7 h and then was concentrated. The residue was diluted in DCM and washed with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography 20 (Hex/EtOAc, 95:1) gave the silyl ether 32 (2.12 g, yield: 69%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) 5: 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H), 4.14-4.01 (m, 2H), 3.80-3.71 (ria, 1H), 2.31-2.28 (m, 2H), 1.94-1.80 (m, 25 2H), 1.79 (t, 3H, J = 2.4 Hz), 1.07 (s, 9H). Synthesis of intermediate 33. OTBDPS (0.82 g, 0.82 mmol) in benzene (BAIB) (1.93 g, 6.00 mmol) was added to a solution of alcohol 32 (2.0 g, 5.46 mmol) affording 1.64 g (yield: 68%) of iodide 23. ¹H NMR (CDCl₃, 300 MHz) δ: 6.18 (s, 1H), 3.79 (m, 1H), 3.67 (s, 2H), 2.57 (m, 1H), 1.75-1.63 (m, 2H), 0.96 (d, 3H, J = 6.9 Hz), 0.89 (m, 18H), 0.04 (m, 12H). The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 10 10:1) to afford 33 as colourless oil (1.64g; yield: 82%). ¹H NMR (CDCl₃, 300 MHz) 8: 9.72 (s, 1H), 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H), 4.29 (m, 1H), 2.65 (m, 2H), 2.33 (m, 2H), 1.70 (s, 3H), 1.04 (s, 9H). 15 Synthesis of intermediate 34. 20 to a suspension of iodomethyltriphenylphosphonium iodide (10.14 g; 6.04 mmol) in anhydrous THF (60 mL), at room temperature, a 1M solution of NaHMDS in THF (6.0 mL) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -18 °C and a solution of 33 (1.57 g, 4.31 mmol) in anhydrous THF (35 mL) was then added. The



To a solution of iodide **23** (520 mg, 1.07 mmol) in EtOH (5.3 mL) pyridinium p-toluenesulfonate (PPTS) (94.4 mg, 0.38 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 380 mg (yield: 87%) of alcohol **24**. ¹H NMR (CDCl₃, 300 MHz) δ: 6.20 (d, 1H, J = 7.5 Hz), 6.08 (m, 1H), 3.87-3.72 (m, 3H), 2.69 (m, 1H), 1.85-1.80 (m, 1H), 1.71-1.65 (m, 1H), 0.99 (d, 3H, J = 6.6 Hz), 0.90 (m, 9H), 0.09 (m, 6H)

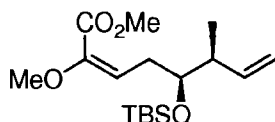
Synthesis of intermediate 25



25

To a 0 °C solution of alcohol **24** (380 mg, 1.03 mmol) in anhydrous DCM (10.3 mL), Dess-Martin periodinane (870 mg, 2.05 mmol) was added.

25 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(r). The plug was rinsed with hexane and the combined filtrates were evaporated under reduced pressure and the resulting oil was purified by column chromatography (Hexane/EtOAc 50:1) affording 34 as yellow oil 30 (1.31 g, yield: 62%). ¹H NMR (500 MHz, CDCl₃) δ: 7.70-7.66 (m, 4H), 7.44-7.34 (m, 6H), 6.27-6.24 (m, 2H), 3.99-3.95 (m, 1H), 2.47-2.41 (m, 2H), 2.27-2.23 (m, 2H), 1.71 (t, 3H, J = 2.7 Hz), 1.07 (s, 9H). After 1 h, a saturated aqueous solution of NaHCO₃ (50 mL) was added and the organic layer was decanted, dried over anhydrous MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 1:1) afforded 350 mg (yield: 93%) of aldehyde **25**. ¹H NMR (CDCl₃, 300 MHz) δ: 9.82 (t, 1H, J = 2.1 Hz), 6.26 (dd, 1H, J = 0.6, 7.5 Hz), 6.05 (dd, 1H, J = 1.5, 9.0 Hz), 4.14 (m, 1H), 2.68 (m, 1H), 2.58 (m, 2H), 1.01 (d, 3H, J = 6.6 Hz), 0.87 (m, 9H), 0.07 (s, 3H), 0.03 (s, 3H). 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 35 (388 mg, yield: 44%) was obtained as an oil. ¹H NMR (300 MHz, CDCl₃) δ: 7.70-7.66 (m, 4H), 7.53 (d, 1H, J = 10.5 Hz), 7.43-7.26 (m, 6H), 6.73 (t, 1H, J = 9.6 Hz), 5.29 (m, 1H), 4.79 (m, 1H), 3.81 (m, 2H), 2.39-2.30 (m, 1H), 2.27-2.21 (m, 3H), 1.88 (s, 3H), 1.43 (s, 9H), 1.06 (s, 9H), 0.97 (s, 9H). Synthesis of intermediate 36 HN O



To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (362 mg, 1.42 mmol) and 18-crown-6 (754 mg, 2.85 mmol) in anhydrous THF (27 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide solution (KHMDs) (2.85 mL, 1.42 mmol) was added dropwise. After 15 min aldehyde **25** (350 mg, 0.95 mmol) in anhydrous THF (14mL) was added dropwise over a period of 30 min and stirred at -78°C for 90 min. Then, the reaction was quenched with a saturated NH₄Cl solution (20 mL), warmed to room temperature and diluted with Dichloromethane (50 mL). The organic phase was dried (anhydrous Na₂SO₄) and evaporated at reduced pressure. Purification by column chromatography (hexane/Et₂O 20:1) afforded pure 370 mg (86%) of (**E**)-**26**.

¹H NMR (CDCl₃, 300 MHz) δ: 6.12 (d, 1H, J = 7.2 Hz), 6.03 (m, 1H), 5.32 (t, 1H, J = 7.5 Hz), 3.78 (s, 3H), 3.77-3.70 (m, 1H), 3.63 (s, 3H), 2.69 (m, 2H), 2.58 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.88 (s, 9H), 0.04 (s, 6H).

30 Synthesis of intermediate 27

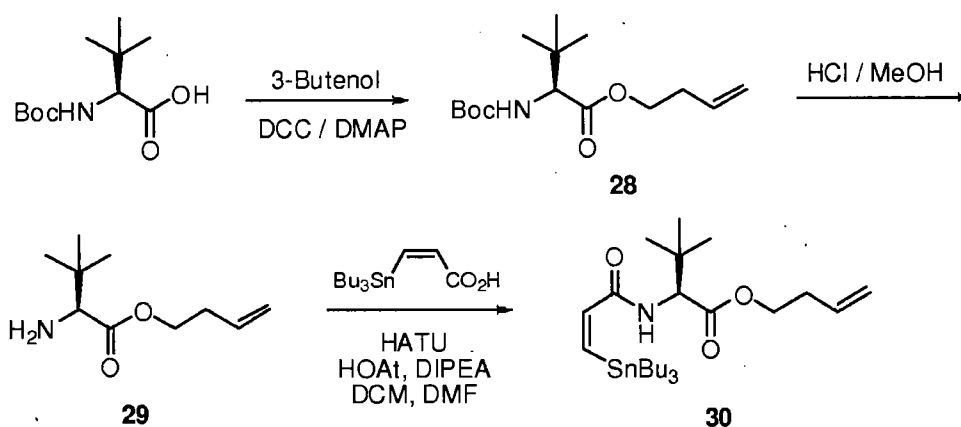
A solution of amino protected derivative 35 (288 mg, 0.487 mmol) in ethylenglycol (17 mL) was heated at 200 C for 15 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtrated and concentrated in vacuo to afford the 10 primary amine 36 (165 mg, yield: 69 %) as a yellow oil which was used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ : 8.46 (d, 1H, J= 11.1 Hz), 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H), 6.76 (t, 1H, J= 10.2 Hz), 6.77 (q, 1H, J= 10.2 15 Hz), 3.89 (m, 1H), 3.06 (s, 1H), 2.30 (m, 2H), 2.24 (m, 2H), 1.70 (s, 3H), 1.05 (s, 9H), 0.98 (s, 9H). Synthesis of intermediate 37. To a solution of amine 36 (221 mg, 0.450 mmol) in anhydrous DCM/DMF (4:1, 5 mL), a solution of (Z)-3-tributylstannylpropenoic acid (195 mg, 0.54 mmol) in anhydrous DCM was added, under argon 25 atmosphere, and then was cooled at 0 C. DIPEA (0.094 mL, 0.54 mmol), HOAt (73.5 mg, 0.54 mmol), and HATU (205 mg, 0.54 mmol) were added. To a solution of ester 26 (95 mg, 0.21 mmol) in MeOH (3.15 mL) at

- 5 room temperature, HCl 37% (26 μ L) was added and the reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with Dichloromethane (4 x 20 mL), dried and evaporated.
- 10 Filtration by column chromatography (hexane/EtOAc 10:1 to 2:1) afforded 210 mg (yield: 84%) of lactone 27.

¹H NMR (CDCl₃, 300 MHz) δ : 6.32 (dd, 1H, J = 0.6, 7.5 Hz), 6.08 (dd, 1H, J = 1.5, 9.3 Hz), 5.62 (dd, 1H, J = 3.0, 6.3 Hz), 4.28 (m, 1H), 3.63 (s, 3H), 2.84 (m, 1H), 2.54 (m, 1H), 2.34 (m, 1H), 1.13 (d, 3H, J = 6.6Hz).

EXAMPLE 4: SYNTHESIS OF FRAGMENT 30

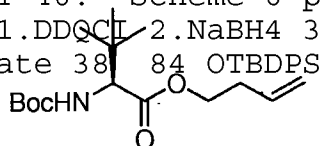
- 20 Scheme 4 provides an example of the synthesis of fragment 30.



Scheme 4

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 **37** (288 mg, yield: 77%) as an oil. ^1H NMR (300 MHz, CDCl_3) δ : 7.70-7.66 (m, 4H), 7.61 (d, 1H, $J = 10.2$ Hz), 7.42-7.38 (m, 6H), 7.02 (d, 1H, $J = 12.0$ Hz), 6.77-6.70 (m, 2H), 6.28 (d, 1H, $J = 9.6$ Hz), 4.82 (q, 1H, $J = 8.4$ Hz), 4.36 (d, 1H, $J = 9.6$ Hz), 3.89-3.86 (m, 1H), 2.24 (m, 4H), 1.94 (s, 3H), 1.50-1.41 (m, 6H), 1.30-1.23 (m, 6H), 1.07 (s, 9H), 0.92 (s, 9H), 0.92-0.84 (m, 15H).

EXAMPLE 6: SYNTHESIS OF FRAGMENT 40. Scheme 6 provides the synthesis of the fragment 40. OPMBOTBDPS Cl1.DDQCT 2.NaBH4 3 TBDPSCI, 17Imidazole



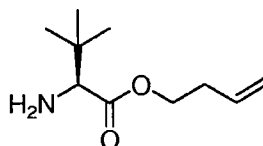
5

To a mixture of L-Boc-tert-leucine (300 mg, 1.3 mmol) in anhydrous DCM (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 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 ester **28** (300 mg, yield:81%).

15

^1H NMR (CDCl_3 , 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).

20 Synthesis of intermediate 29



25

The solution of the ester **28** (180 mg, 0.63mmol) in $\text{HCl}\cdot\text{MeOH}$ 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 H_2O , the resulting organic phase

2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) (8.70 g, 38 mmol) was added to a solution of 17 (12 g; 30 mmol) in dichloromethane-H₂O 5 (20:1) (236 mL) under Ar atmosphere at room temperature. After 1:30 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et₂O (400 mL) and washing with aqueous 1M NaOH (3 x 200 mL) and brine (200 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. Chromatographic separation of p-methoxybenzaldehyde was facilitated by reduction to p-methoxybenzyl alcohol. Towards this end, a solution of the residue obtained in MeOH (238 mL) with NaBH₄ (1.5 g, 38 mmol) under Ar atmosphere was maintained at room temperature for 1 h. The reaction mixture was then quenched by pouring into Et₂O (400 mL) and washing 15 with aqueous 1 M HCl (200 mL) and brine (200 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting oil was purified on silica gel (Hexane/EtOAc 10:1 to 4:1) to provide 5 (t, 2H, J = 6.7 Hz), 3.15 (s, 1H), 4.44-4.37 (m, 2H), 6.096 (s, 9H) yield). To a solution of secondary alcohol (6 g; 21 mmol) in anhydrous DMF (25 20 mL), under Ar atmosphere and at room temperature, imidazole (3.3 g, 48.6 mmol) was added in portions, followed by addition of tertButyldiphenylsilyl chloride (TBDPSCI) (7.6 mL, 29.3 mmol) and DMAP (77 mg, 0.63 mmol). The mixture was stirred overnight and at this point the crude was quenched with water (30 mL) and extracted with Et₂O (3 25 x 30 mL). The combined organic layers were washed thoroughly with water and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated. Flash chromatography (Hexane /EtOAc 100:1 to 30:1) provided 38 (9.6 g, 92%) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.67 (m, 4H), 7.45-7.37 (m, 6H), 6.25 (m, 2H), 5.51 (t, 1H, J = 7.8 Hz), 3.89 (m, 1H), 2.30 (t, 2H, J = 5.5 Hz), 1.02-1.14 (t, 2H, J = 6.4 Hz), 1.85 (s, 3H), 1.07 (s, 9H). 5 Synthesis of intermediate 39 HN CI A resealable Schlenk tube was charged with copper (I) iodide (1.05 g, 5.34 mmol), HOAc (123.3 mg, 0.9 mmol), and HATU (345 mg, 0.9 mmol) were added to a solution of 29 (168 mg, 0.9 mmol), and Boc-tert-10 LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., Tetrahedron Letters 1995, 36, 7115-7118) (6.8 g, 29.6 mmol), evacuated, stirred in anhydrous DME (1.18 mL, 11.1 mmol), vinyl iodide 38 (9.7 g, 18.5 mmol), and anhydrous DMF (92 mL) were added under argon. The Schlenk tube 15 was sealed, heated at 90C for 18h, bath was removed and the reaction mixture was stirred at room temperature for 1 hour, quenched with saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined 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 30 (340 mg; yield: 72%).

¹H NMR (CDCl₃, 300 MHz) δ: 7.01 (d, 1H, J = 12.3 Hz), 6.75 (d, 1H, J = 12.3Hz), 6.03 (d, 1H, J = 9.73 Hz), 5.84-5.69 (m, 1H), 5.14-5.05 (m, 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)

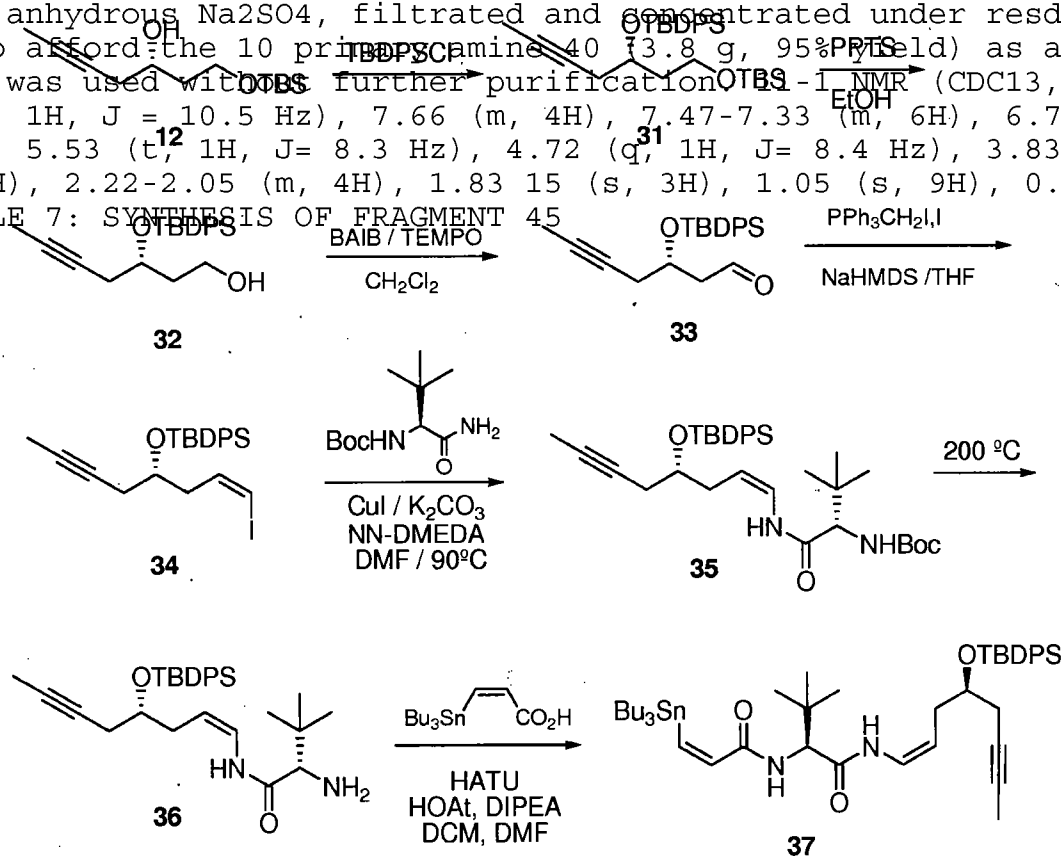
EXAMPLE 5: SYNTHESIS OF FRAGMENT 37.

¹H NMR (CDCl₃, 300 MHz) 6: 7.67 (m, 4H), 7.47-7.37 (m, 6H), 7.02 (d, 1H, J= 10.2 Hz), 6.67 (t, 1H, J= 9.4 Hz), 5.51 (t, 1H, J= 7.3 Hz), 5.23 (d, 1H, J= 8.4 Hz), 4.72 (q, 1H, J= 8.1 Hz), 3.81 (m, 2H), 2.18-2.04 (m, 25 4H), 1.86 (s, 3H), 1.42 (s, 9H), 1.05 (s, 9H), 0.97 (s, 9H). Synthesis of compound 40

86 CI A solution of amino protected derivative 39 (4.75 g, 7.6 mmol) in ethylene-glycol (140 mL) was heated at 200 °C for 15 min. The reaction mixture was then cooled at room temperature, diluted with 5 dichloromethane, 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 dichloromethane. The combined organic phases were washed with water, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to afford the 10 primary amine 40 (3.8 g, 95% yield) as a yellow oil which was used without further purification.

¹H NMR (CDCl₃, 300 MHz) 6: 8.66 (d, 1H, J = 10.5 Hz), 7.66 (m, 4H), 7.47-7.33 (m, 6H), 6.71 (t, 1H, J= 9.3 Hz), 5.53 (t, 1H, J= 8.3 Hz), 4.72 (q, 1H, J= 8.4 Hz), 3.83 (m, 1H), 3.19 (s, 1H), 2.22-2.05 (m, 4H), 1.83 15 (s, 3H), 1.05 (s, 9H), 0.99 (s, 9H).

EXAMPLE 7: SYNTHESIS OF FRAGMENT 45

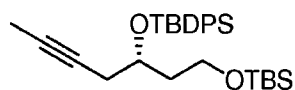


5

Scheme 5

Synthesis of intermediate 31

10



A solution of alcohol **12** (2.88 g, 11.9 mmol), tert-butyldiphenylsilyl chloride (4.39 mL, 16.89 mmol), and 4-(dimethylamino)pyridine (43.6 mg) in DMF (14 mL) was stirred overnight at room temperature. The mixture was diluted with water and extracted with Et₂O, and the organic phase was washed with brine, dried over anhydrous Na₂SO₄,

15

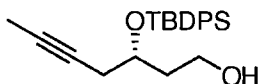
79

filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether **31** (5.3 g, 93%) as a colourless liquid.

¹H NMR (300 MHz, CDCl₃) δ: 7.70-7.66 (m, 4H), 7.40-7.34 (m, 6H),
5 3.99-3.95 (m, 1H), 3.70-3.62 (m, 2H), 2.23-2.22 (m, 2H), 1.84-1.81 (m, 2H), 1.69 (t, 3H, J = 2.7 Hz), 1.05 (s, 9H), 0.84 (s, 9H), 0.01 (s, 6H).

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

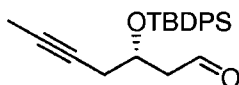
10 Synthesis of intermediate 32



PPTS (837.7 mg, 3.33 mmol) was added in one portion to a solution of
15 **31** (4 g, 8.33 mmol) in ethanol (80 mL). The reaction mixture was stirred at room temperature for 7 h and then was concentrated. The residue was diluted in DCM and washed with a saturated aqueous solution of NaHCO₃. The organic layer was extracted, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography
20 (Hex/EtOAc, 95:1) gave the silyl ether **32** (2.12 g, yield: 69%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H),
4,14-4.01 (m, 2H), 3.80-3.71 (m, 1H), 2.31-2.28 (m, 2H), 1.94-1.80 (m,
25 2H), 1.79 (t, 3H, J = 2.4 Hz), 1.07 (s, 9H).

Synthesis of intermediate 33



30

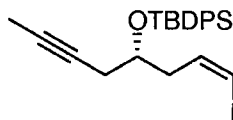
43 Scheme 7 5 Synthesis of intermediate 41 TBSO To a solution of anhydrous CrCl₂ (2.03 g, 16.55 mmol) in anhydrous THF (30 mL) at 0°C was added a solution of the aldehyde 1 (0.995 g, 10.276 mmol) and iodoform (2.17 g, 5.52 mmol) in anhydrous THF (10 mL). After 4 hours of stirring at 23°C, the mixture was diluted with Et₂O and filtered through Celite(r). The filtrate was concentrated to afford a residue which was purified by flash chromatography on silica (hexane/dichloromethane from 50:1 to 5:1) to give vinyl iodide 41 (0.7915 g, 57% yield) as a slightly yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ: 8.38 (dd, 1H, J = 14.5, 8.7 Hz), 8.14 (s, 1H), 7.72 (dd, 1H, J = 14.5, 8.7 Hz), 5.98 (dd, 1H, J = 14.5, 1.3 Hz), 3.76-3.70 (m, 1H), 3.67-3.58 (m, 2H), 2.37-2.32 (m, 2H), 1.62-1.53 (m, 2H), 0.96 (d, 3H, J = 7.2 Hz), 0.89 (m, 18H), 0.04 (s, 12H).

80
 (Diacetoxyiodo)benzene (BAIB) (1.93 g, 6.00 mmol) was added to a solution of alcohol **32** (2.0 g, 5.46 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (85 mg, 0.55 mmol) in anhydrous dichloromethane (27 mL). The reaction mixture was stirred at room temperature for 18 h until the alcohol was no longer detectable (TLC), and then it was quenched with a saturated aqueous solution of NH₄Cl and extracted with DCM (3 x 500 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 10:1) to afford **33** as colourless oil (1.64 g; yield: 82%).

¹H NMR (CDCl₃, 300 MHz) δ: 9.72 (s, 1H), 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H), 4.29 (m, 1H), 2.65 (m, 2H), 2.33 (m, 2H), 1.70 (s, 3H), 1.04 (s, 9H).

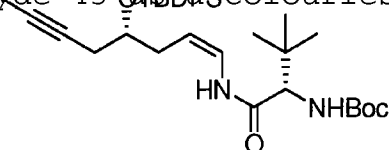
15

Synthesis of intermediate 34



20 To a suspension of iodomethyltriphenylphosphonium iodide (3.14 g; 6.04 mmol) in anhydrous THF (60 mL), at room temperature, a 1M solution of NaHMDS in THF (6.0 mL) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78 °C and a solution of **33** (1.57 g, 4.31 mmol) in anhydrous THF (35 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 and the combined filtrates were evaporated under reduced pressure and the resulting oil was purified by column chromatography (Hexane/EtOAc 50:1) affording **34** as yellow oil (1.31 g, yield: 62%).

88 Synthesis of intermediate 42 TBSO 5 To a solution of iodide 41 (786 mg, 1.58 mmol) in EtOH (15 mL) pyridinium p-toluenesulfonate (PPTS) (139 mg, 0.55 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the 10 resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 379.7 mg (63% yield) of alcohol 42 as colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 6.56 (dd, 1H, J = 14.5, 6.7 Hz), 6.01 (dd, 1H, J = 14.5, 1.3 Hz), 3.78-3.369 (m, 3H), 2.45-2.39 (m, 1H), 1.87-1.83 (m, 1H), 1.71-1.59 (m, 2H), 1.70-1.66 (m, 4H), 7.44-7.34 (m, 6H), 0.90 (s, 9H), 15 0.08 (s, 3H), 0.07 (s, 3H). Synthesis of intermediate 43 TBSO 20 To a 0C solution of alcohol 42 (389 mg, 1.01 mmol) in anhydrous DCM (10 mL), Dess-Martin periodinane (2.75 g, 1.07 mmol) was added. After 1 hour stirring at 0C and 30 min at 23C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic 25 layer was decanted, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc 20:1 to 2:1) afforded 349.3 mg (90% yield) of aldehyde 43 as a colourless oil.



A resealable Schlenk tube was charged with copper (II) iodide (85.1 mg, 0.447 mmol), potassium carbonate (0.618 g, 4.47 mmol) and Boc-*tert*-LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (0.514 g, 2.23 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (DMEDA) (0.095 mL, 0.89 mmol), vinyl iodide **34** (0.727g, 1.49 mmol) and anhydrous DMF (11 mL) were added under argon. 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 **35** (388 mg, yield: 44%) was obtained as an oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.70-7.66 (m, 4H), 7.53 (d, 1H, J = 10.5 Hz), 7.43-7.26 (m, 6H), 6.73 (t, 1H, J = 9.6 Hz), 5.29 (m, 1H), 4.79 (m, 1H), 3.85-3.81 (m, 2H), 2.39-2.30 (m, 1H), 2.27-2.21 (m, 3H), 1.88 (s, 3H), 1.43 (s, 9H), 1.06 (s, 9H), 0.97 (s, 9H).

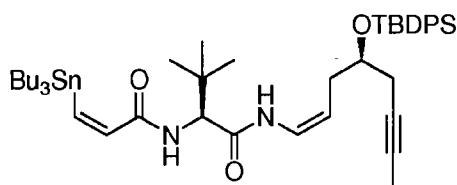
Synthesis of intermediate 36

89 ¹H NMR (CDCl₃, 300 MHz) δ: 9.77 (t, 1H, J = 2.1 Hz), 6.52 (dd, 1H, J = 14.7, 7.5 Hz), 6.05 (dd, 1H, J = 14.7, 1.2 Hz), 4.12-4.07 (m, 1H), 2.52-2.47 (m, 2H), 2.24-2.36 (m, 1H), 0.98 (d, 3H, J = 7.2 Hz), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). 5 Synthesis of intermediate 44 To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate 10 (348.4 mg, 1.37 mmol) and 18-crown-6 (722.3 mg, 2.73 mmol) in anhydrous THF (13 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (2.74 mL, 1.37 mmol) was added dropwise. After 15 min, aldehyde 43 (349.4 mg, 0.91 mmol) in anhydrous THF (9 mL) was added dropwise over a 15 period of 30 min and stirred at -78°C for 90 min. Then, the reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL), warmed to room temperature and diluted with dichloromethane (50 mL). The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography 20 (hexane/EtOAc 30:1 to 5:1) afforded 410. mg (99% yield) of 44 as a colorless oil. A solution of amino-protected derivative 5 (288 mg, 0.487 mmol) in ethyleneglycol (17 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 in MeOH (13.5 mL) were added until the solution reached pH 14 and then was extracted

thoroughly with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtrated and concentrated in vacuo to afford the primary amine **36** (165 mg, yield: 69 %) as a yellow oil which was used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ: 8.46 (d, 1H, J = 11.1 Hz), 7.71-7.63 (m, 4H), 7.45-7.26 (m, 6H), 6.76 (t, 1H, J = 10.2 Hz), 4.77 (q, 1H, J = 10.2 Hz), 3.89 (m, 1H), 3.06 (s, 1H), 2.30 (m, 2H), 2.24 (m, 2H), 1.70 (s, 3H), 1.05 (s, 9H), 0.98 (s, 9H).

Synthesis of intermediate 37



20

To a solution of amine **36** (221 mg, 0.450 mmol) in anhydrous DCM/DMF (4:1, 5 mL), a solution of (Z)-3-tributylstannylpropenoic acid (195 mg, 0.54 mmol) in anhydrous DCM was added, under argon atmosphere, and then was cooled at 0 °C. DIPEA (0.094 mL, 0.54 mmol), HOAt (73.5 mg, 0.54 mmol), and HATU (205 mg, 0.54 mmol)

25

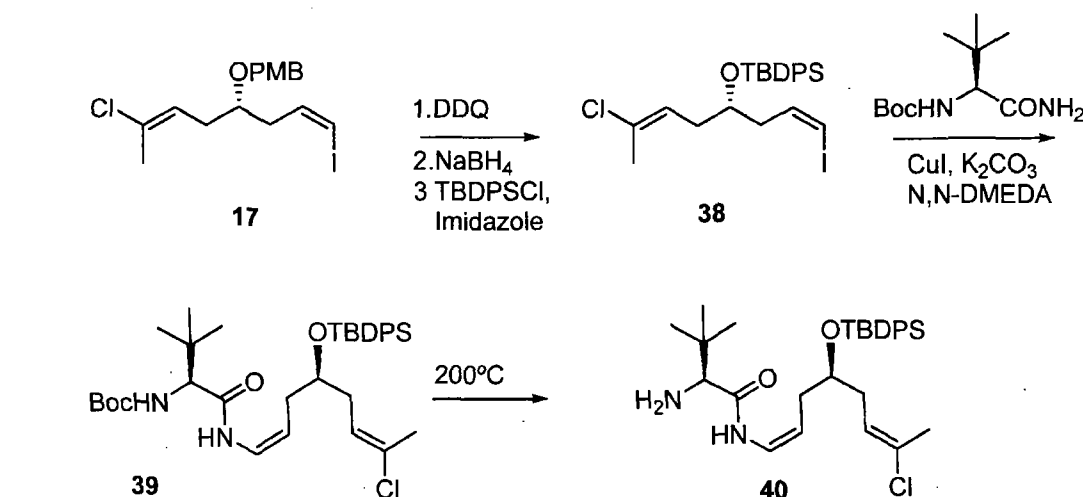
room temperature, aqueous HCl 37% (160 mL) was added and the 5 reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane (4 x 20 mL), dried and evaporated. The crude was purified by column chromatography (hexane/EtOAc 10:1 to 2:1) to yield 192 mg (69% yield) of lactone **45** as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ : 6.32 (dd, 1H, J = 14.7, 8.4 Hz), 6.21 (dd, 1H, J = 14.7, 1.2 Hz), 5.62 (dd, 1H, J = 8.6, 2.7 Hz), 4.27-4.19 (m, 1H), 3.64 (s, 3H), 2.61-2.54 (m, 1H), 2.43-2.34 (m, 2H), 1.14 (d, 3H, J = 6.8 Hz). MS (ESI) m/z 170 [M+Na]⁺. EXAMPLE 8: SYNTHESIS OF FRAGMENT 51. Scheme 8 provides an example of the synthesis of fragment 51. 91-150130-4748 0-170E02 MeOAC02Me CO₂Me HCl

- 5 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 anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **37** (288 mg, yield: 77%) as an oil.

¹H NMR (300 MHz, CDCl₃) δ : 7.70-7.66 (m, 4H), 7.61 (d, 1H, J = 10.2 Hz), 7.42-7.38 (m, 6H), 7.02 (d, 1H, J = 12.0 Hz), 6.77-6.70 (m, 2H), 6.28 (d, 1H, J = 9.6 Hz), 4.82 (q, 1H, J = 8.4 Hz), 4.36 (d, 1H, J = 9.6 Hz), 3.89-3.86 (m, 1H), 2.39-2.24 (m, 4H), 1.94 (s, 3H), 1.50-1.41 (m, 6H), 1.30-1.23 (m, 6H), 1.07 (s, 9H), 0.92 (s, 9H), 0.92-0.84 (m, 15H).

15 EXAMPLE 6: SYNTHESIS OF FRAGMENT 40.

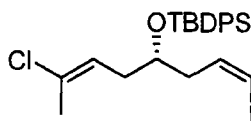
Scheme 6 provides the synthesis of the fragment 40.



Scheme 6

Synthesis of intermediate 38

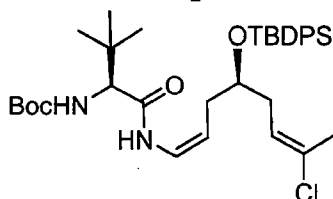
84



2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (8.70 g, 38 mmol) was added to a solution of **17** (12 g; 30 mmol) in dichloromethane-H₂O (20:1) (236 mL) under Ar atmosphere at room temperature. After 1:30 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et₂O (400 mL) and washing with aqueous 1M NaOH (3 x 200 mL) and brine (200 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. Chromatographic separation of *p*-methoxybenzaldehyde was facilitated by reduction to *p*-methoxybenzyl alcohol. Towards this end, a solution of the residue obtained in MeOH (236 mL) with NaBH₄ (1.5 g, 38 mmol) under Ar atmosphere was maintained at room temperature for 1 h. The reaction mixture was then quenched by pouring into Et₂O (400 mL) and washing with aqueous 1 M HCl (200 mL) and brine (200 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting oil was purified on silica gel (Hexane/EtOAc 10:1 to 4:1) to provide the secondary alcohol as colourless oil. (6 g, 73 % yield).

To a solution of secondary alcohol (6 g; 21 mmol) in anhydrous DMF (25 mL), under Ar atmosphere and at room temperature, imidazole (3.3 g, 48.6 mmol) was added in portions, followed by addition of *tert*-Butyldiphenylsilyl chloride (TBDPSCl) (7.6 mL, 29.3 mmol) and DMAP (77 mg, 0.63 mmol). The mixture was stirred overnight and at this point the crude was quenched with water (30 mL) and extracted with Et₂O (3 x 30 mL). The combined organic layers were washed thoroughly with water and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated. Flash chromatography (Hexane /EtOAc 100:1 to 30:1) provided **38** (9.6 g, 92%) as a colourless oil.

To a solution of carbon tetrabromide (8.74 g, 26.35 mmol) in dry dichloromethane (26 mL) was added dropwise a solution of 10 triphenylphosphine (1.38 g, 52.69 mmol) in anhydrous DCM (50 mL) at 0 C. The dark yellow solution was cooled to -78 C and aldehyde **1** (4.75 g, 13.2 mmol) in anhydrous DCM (13 mL) was added quickly. The resulting mixture was stirred at -78C (30 min) and at 0 C (10 min). The reaction was diluted with Et₂O and then washed with brine. The 15 aqueous layer was extracted with Et₂O and the organic layers were combined, dried, filtered and evaporated under reduced pressure. Purification by flash chromatography (hexane/dichloromethane, 5:1) afforded compound **38** (0.5 g, 15%) as a colourless oil. To a solution of the dibromocolefin in anhydrous THF (80 mL) was added dropwise a solution of *n*-butyllithium in hexane (7.03 mL) at -78 C. The reaction was warmed to -25 C and stirred for 1 h. The reaction was cooled back down to -78 C and methyl iodide (0.55 mL, 8.79 mmol) in anhydrous THF (20 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stir for an additional 1h. The reaction was quenched with a saturated aqueous



A resealable Schlenk tube was charged with copper (I) iodide (1.05 g, 5.54 mmol), potassium carbonate (7.65 g, 55.4 mmol) and Boc-*tert*-LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (6.8 g, 29.6 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (DMEDA) (1.18 mL, 11.1 mmol), vinyl iodide **38** (9.7 g, 18.5 mmol) and anhydrous DMF (92 mL) were added under argon. 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) affording compound **39** (5.8 g, yield 51%) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ: 7.67 (m, 4H), 7.47-7.37 (m, 6H), 7.02 (d, 1H, *J* = 10.2 Hz), 6.67 (t, 1H, *J* = 9.4 Hz), 5.51 (t, 1H, *J* = 7.3 Hz), 5.23 (d, 1H, *J* = 8.4 Hz), 4.72 (q, 1H, *J* = 8.1 Hz), 3.81 (m, 2H), 2.18-2.04 (m, 4H), 1.86 (s, 3H), 1.42 (s, 9H), 1.05 (s, 9H), 0.97 (s, 9H).

Synthesis of compound 40

10 solution of NH₄Cl then diluted with Et₂O. The organic layer was dried, filtered and evaporated under reduced pressure. Purification by flash chromatography (hexane/ dichloromethane from 50:1 to 5:1) afforded 2.77 mg (89% yield) of alkyne **46** as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) : 3.74-3.66 (m, 3H), 2.49-2.46 (m, 1H), 1.83-1.72 (m, 2H), 1.78 (s, 3H), 1.08 (d, 3H, J= 7.2 Hz), 0.89 (m, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H). Synthesis of intermediate **47** TBSO To a solution of **46** (200 mg, 0.56 mmol) in anhydrous toluene (7 mL), under Ar and at 23 C bis(cyclopentadienyl)zirconium(IV) chloride hydride (432.3 mg, 1.68 mmol) was added and the reaction was stirred at 50C for 1 hour. During this time the reaction solution turned of orange colour. The reaction was cooled to 23 C and iodine (284.3 mg, 1.12 mmol) was added in one portion. Stirring was continued for 30 min at room temperature and the reaction was diluted with hexane and filtered through Celite(r). The filtrate was concentrated to afford a solution of which was purified by flash chromatography (hexane/ dichloromethane from 50:1 to 5:1) to afford **48** (4.75 g, 76% yield) as a yellow oil.

- 5 ethylene-glycol (140 mL) was heated at 200 °C for 15 min. The reaction mixture was then cooled at room temperature, diluted with dichlorometane, 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 dichloromethane. The combined organic phases were washed with water, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to afford the primary amine **40** (3.8 g, 95% yield) as a yellow oil which was used without further purification.
- 10 ¹H NMR (CDCl₃, 300 MHz) δ: 8.66 (d, 1H, J = 10.5 Hz), 7.66 (m, 4H), 7.47-7.33 (m, 6H), 6.71 (t, 1H, J = 9.3 Hz), 5.53 (t, 1H, J = 8.3 Hz), 4.72 (q, 1H, J = 8.4 Hz), 3.83 (m, 1H), 3.19 (s, 1H), 2.22-2.05 (m, 4H), 1.83 (s, 3H), 1.05 (s, 9H), 0.99 (s, 9H).

EXAMPLE 7: SYNTHESIS OF FRAGMENT 45

Scheme 7 provides an example of the synthesis of fragment 45.

To a 0°C solution of alcohol **48** (87 mg, 0.22 mmol) in anhydrous DCM (2 mL), Dess-Martin periodinane (140 mg, 0.33 mmol) was added. After 1 hour stirring at 0°C and 30 min at 23°C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic 5 layer was decanted, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc 20:1 to 2:1) afforded 76.6 mg (86% yield) of aldehyde **49** as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 9.79 (t, 1H, J = 2.4 Hz), 5.98 (dd, 1H, J = 9.9, 1.5 Hz), 4.02-3.97 (m, 1H), 2.57-2.51 (m, 3H), 2.38 (s, 3H), 0.97 (d, 3H, J = 6.6 Hz), 0.87 (s, 3H), 0.04 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ: 201.5, 143.5, 95.1, 71.3, 49.3, 41.9, 28.3, 26.0, 18.2, 15.8, -4.2, -4.4.

Synthesis of intermediate 42

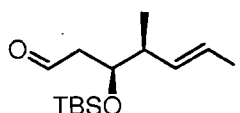
15 To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (73.7 mg, 0.29 mmol) and 18-crown-6 (153.4 mg, 0.58 mmol) in anhydrous THF (3 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide (KHMDS) solution in toluene (0.58 mL, 0.29 mmol) was added dropwise. After 15 min aldehyde **49** (76.6 mg, 0.19 mmol) was added drop wise in anhydrous THF (2 mL) over a period of 10 min and stirred at -78°C for 90 min. Then, the reaction was quenched with a saturated aqueous solution of NH₄Cl, warmed to room temperature and diluted with dichloromethane. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure.

and the reaction mixture was stirred at room temperature for 25 hours.

Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 379.7 mg (63% yield) of alcohol **42** as colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 6.56 (dd, 1H, J = 14.5, 6.7 Hz), 6.01 (dd, 1H, J = 14.5, 1.3 Hz), 3.78-3.3.69 (m, 3H), 2.45-2.39 (m, 1H), 1.87-1.83 (m, 1H), 1.71-1.59 (m, 2H), 1.00 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

Synthesis of intermediate 43



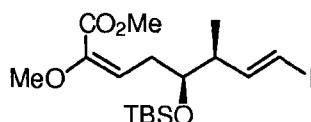
20

To a 0°C solution of alcohol **42** (389 mg, 1.01 mmol) in anhydrous DCM (10 mL), Dess-Martin periodinane (644 mg, 1.52 mmol) was added. After 1 hour stirring at 0°C and 30 min at 23°C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic layer was decanted, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc 20:1 to 2:1) afforded 349.3 mg (90% yield) of aldehyde **43** as a colourless oil.

30 Purification by column chromatography (hexane/EtOAc 30:1 to 5:1) 95
afforded 89.0 mg (100% yield) of **50** as a mixture E/Z (regioselectivity >
2.5:1 determined by ^1H NMR) as a colourless oil mixture. ^1H NMR (CDCl_3 , 300
MHz) for (2E,7E)-**50** δ : 6.28 (d, 1H, $J = 9.0$ Hz), 5.33 (t, 1H, $J = 9.0$ Hz),
3.84 (s, 3H), 3.61-3.57 (m, 1H), 3.61 (s, 3H), 2.77-2.70 (m, 1H),
2.64-2.55 (m, 1H), 2.49-2.37 (m, 1H), 2.30 (s, 3H), 0.96 (d, 3H, $J = 6.6$
Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).
10

^1H NMR (CDCl_3 , 300 MHz) δ : 9.77 (t, 1H, $J = 2.1$ Hz), 6.52 (dd, 1H, $J =$
14.7, 7.5 Hz), 6.05 (dd, 1H, $J = 14.7, 1.2$ Hz), 4.12-4.07 (m, 1H), 2.52-
2.47 (m, 2H), 2.2.43-2.36 (m, 1H), 0.98 (d, 3H, $J = 7.2$ Hz), 0.87 (s, 9H),
0.07 (s, 3H), 0.03 (s, 3H).

5 Synthesis of intermediate 44



To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate
10 (348.4 mg, 1.37 mmol) and 18-crown-6 (722.3 mg, 2.73 mmol) in
anhydrous THF (13 mL) stirred under argon atmosphere at -78°C , a 0.5
M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (2.74
mL, 1.37 mmol) was added dropwise. After 15 min aldehyde **43** (349.4
mg, 0.91 mmol) in anhydrous THF (9 mL) was added dropwise over a
15 period of 30 min and stirred at -78°C for 90 min. Then, the reaction was
quenched with a saturated aqueous solution of NH_4Cl (20 mL), warmed
to room temperature and diluted with dichloromethane (50 mL). The
organic phase was dried (anhydrous Na_2SO_4) and evaporated under
reduced pressure. Purification by column chromatography
20 (hexane/EtOAc 30:1 to 5:1) afforded 410. mg (99% yield) of **44** as a
mixture E/Z (regioselectivity > 5:1 determined by ^1H NMR).

^1H NMR (CDCl_3 , 300 MHz) for (2E,7E)-**44** δ : 6.51 (dd, 1H, $J = 14.4, 7.8$
Hz), 5.97 (dd, 1H, $J = 14.4, 1.2$ Hz), 5.29 (t, 1H, $J = 7.7$ Hz), 3.82 (s,
3H), 3.77-3.70 (m, 1H), 3.60 (s, 3H), 2.65-2.61 (m, 2H), 2.39-2.21 (m,
25 1H), 1.00 (d, 3H, $J = 6.9$ Hz), 0.89 (s, 9H), 0.04 (s, 6H).

Synthesis of intermediate 45

To a solution of ester 50 (90.8 mg, 0.19 mmol) in MeOH (3 mL) at room temperature, aqueous HCl 37% (34 mL) was added and the reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane, dried and evaporated. The crude was purified by column chromatography (hexane/EtOAc 10:1 to 2:1) to yield 34 mg (50% yield) of lactone 51 as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ : 5.99 (dd, 1H, *J* = 9.9, 1.2 Hz), 5.62 (dd, 1H, *J* = 5.1, 4.2 Hz), 4.19-4.11 (m, 1H), 3.64 (s, 3H), 2.78-2.70 (m, 1H), 2.41 (s, 3H), 2.42-2.37 (m, 2H), 1.11 (d, 3H, *J* = 6.6 Hz). 25

EXAMPLE 9: SYNTHESIS OF FRAGMENT 56 Scheme 9 provides an example of the synthesis of fragment 56. 96 OTBSOTBS 452

To a solution of ester **44** (410.9 mg, 0.90 mmol) in MeOH (13.5 mL) at room temperature, aqueous HCl 37% (160 μ L) was added and the reaction mixture was stirred for 6 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane (4 x 20 mL), dried and evaporated. The crude was purified by column chromatography (hexane/EtOAc 10:1 to 2:1) to yield 192 mg (69% yield) of lactone **45** as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ : 6.32 (dd, 1H, *J* = 14.7, 8.4 Hz), 6.21 (dd, 1H, *J* = 14.7, 1.2 Hz), 5.62 (dd, 1H, *J* = 6.6, 2.7 Hz), 4.27-4.19 (m, 1H), 3.64 (s, 3H), 2.61-2.54 (m, 1H), 2.43-2.34 (m, 2H), 1.14 (d, 3H, *J* = 6.9 Hz).

MS (ES) [*m/z*] = 331.1 [M+Na]⁺.

EXAMPLE 8: SYNTHESIS OF FRAGMENT 51

20

Scheme 8 provides an example of the synthesis of fragment 51.

OTBS To a solution of **52** (2.05 g, 5.17 mmol) in EtOH (50 mL) pyridinium p-toluenesulfonate (PPTS) (511.7 mg, 2.04 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then 15 the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 1.055 g (72% yield) of alcohol **53** as colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 5.76 (d, 1H, J = 9.9 Hz), 3.73-3.63 (m, 3H), 2.79 (s, 1H), 2.64-2.59 (m, 1H), 2.24 (bs, 1H), 1.80 (s, 3H), 1.70-1.60 (m, 2H), 0.95 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). Synthesis of intermediate **54** 25 OTBS

98 After 30 min stirring at 0 °C and 60 min at -23 °C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic layer was decanted, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/dichloromethane 5:1 to 1:1) afforded 100 mg (73% yield) of aldehyde **54** as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 9.79 (s, 1H), 7.91 (d, 1H, J = 10.2 Hz), 4.02-3.96 (m, 1H), 2.77 (s, 1H), 2.64-2.53 (m, 3H), 1.80 (s, 3H). The reaction was warmed to -25 °C and stirred for 1 h. The reaction

was cooled back down to -78 °C and methyl iodide (0.55 mL, 8.79

mmol) in anhydrous THF (9 mL) was added dropwise. The resulting

mixture was allowed to warm to room temperature and stir for an

additional 1h. The reaction was quenched with a saturated aqueous

10 solution of NH₄Cl then diluted with Et₂O. The organic layer was dried,

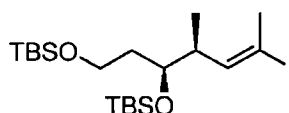
filtered and evaporated under reduced pressure. Purification by flash

chromatography (hexane/ dichloromethane from 50:1 to 5:1) afforded

2.77 mg (89% yield) of alkyne **46** as a colourless oil.

15 ¹H NMR (CDCl₃, 300 MHz) δ: 3.74-3.66 (m, 3H), 2.49-2.46 (m, 1H), 1.83-1.72 (m, 2H), 1.78 (s, 3H), 1.08 (d, 3H, J = 7.2 Hz), 0.89 (m, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H).

Synthesis of intermediate 47



20

To a solution of **46** (200 mg, 0.56 mmol) in anhydrous toluene (7 mL),

under Ar and at 23 °C bis(cyclopentadienyl)zirconium(IV) chloride

hydride (432.3 mg, 1.68 mmol) was added and the reaction was stirred

25 at 50°C for 1 hour. During this time the reaction solution turned of

orange colour. The reaction was cooled to 23 °C and iodine (284.3 mg,

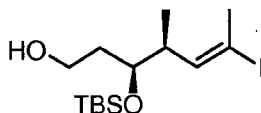
1.12 mmol) was added in one portion. Stirring was continued for 30 min

at room temperature and the reaction was diluted with hexane and

filtered through Celite®. The filtrate was concentrated to afford a

30 residue which was purified by flash chromatography eluting with

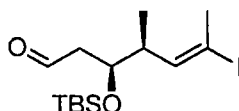
10 3H), 0.98 (d, 3H, J = 6.9 Hz), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H).
¹³C NMR (CDCl₃, 75 MHz) δ: 201.7, 141.2, 117.9, 86.6, 74.5, 71.8, 49.4, 39.7, 26.0, 18.2, 17.6, 16.2, -4.3, -4.4. Synthesis of intermediate 55 To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (768.6 mg, 3.02 mmol) and 18-crown-6 (1.60 g, 6.06 mmol) in 20 anhydrous THF (30 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide (KHMSD) solution in toluene (6.1 mL, 3.05 mmol) was added dropwise. After 15 min aldehyde 54 (578 mg, 2.02 mmol) in anhydrous THF (20 mL) was added dropwise over a period of 10 min and stirred at -78°C for 90 min. Then the reaction was 25 quenched with a saturated aqueous solution of NH₄Cl, warmed to room temperature and diluted with dichloromethane. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (hexane/EtOAc 30:1 to 5:1) afforded 839.4 mg (>100% yield) of 55 as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 6.07 (dd, 1H, J = 9.9, 1.5 Hz), 3.72-3.67 (m, 3H), 3.65-3.61 (m, 2H), 2.53-2.47 (m, 1H), 2.37 (s, 3H), 1.68-1.61 (m, 2H), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ¹³C NMR (CDCl₃, 300 MHz) δ: 201.7, 141.2, 117.9, 86.6, 74.5, 71.8, 49.4, 39.7, 26.0, 18.2, 17.6, 16.2, -4.3, -4.4. Synthesis of intermediate 56 10 To a solution of ester 55 (839.4 mg, 2.29 mmol) in MeOH (30 mL) at room temperature, aqueous HCl 37% (766 mL, 9.16 mmol) was added and the reaction mixture was stirred for 4 hours. Then the mixture 10 was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and



- To a solution of iodide **47** (140.4 mg, 0.27 mmol) in EtOH (2 mL) pyridinium p-toluenesulfonate (PPTS) (24 mg, 0.09 mmol) was added
 15 and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 90.3 mg (83% yield) of alcohol **48** as colourless oil.
- 20 ¹H NMR (CDCl₃, 300 MHz) δ: 6.01 (dd, 1H, J = 9.9, 1.5 Hz), 3.78-3.67 (m, 3H), 2.62-2.55 (m, 1H), 2.39 (s, 3H), 2.00-1.98 (m, 1H), 1.80-1.62 (m, 2H), 0.96 (d, 3H, J = 6.6 Hz), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

Synthesis of intermediate 49

25



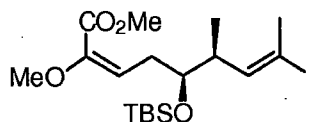
15 the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane, dried and evaporated. The crude was purified by column chromatography (hexane/EtOAc 10:1 to 1:3) to yield 312.7 mg (62% yield) of lactone **56** as a white solid. 20 ¹H NMR (CDCl₃, 300 MHz) δ: 5.72 (dd, 1H, J = 10.2, 1.8 Hz), 5.60 (dd, 1H, J = 5.1, 4.2 Hz), 4.20-4.10 (m, 1H), 3.64 (s, 3H), 2.85-2.2.77 (m, 1H), 2.81 (s, 1H), 2.41-2.36 (m, 2H), 1.84 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz) 25 ¹³C NMR (CDCl₃, 125 MHz) δ: 161.3, 145.1, 138.6, 118.9, 108.0, 85.9, 81.3, 74.8, 55.4, 37.2, 26.2, 17.5, 16.2. MS (ES) [m/z] = 243.2 [M+Na]⁺. EXAMPLE 10: SYNTHESIS OF FRAGMENT 62. 100. Scheme 10 provides an example of the synthesis of fragment 62. 31 OTBDPS BAIB / TEMPO CH₂Cl₂ 57 OTBDPS

1 hour stirring at 0 °C and 30 min at 23 °C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic layer was decanted, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/EtOAc 20:1 to 2:1) afforded 76.6 mg (86% yield) of aldehyde **49** as a colourless oil.

10 ¹H NMR (CDCl₃, 300 MHz) δ: 9.79 (t, 1H, J = 2.4 Hz), 5.98 (dd, 1H, J = 9.9, 1.5 Hz), 4.02-3.97 (m, 1H), 2.57-2.51 (m, 3H), 2.38 (s, 3H), 0.97 (d, 3H, J = 6.6 Hz), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H).
¹³C NMR (CDCl₃, 75 MHz) δ: 201.5, 143.5, 95.1, 71.3, 49.3, 41.9, 28.3, 26.0, 18.2, 15.8, -4.2, -4.4.

15

Synthesis of intermediate 50



20 To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (73.7 mg, 0.29 mmol) and 18-crown-6 (153.4 mg, 0.58 mmol) in anhydrous THF (3 mL) stirred under argon atmosphere at -78 °C, a 0.5 M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (0.58 mL, 0.29 mmol) was added dropwise. After 15 min aldehyde **49** (76.6 mg, 0.19 mmol) was added drop wise in anhydrous THF (2 mL) over a period of 10 min and stirred at -78°C for 90 min. Then, the reaction was quenched with a saturated aqueous solution of NH₄Cl, warmed to room temperature and diluted with dichloromethane. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure.

30 Purification by column chromatography (hexane/EtOAc 30:1 to 5:1)

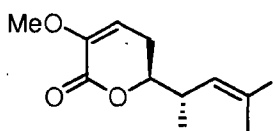
95

afforded 89.0 mg (100% yield) of **50** as a mixture E/Z (regioselectivity > 2.5:1 determined by ¹H NMR) as a colourless oil mixture.

¹H NMR (CDCl₃, 300 MHz) for (2*E*,7*E*)-**50** δ: 6.28 (d, 1H, *J* = 9.0 Hz),
5 5.33 (t, 1H, *J* = 9.0 Hz), 3.84 (s, 3H), 3.61-3.57 (m, 1H), 3.61 (s, 3H),
2.77-2.70 (m, 1H), 2.64-2.55 (m, 1H), 2.49-2.37 (m, 1H), 2.30 (s, 3H),
0.96 (d, 3H, *J* = 6.6 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

Synthesis of intermediate 51

10



To a solution of ester **50** (90.8 mg, 0.19 mmol) in MeOH (3 mL) at room
15 temperature, aqueous HCl 37% (34 μL) was added and the reaction
mixture was stirred for 6 hours. Then the mixture was neutralized with
a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic
solvent was evaporated under reduced pressure. The resulting
suspension was extracted with dichloromethane, dried and evaporated.
20 The crude was purified by column chromatography (hexane/EtOAc 10:1
to 2:1) to yield 34 mg (50% yield) of lactone **51** as a white solid.

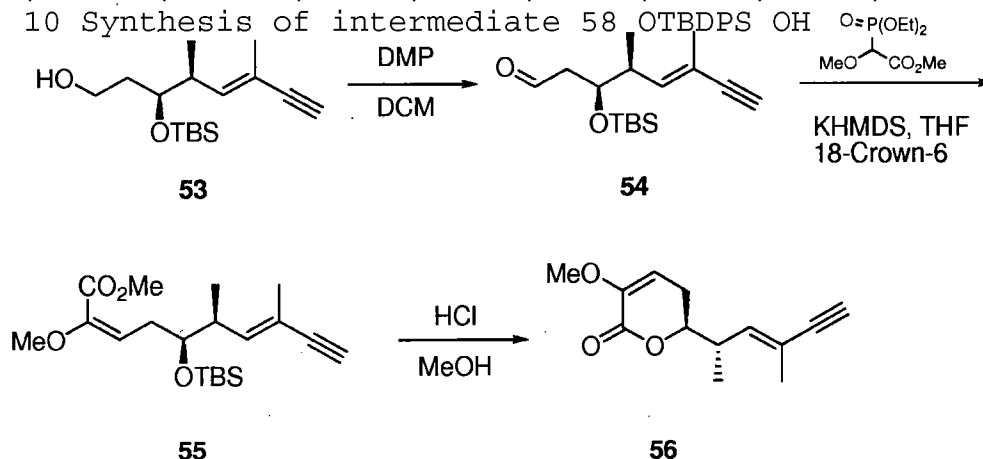
¹H NMR (CDCl₃, 300 MHz) δ: 5.99 (dd, 1H, *J* = 9.9, 1.2 Hz), 5.62 (dd,
1H, *J* = 5.1, 4.2 Hz), 4.19-4.11 (m, 1H), 3.64 (s, 3H), 2.78-2.70 (m, 1H),
2.41 (s, 3H), 2.42-2.37 (m, 2H), 1.11 (d, 3H, *J* = 6.6 Hz).

25

EXAMPLE 9: SYNTHESIS OF FRAGMENT 56

Scheme 9 provides an example of the synthesis of fragment 56.

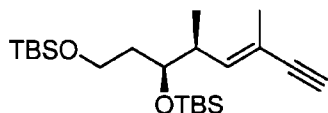
OTBS 10 A flask containing a mixture of **31** (4.73 g, 9.85 mmol), quinoline (0.582 mL, 4.92 mmol) and Lindlar catalyst (2.18 g) in ethyl acetate was evacuated and flushed with H₂. The reaction mixture was stirred at room temperature under H₂ (1 atm) for 2 h and then filtered through a 15 plug of celite. The plug was rinsed with ethyl acetate and the combined filtrates were washed with 0.1 % HCl. The organic layer was dried over 101 anhydrous Na₂SO₄, filtered and concentrated to afford intermediate **57** (4.27 g, yield: 90%) as a colourless oil that was used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ : 7.70-7.67 (m, 1H), 7.44-7.36 (m, 6H), 5.48-5.36 (m, 1H), 5.36-5.27 (m, 1H), 3.95-3.81 (m, 1H), 3.71-3.55 (m, 2H), 2.16 (dd, 2H, J = 6.9, 6.3 Hz), 1.73-1.65 (m, 2H), 1.41 (dd, 3H, J = 6.6, 1.2 Hz), 1.05 (s, 9H), 0.84 (s, 9H), -0.02 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ : 136.2, 134.8, 129.8, 127.8, 126.4, 125.8, 70.9, 60.4, 39.6, 34.8, 27.3, 26.2, 19.7, 18.5, 13.1, -5.1.



Scheme 9

5

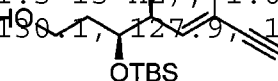
Synthesis of intermediate 52



10 A solution of 1.8 M of Lithium diisopropylamide in heptane/THF/ethylbenzene (8.96 mL, 16.13 mmol) was diluted in 88 mL of anhydrous THF. After cooling down to -78°C, trimethylsilyldiazomethane (8.06 mL, 2M in THF, 16.13 mmol) was added and the resulting mixture was stirred for 30 min. A solution of **4** 15 (4.377 g, 10.75 mmol) in anhydrous THF (35 mL) was added and stirring was maintained for 1h at -78 °C and for 2h at 23 °C. The reaction mixture was added to ice-cooled water, and extracted with Et₂O. The combined organic layers were dried (anhydrous Na₂SO₄) and the solvent was removed. The residue was purified by flash 20 chromatography to afford 2.38 g (55% yield) of **52** as yellow oil.

15 PPTS (837.7 mg, 3.33 mmol) was added in one portion to a solution of **57** (4 g, 8.33 mmol) in ethanol (80 mL). The reaction mixture was stirred at room temperature for 7 h and then was concentrated. The residue was diluted in DCM and washed with a saturated solution of NaHCO₃. The organic layer was extracted, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether **58** (2.12 g, yield: 69%) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.73-7.69 (m, 4H), 7.44-7.36 (m, 6H), 5.44-5.38 (m, 1H), 5.21-5.17 (m, 1H), 4.01-3.94 (m, 1H), 3.84-3.76 (m, 1H), 3.69-3.64 (m, 1H), 2.32-2.14 (m, 2H), 1.89-1.78 (m, 1H), 1.70-1.60 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ: 136.2, 134.1, 130.0, 127.8, 126.3, 125.9, 72.3, 60.1, 37.7, 34.3, 27.4, 22.7, 19.3, 13.0. Synthesis of intermediate 59 102 OTBPS BAIB (1.97 g, 6.11 mmol) was added to a solution of alcohol **58** (2.05 g, 5.56 mmol) and TEMPO (86.87 mg, 0.56 mmol) in 25 mL of DCM. The reaction mixture was stirred at room temperature for 143 h, 166.3, 187.1, 73.7, 72.8, 69.0, 38.6, 38.0, 26.1, 26.1, 18.5, 18.3, 17.4, 15.3, 4.2, 5.1. and then it was quenched with a saturated aqueous solution of NH₄Cl, and extracted with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography 10 (Hexane/DCM 5:1 to 1:2) to give **59** (1.15 g, 53%) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 9.72 (t, 1H, J = 2.7 Hz), 7.74-7.67 (m, 4H), 7.48-7.37 (m, 6H), 5.56-5.45 (m, 1H), 5.32-5.23 (m, 1H), 4.29-4.20 (m, 1H), 2.51-2.48 (m, 2H), 2.31-2.27 (m, 2H), 1.43 (dd, 3H, J = 6.9, 1.5 Hz), 1.06 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) δ: 202.3, 136.1, 134.0, 130.1, 127.9, 127.4,

10

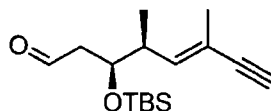


To a solution of **52** (2.05 g, 5.17 mmol) in EtOH (50 mL) pyridinium p-toluenesulfonate (PPTS) (511.7 mg, 2.04 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 1.055 g (72% yield) of alcohol **53** as colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 5.76 (d, 1H, J = 9.9 Hz), 3.73-3.63 (m, 3H), 2.79 (s, 1H), 2.64-2.59 (m, 1H), 2.24 (bs, 1H), 1.80 (s, 3H), 1.70-1.60 (m, 2H), 0.95 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

Synthesis of intermediate 54

25



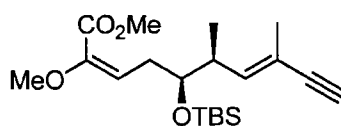
To a 0°C solution of alcohol **53** (140 mg, 0.48 mmol) in anhydrous DCM (5 mL), Dess-Martin periodinane (308.5 mg, 0.73 mmol) was added.

125.1, 69.4, 50.1, 35.1, 27.2, 19.5, 13.1. Synthesis of intermediate 60 20
 OTBDPS To a suspension of iodomethyltriphenylphosphorane (3.32 g, 6.38
 mmol) in anhydrous THF (60 mL) at room temperature 6.83 mL of a 1M 25
 solution of NaHMDS (6.38 mmol) in THF was slowly added. After stirring for
 2 min, the yellow mixture was cooled to -78 °C and a solution of 59 (1.67 g,
 4.56 mmol) in anhydrous THF (40 mL) was then added. The reaction mixture
 was stirred at -78 °C for 90 min, then at room temperature for 5 min,
 diluted with hexane and filtered through a 103 plug celite/SiO₂. The plug
 was rinsed with hexane/EtOAc (10:1 to 5:1) to afford compound 60 (2 g,
 yield: 89%) as a colourless oil that was used without further purification.
 After 30 min stirring at 0 °C and 60 min at 23 °C the reaction mixture
 was quenched with a saturated aqueous solution of NaHCO₃. The
 organic layer was decanted, dried over anhydrous Na₂SO₄ and
 concentrated under reduced pressure. Purification by column
 chromatography (hexane/EtOAc 10:1 to 5:1) afforded 100 mg
 (73% yield) of aldehyde **54** as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 9.79 (t, 1H, *J* = 2.4 Hz), 5.72 (d, 1H, *J* =
 10.2 Hz), 4.02-3.96 (m, 1H), 2.77 (s, 1H), 2.64-2.53 (m, 3H), 1.80 (s,
 10 3H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H).
¹³C NMR (CDCl₃, 75 MHz) δ: 201.7, 141.2, 117.9, 86.6, 74.5, 71.8, 49.4,
 39.7, 26.0, 18.2, 17.6, 16.2, -4.3, -4.4.

Synthesis of intermediate 55

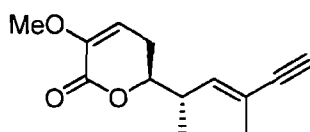
15



To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate
 (768.6 mg, 3.02 mmol) and 18-crown-6 (1.60 g, 6.06 mmol) in
 20 anhydrous THF (30 mL) stirred under argon atmosphere at -78°C, a 0.5
 M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (6.1
 mL, 3.05 mmol) was added dropwise. After 15 min aldehyde **54** (578
 mg, 2.02 mmol) in anhydrous THF (20 mL) was added dropwise over a
 period of 10 min and stirred at -78°C for 90 min. Then, the reaction was
 25 quenched with a saturated aqueous solution of NH₄Cl, warmed to room
 temperature and diluted with dichloromethane. The organic phase was
 dried (anhydrous Na₂SO₄) and evaporated under reduced pressure.
 Purification by column chromatography (hexane/EtOAc 30:1 to 5:1)
 afforded 839.4 mg (>100% yield) of **55** as a colourless oil mixture E/Z
 30 (regioselectivity > 4:1 determined by ¹H NMR).

Synthesis of intermediate 61 OTBDPS BOCHNiN 0 15 A resealable Schlenk tube was charged with copper (I) iodide (232.4 mg, 1.22 mmol), potassium carbonate (1.688 g, 12.23 mmol) and Boc-tertLeuCONH2 (2.474 g, 6.12 mmol), evacuated and filled with argon. N,NDimethylethylenediamine (0.26 mL, 2.45 mmol), vinyl iodide 60 (2 g, 4.08 mmol) and anhydrous DMF (35 mL) were added under argon. The 20 Schlenk tube was sealed, heated at 90C 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 15 silica gel (Hexane/ EtOAc, 20:1 to 15:1). Intermediate 61 (1.06 g, yield: 44 %) was obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ: 5.72 (dd, 1H, J = 10.2, 1.8 Hz), 5.60 (dd, 1H, J = 5.1, 4.2 Hz), 4.20-4.10 (m, 1H), 3.64 (s, 3H), 2.85-2.27 (m, 1H), 2.81 (s, 1H), 2.41-2.36 (m, 2H), 1.84 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz). ¹³C NMR (CDCl₃, 125 MHz) δ: 161.3, 145.1, 138.6, 118.9, 108.0, 85.9, 81.3, 74.8, 55.4, 37.2, 26.2, 17.5, 16.2. MS (ES) [m/z] = 243.2 [M+Na]⁺.

Synthesis of intermediate 56 The reaction



10

To a solution of ester **55** (839.4 mg, 2.29 mmol) in MeOH (30 mL) at room temperature, aqueous HCl 37% (766 µL, 9.16 mmol) was added and the reaction mixture was stirred for 4 hours. Then the mixture was neutralized with a saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent was evaporated under reduced pressure. The resulting suspension was extracted with dichloromethane, dried and evaporated. The crude was purified by column chromatography (hexane/EtOAc 10:1 to 1:3) to yield 312.7 mg (62% yield) of lactone **56** as a white solid.

20

¹H NMR (CDCl₃, 300 MHz) δ: 5.72 (dd, 1H, J = 10.2, 1.8 Hz), 5.60 (dd, 1H, J = 5.1, 4.2 Hz), 4.20-4.10 (m, 1H), 3.64 (s, 3H), 2.85-2.27 (m, 1H), 2.81 (s, 1H), 2.41-2.36 (m, 2H), 1.84 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz).

25

¹³C NMR (CDCl₃, 125 MHz) δ: 161.3, 145.1, 138.6, 118.9, 108.0, 85.9, 81.3, 74.8, 55.4, 37.2, 26.2, 17.5, 16.2.

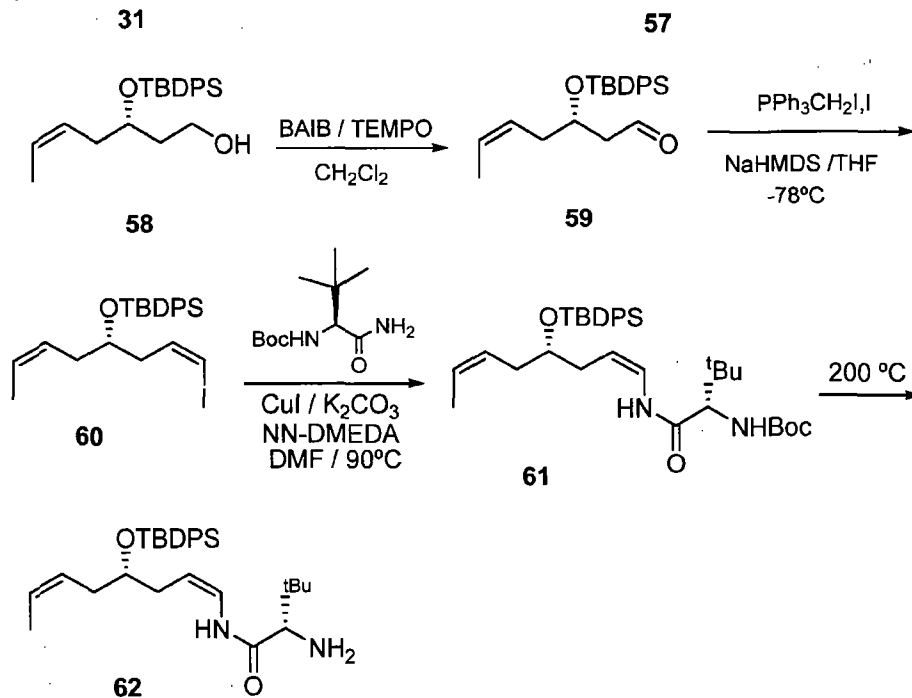
MS (ES) [m/z] = 243.2 [M+Na]⁺.

EXAMPLE 10: SYNTHESIS OF FRAGMENT 62

30

10 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 Na₂SO₄, filtrated and concentrated in vacuo to afford the 15 primary amine 62 (435 mg, 62%) as a white foam after purification by flash chromatography (Hexane/EtOAc 10:1 to 1:2). ¹H NMR (CDCl₃, 300 MHz) δ : 8.50 (d, 1H, J = 10.8 Hz), 7.70-7.66 (m, 4H), 7.45-7.33 (m, 6H), 6.67 (dd, 1H, J = 11.1, 9.3 Hz), 5.48-5.40 (m, 1H), 5.36-5.28 (m, 1H), 4.79 (dd, 1H, J = 16.2, 7.5 Hz), 3.87-3.79 (m, 20 1H), 3.08 (s, 1H), 2.22-2.14 (m, 4H), 1.43 (d, 3H, J = 6.9 Hz), 1.05 (s, 9H), 0.97 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) δ : 171.0, 136.1, 134.5, 129.8, 127.8, 126.3, 126.2, 122.1, 107.6, 72.6, 64.4, 34.0, 33.4, 32.8, 27.2, 26.9, 19.6, 13.2. 25

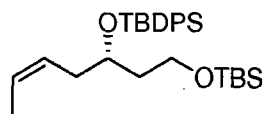
EXAMPLE 11: SYNTHESIS OF FRAGMENT 63 Scheme 11 provides an example of the synthesis of fragment 63. Scheme 11 Synthesis of intermediate 63 OTBDPS



Scheme 10

5

Synthesis of intermediate 57



10

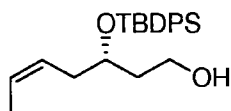
A flask containing a mixture of **31** (4.73 g, 9.85 mmol), quinoline (0.582 mL, 4.92 mmol) and Lindlar catalyst (2.18 g) in ethyl acetate was evacuated and flushed with H₂. The reaction mixture was stirred at room temperature under H₂ (1 atm) for 2 h and then filtered through a plug of celite. The plug was rinsed with ethyl acetate and the combined filtrates were washed with 0.1 % HCl. The organic layer was dried over

15

To a solution of amine 62 (575 mg, 1.17 mmol) in anhydrous DCM/DMF (4:1, 12.5 mL), a solution of (Z)-3-tributylstannylpropenoic 10 acid (505.6 mg, 1.4 mmol) in anhydrous DCM was added, under argon atmosphere, and then was cooled at 0°C. DIPEA (0.243 mL, 1.76 mmol), 7-hydroxybenzotriazole (HOBt) (189.2 mg, 1.4 mmol), and HATU (532.28 mg, 1.4 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2 h, quenched with a saturated aqueous solution of NEt_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 63 (780.4 mg; yield: 77%) as a white foam. ^1H NMR (CDCl_3 , 300 MHz) δ : 7.70-7.68 (m, 4H), 7.43-7.36 (m, 6H), 7.02 (d, 1H, $J = 12.3$ Hz), 7.00 (d, 1H, $J = 10.8$ Hz), 6.75 (d, 1H, $J = 12.3$ Hz), 6.66 (t, 1H, $J = 9.3$ Hz), 7.70-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.48 (m, 1H), 5.38-5.28 (m, 1H), 5.36-5.27 (m, 1H), 3.95-3.87 (m, 1H), 3.71-3.55 (m, 2H), 2.16 (m, 1H), 3.89-3.82 (m, 1H), 2.26-2.02 (m, 4H), 1.50-1.42 (m, 6H), 1.43 (d, 106 3H, $J = 6.9$ Hz), 1.37 (d, 3H, $J = 6.9$ Hz), 1.07 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz) δ : 168.0, 166.2, 153.8, 136.3, 136.1, 134.3, 130.0, 127.8, 126.7, 126.0, 121.6, 109.0, 72.6, 60.7, 3.7, 34.0, 32.7, 13.0. Scheme 12 provides the synthesis of several compounds of the 10 invention.

10

Synthesis of intermediate 58



- 15 PPTS (837.7 mg, 3.33 mmol) was added in one portion to a solution of **57** (4 g, 8.33 mmol) in ethanol (80 mL). The reaction mixture was stirred at room temperature for 7 h and then was concentrated. The residue was diluted in DCM and washed with a saturated solution of NaHCO_3 . The organic layer was extracted, dried over anhydrous Na_2SO_4 , filtered and concentrated. Flash chromatography (Hex/EtOAc, 95:1) gave the silyl ether **58** (2.12 g, yield: 69%) as a colourless oil.
- 20 ^1H NMR (CDCl_3 , 300 MHz) δ : 7.73-7.69 (m, 4H), 7.44-7.36 (m, 6H), 5.44-5.38 (m, 1H), 5.21-5.17 (m, 1H), 4.01-3.94 (m, 1H), 3.84-3.76 (m, 1H), 3.69-3.64 (m, 1H), 2.32-2.14 (m, 2H), 1.89-1.78 (m, 1H), 1.70-1.60 (m, 1H), 1.37 (d, 3H, $J = 6.9$ Hz), 1.07 (s, 9H).
- 25 ^{13}C NMR (CDCl_3 , 75 MHz) δ : 136.2, 134.1, 130.0, 127.8, 126.3, 125.9, 72.3, 60.1, 37.7, 34.3, 27.2, 19.5, 13.0.

Synthesis of intermediate 59

OTBS 66a R=IBu 066b R=iPr 107 Synthesis of intermediate 64a 5 (Z)
 To a solution of iodo compound 9 (11 mg, 0.033 mmol) in DMF/Et₃N (0.25 ml and 0.05 ml) under N₂ at -20°C, Pd(Ph₃P)₂Cl₂ (2.3 mg, 0.0033 mmol) and CuI (1.9 mg, 0.01 mmol) were added. Then, compound 22a 10 (15 mg, 0.03 mmol in 0.1 ml DMF) was added and the reaction mixture was stirred at -20 °C to room temperature for 3 hours. The crude was quenched with H₂O and extracted with ethyl acetate. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (Ethyl acetate/hexanes 15 mixture) to afforded pure compound 64a (10 mg, yield: 46%). ¹H NMR (CDCl₃, 300 MHz) δ: 7.75 (d, 1H, J = 10.5 Hz), 6.70 (t, 1H, J = 10.2 Hz), 6.50 (d, 1H, J = 9.3 Hz), 6.38 (d, 1H, J = 12.3 Hz), 5.60 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 4.87 (q, 1H, J = 8.1 Hz), 4.37 (d, 1H, J = 9.3 Hz), 4.21 (m, 1H), 3.77 (m, 1H), 3.64 (s, 3H), 2.87 (m, 1H), 2.40 (m, 2.2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.01 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). Synthesis of intermediate 59

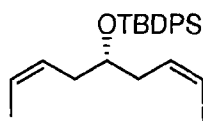
5 reaction mixture was stirred at room temperature for 16-18 h until the alcohol was no longer detectable (TLC), and then it was quenched with a saturated aqueous solution of NH₄Cl, and extracted with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/DCM 5:1 to 1:2) to give **59** (1.733 mg, yield: 79%) as a colourless oil.

¹H NMR (CDCl₃, 300 MHz) δ: 9.72 (t, 1H, J = 2.7 Hz), 7.74-7.67 (m, 4H), 7.48-7.37 (m, 6H), 5.56-5.45 (m, 1H), 5.32-5.23 (m, 1H), 4.29-4.20 (m, 1H), 2.51-2.48 (m, 2H), 2.31-2.27 (m, 2H), 1.43 (dd, 3H, J = 6.9, 1.5 Hz), 1.06 (s, 9H).

¹³C NMR (CDCl₃, 75 MHz) δ: 202.3, 136.1, 134.0, 130.1, 127.9, 127.4, 125.1, 69.4, 50.1, 35.1, 27.2, 19.5, 13.1.

Synthesis of intermediate 60

20

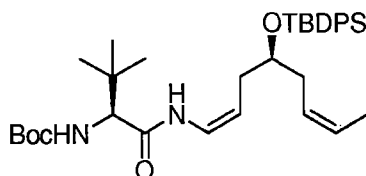


To a suspension of iodomethyltriphenylphosphorane (3.32 g, 6.38 mmol) in anhydrous THF (60 mL) at room temperature 6.83 mL of a 1M solution of NaHMDS (6.38 mmol) in THF was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78 °C and a solution of **59** (1.67 g, 4.56 mmol) in anhydrous THF (40 mL) was then added. The reaction mixture was stirred at -78 °C for 90 min, then at room temperature for 5 min, diluted with hexane and filtered through a

OMe To a solution of **9** (40 mg, 0.113 mmol) in DMF/Et₃N (1 ml and 0.19 ml) at -20°C, Pd(Ph₃P)₂Cl₂ (7.9 mg, 0.113 mmol) and CuI (6.5 mg, 0.0345 mmol) were added. Then, **22b** (50 mg, 0.113 mmol in 0.4 ml DMF) was added and the reaction was stirred at -20°C to room temperature for 3 hours. The crude mixture was quenched with H₂O and extracted with Ethyl acetate. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column 10 chromatography (Ethyl acetate/hexanes mixture) to afford pure **64h** (40 mg, yield: 54%). ¹H NMR (CDCl₃, 300 MHz) δ: 7.77 (d, 1H, J = 11.4 Hz), 6.75 (t, 1H, J = 10.2 Hz), 6.41-6.36 (m, 2H), 5.64-5.56 (m, 3H), 5.46 (d, 1H, J = 11.7 Hz), 4.25-4.16 (m, 1H), 3.84-3.76 (m, 1H), 3.65 (s, 3H), 2.92-2.81 (m, 1H), 2.44-2.39 (m, 2H), 2.22-2.12 (m, 5H), 2.10 (s, 3H), 2.03 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 0.99 (dd, 6H, J = 9.3; 6.9 Hz), 0.89 (s, 9H), 0.0080 (s, 3H), 0.0064 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ: 138.2, 136.2, 134.3, 129.9, 127.8, 126.4, 126.0, 84.1, 71.9, 41.6, 34.5, 27.2, 19.6, 13.2. (Hexane/EtOAc 3:1 to 1:2) to give 10 alcohol **65a** (5 mg; yield: 42 %).

10

Synthesis of intermediate 61



- 15 A resealable Schlenk tube was charged with copper (I) iodide (232.4 mg, 1.22 mmol), potassium carbonate (1.688 g, 12.23 mmol) and Boc-*tert*-LeuCONH₂ (2.474 g, 6.12 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (0.26 mL, 2.45 mmol), vinyl iodide **60** (2 g, 4.08 mmol) and anhydrous DMF (35 mL) were added under argon. The
- 20 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
- 25 silica gel (Hexane/ EtOAc, 20:1 to 15:1). Intermediate **61** (1.06 g, yield: 44 %) was obtained as an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.67 (m, 4H), 7.43-7.35 (m, 6H), 7.13 (d, 1H, J = 10.5 Hz), 6.67 (dd, 1H, J = 10.2, 9.6 Hz), 5.56-5.45 (m, 1H),

¹H NMR (CDCl₃, 300 MHz) δ: 8.78 (d, 1H, J = 9.6 Hz), 6.77 (t, 1H, J = 9.0 Hz), 6.57 (d, 1H, J = 9.0 Hz), 6.38 (d, 1H, J = 12.3 Hz), 5.60 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 4.90 (q, 1H, J = 8.7 Hz), 4.29 (d, 1H, J = 9.6 Hz), 4.23 (m, 1H), 3.80 (m, 1H), 3.65 (s, 3H), 2.86 (m, 1H), 2.66 (bs, 1H), 2.40 (m, 2H), 2.21 (m, 4H), 2.07 (s, 3H), 2.04 (s, 3H), 1.15 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H). Synthesis of compound 65b OMe To a solution of 64h (40 mg, 0.06 mmol) in anhydrous THF (0.9 ml) under N₂ and at room temperature, TBAF 1M in THF (0.12 ml, 0.0675 mmol) was added. The reaction was stirred at room temperature for 16 hours and then quenched with NH₄Cl and extracted with CH₂Cl₂. The organic phase was dried (anhydrous Na₂SO₄), evaporated under reduced pressure. Purification by column chromatography (Ethyl acetate/hexanes mixture) afforded pure 65b (15 mg, yield: 45%). ¹H NMR (CDCl₃, 300 MHz) δ: 8.95 (d, 1H, J = 10.2 Hz), 6.77 (t, 1H, J = 9.3 Hz), 6.60 (d, 1H, J = 9.0 Hz), 6.38 (d, 1H, J = 12.6 Hz), 5.64-5.60 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 4.88 (q, 1H, J = 8.4 Hz), 4.34 (dd, 1H, J = 8.7; 7.2 Hz), 4.27-4.20 (m, 1H), 3.82-3.74 (m, 1H), 3.65 (s, 3H), 2.92-2.82 (m, 1H), 2.45-2.38 (m, 2H), 2.11-2.04 (m, 5H), 1.57-1.45 (m, 6H), 1.28-1.23 (m, 3H), 1.15 (d, 6H, J = 6.6 Hz). Synthesis of compound 66a OMe To a solution of 65a (3.5 mg, 0.0062 mmol) in anhydrous DCM (0.45 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (1 µl, 0.0075 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (100 mg). 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 (50 mL) was heated at 200 °C for 10-20 min. The reaction

10 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 Na₂SO₄, filtrated and concentrated in vacuo to afford the

15 primary amine **62** (435 mg, 62%) as a white foam after purification by flash chromatography (Hexane/EtOAc 10:1 to 1:2).

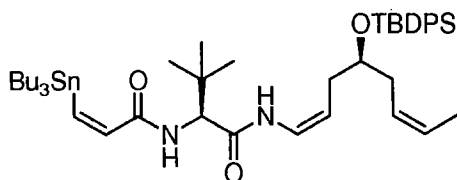
¹H NMR (CDCl₃, 300 MHz) δ: 8.50 (d, 1H, J = 10.8 Hz), 7.70-7.66 (m, 4H), 7.45-7.33 (m, 6H), 6.67 (dd, 1H, J = 11.1, 9.3 Hz), 5.48-5.40 (m, 1H), 5.36-5.28 (m, 1H), 4.79 (dd, 1H, J = 16.2, 7.5 Hz), 3.87-3.79 (m, 20 1H), 3.08 (s, 1H), 2.22-2.14 (m, 4H), 1.43 (d, 3H, J = 6.9 Hz), 1.05 (s, 9H), 0.97 (s, 9H).

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

25 EXAMPLE 11: SYNTHESIS OF FRAGMENT 63

Scheme 11 provides an example of the synthesis of fragment 63.

10 product which was purified by column chromatography (Hexane/EtOAc 2:1 to 1:2) affording compound 66a (2.5 mg, yield: 70%). NMR (CDCl₃, 500 MHz) δ : 8.72 (d, 1H, J = 10.5 Hz), 6.84 (t, 1H, J = 9.0 Hz), 6.66 (d, 1H, J = 10.0 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.60 (m, 3H), 5.46 (d, 1H, J = 12.0 Hz), 4.82 (q, 1H, J = 8.0 Hz), 4.42 (m, 2H), 4.22 (m, 1H), 3.65 (s, 3H), 2.88 (m, 1H), 2.44-2.32 (m, 6H), 2.10 (s, 3H), 2.06 (s, 3H), 1.15 (d, 3H, J = 7.0 Hz), 1.05 (s, 9H). MS (ES) (m/z) 604.2 [M+], 626.2 (M+Na⁺). Synthesis of compound 66b To a solution of 65b (32 mg, 0.06 mmol) in CH₂Cl₂ (4.2 ml) at r.t., triethylacetate isocyanate (TCAI) (8.5 μ l, 0.072 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral 5 Alumina was added (450 mg) while stirring for additional 30 min. The reaction mixture was filtered over alumina using a mixture of CH₂Cl₂/MeOH 1:1 and after evaporation of the solvent, the product was purified by column chromatography (Hexane/EtOAc mixtures) to afford pure 66b (12 mg, yield: 35%). ¹H NMR (CDCl₃, 300 MHz) δ : 8.90 (d, 1H, J = 10.8 Hz), 6.84 (t, 1H, J = 9.0 Hz), 6.74 (d, 1H, J = 8.7 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.64-5.58 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 5.38 (br s, 2H), 4.86-4.78 (m, 1H), 4.44-4.39 (m, 2H), 4.27-4.19 (m, 1H), 3.65 (s, 3H), 2.96-2.84 (m, 1H), 2.51-2.39 (m, 2H), 2.37-2.30 (m, 5H), 2.18-2.04 (m, 6H), 1.15 (d, 3H, J = 6.6 Hz), 1.00-0.96 (m, 6H). EXAMPLE 13 Scheme 13 provides the synthesis of several compounds of the 20 invention.



To a solution of amine **62** (575 mg, 1.17 mmol) in anhydrous DCM/DMF (4:1, 12.5 mL), a solution of (Z)-3-tributylstannylpropenoic acid (505.6 mg, 1.4 mmol) in anhydrous DCM was added, under argon atmosphere, and then was cooled at 0°C. DIPEA (0.243 mL, 1.76mol), 7-hydroxybenzotriazole (HOBt) (189.2 mg, 1.4 mmol), and HATU (532.28 mg, 1.4 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of NH₄Cl, poured into water and extracted with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 20:1 to 15:1) to give amide **63** (780.4 mg; yield: 77%) as a white foam.

¹H NMR (CDCl₃, 300 MHz) δ : 7.70-7.68 (m, 4H), 7.43-7.36 (m, 6H), 7.02 (d, 1H, J = 12.3 Hz), 7.00 (d, 1H, J = 10.8 Hz), 6.75 (d, 1H, J = 12.3 Hz), 6.66 (t, 1H, J = 9.3 Hz), 6.26 (d, 1H, J = 9.6 Hz), 5.57-5.34 (m, 1H), 5.38-5.28 (m, 1H), 4.83 (dd, 1H, J = 16.5, 7.8 Hz), 4.31 (d, 1H, J = 9.6 Hz), 3.89-3.82 (m, 1H), 2.26-2.02 (m, 4H), 1.50-1.42 (m, 6H), 1.43 (d,

2721a CI 68 CI 69 Scheme 13 5 Synthesis of compound 67 C I To a solution of alkenylstannane 21a (50 mg, 0.07 mmol) and iodide 27 10 (24.8 mg, 0.08 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1 mL) at 0C,

106

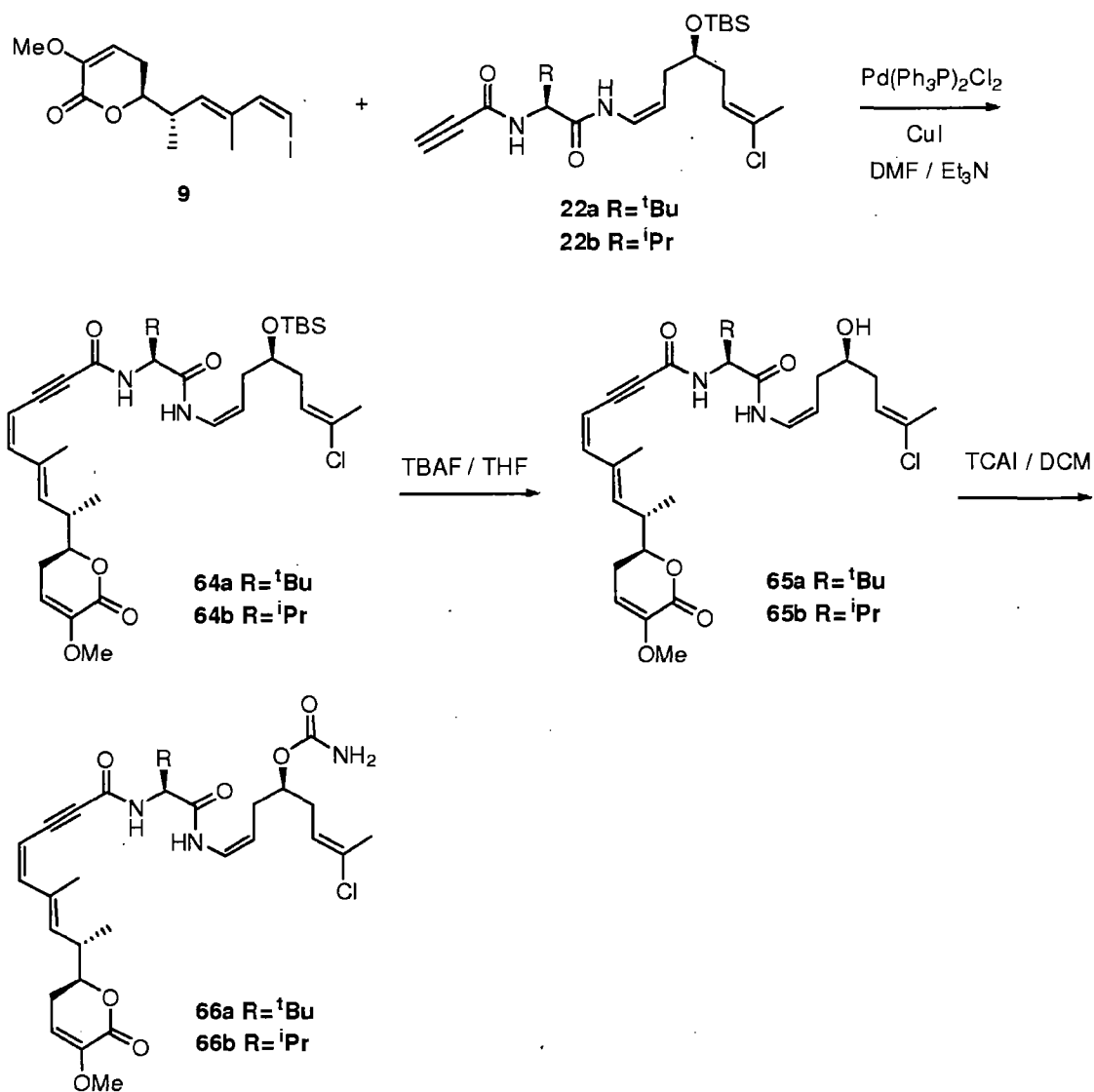
3H, $J = 6.9$ Hz), 1.33-1.20 (m, 6H), 1.06 (s, 9H), 0.96 (s, 9H), 0.95-0.83 (m, 15H).

^{13}C -RMN (CDCl_3 , 75 MHz) δ : 168.0, 166.2, 153.8, 136.3, 136.1, 134.3, 130.0, 127.8, 126.7, 126.0, 121.6, 109.0, 72.6, 60.7, 35.7, 34.0, 32.7,

5 29.5, 27.7, 27.2, 26.7, 19.5, 14.0, 13.2, 11.8.

EXAMPLE 12

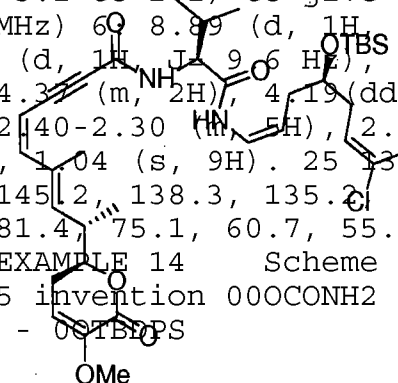
Scheme 12 provides the synthesis of several compounds of the invention.



Scheme 12

114 Copper thiophenecarboxylate (CuTC) (19.2 mg, 0.1 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 10:1 to 6:1) to give triene **67** (19 mg, yield: 44 %) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.73 (d, 1H, J = 10.5 Hz), 7.41 (dd, 1H, J = 10.1, 11.7, 11.1 Hz), 6.77-6.68 (m, 2H), 6.37 (d, 1H, J = 9.3 Hz), 5.74 (d, 1H, J = 11.4 Hz), 5.61-5.52 (m, 3H), 4.87-4.79 (m, 1H), 4.37 (d, 1H, J = 9.3 Hz), 4.21-4.14 (m, 1H), 3.64 (s, 3H), 3.09-2.99 (m, 1H), 2.39-2.35 (m, 2H), 2.20-2.10 (m, 4H), 2.01 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 157.2, 156.8, 156.5, 156.2, 155.8, 155.5, 155.2, 154.8, 154.5, 154.2, 153.8, 153.5, 153.2, 152.8, 152.5, 152.2, 151.8, 151.5, 151.2, 150.8, 150.5, 150.2, 149.8, 149.5, 149.2, 148.8, 148.5, 148.2, 147.8, 147.5, 147.2, 146.8, 146.5, 146.2, 145.8, 145.5, 145.2, 144.8, 144.5, 144.2, 143.8, 143.5, 143.2, 142.8, 142.5, 142.2, 141.8, 141.5, 141.2, 140.8, 140.5, 140.2, 139.8, 139.5, 139.2, 138.8, 138.5, 138.2, 137.8, 137.5, 137.2, 136.8, 136.5, 136.2, 135.8, 135.5, 135.2, 134.8, 134.5, 134.2, 133.8, 133.5, 133.2, 132.8, 132.5, 132.2, 131.8, 131.5, 131.2, 130.8, 130.5, 130.2, 129.8, 129.5, 129.2, 128.8, 128.5, 128.2, 127.8, 127.5, 127.2, 126.8, 126.5, 126.2, 125.8, 125.5, 125.2, 124.8, 124.5, 124.2, 123.8, 123.5, 123.2, 122.8, 122.5, 122.2, 121.8, 121.5, 121.2, 120.8, 120.5, 120.2, 119.8, 119.5, 119.2, 118.8, 118.5, 118.2, 117.8, 117.5, 117.2, 116.8, 116.5, 116.2, 115.8, 115.5, 115.2, 114.8, 114.5, 114.2, 113.8, 113.5, 113.2, 112.8, 112.5, 112.2, 111.8, 111.5, 111.2, 110.8, 110.5, 110.2, 109.8, 109.5, 109.2, 108.8, 108.5, 108.2, 107.8, 107.5, 107.2, 106.8, 106.5, 106.2, 105.8, 105.5, 105.2, 104.8, 104.5, 104.2, 103.8, 103.5, 103.2, 102.8, 102.5, 102.2, 101.8, 101.5, 101.2, 100.8, 100.5, 100.2, 99.8, 99.5, 99.2, 98.8, 98.5, 98.2, 97.8, 97.5, 97.2, 96.8, 96.5, 96.2, 95.8, 95.5, 95.2, 94.8, 94.5, 94.2, 93.8, 93.5, 93.2, 92.8, 92.5, 92.2, 91.8, 91.5, 91.2, 90.8, 90.5, 90.2, 89.8, 89.5, 89.2, 88.8, 88.5, 88.2, 87.8, 87.5, 87.2, 86.8, 86.5, 86.2, 85.8, 85.5, 85.2, 84.8, 84.5, 84.2, 83.8, 83.5, 83.2, 82.8, 82.5, 82.2, 81.8, 81.5, 81.2, 80.8, 80.5, 80.2, 79.8, 79.5, 79.2, 78.8, 78.5, 78.2, 77.8, 77.5, 77.2, 76.8, 76.5, 76.2, 75.8, 75.5, 75.2, 74.8, 74.5, 74.2, 73.8, 73.5, 73.2, 72.8, 72.5, 72.2, 71.8, 71.5, 71.2, 70.8, 70.5, 70.2, 69.8, 69.5, 69.2, 68.8, 68.5, 68.2, 67.8, 67.5, 67.2, 66.8, 66.5, 66.2, 65.8, 65.5, 65.2, 64.8, 64.5, 64.2, 63.8, 63.5, 63.2, 62.8, 62.5, 62.2, 61.8, 61.5, 61.2, 60.8, 60.5, 60.2, 59.8, 59.5, 59.2, 58.8, 58.5, 58.2, 57.8, 57.5, 57.2, 56.8, 56.5, 56.2, 55.8, 55.5, 55.2, 54.8, 54.5, 54.2, 53.8, 53.5, 53.2, 52.8, 52.5, 52.2, 51.8, 51.5, 51.2, 50.8, 50.5, 50.2, 49.8, 49.5, 49.2, 48.8, 48.5, 48.2, 47.8, 47.5, 47.2, 46.8, 46.5, 46.2, 45.8, 45.5, 45.2, 44.8, 44.5, 44.2, 43.8, 43.5, 43.2, 42.8, 42.5, 42.2, 41.8, 41.5, 41.2, 40.8, 40.5, 40.2, 39.8, 39.5, 39.2, 38.8, 38.5, 38.2, 37.8, 37.5, 37.2, 36.8, 36.5, 36.2, 35.8, 35.5, 35.2, 34.8, 34.5, 34.2, 33.8, 33.5, 33.2, 32.8, 32.5, 32.2, 31.8, 31.5, 31.2, 30.8, 30.5, 30.2, 29.8, 29.5, 29.2, 28.8, 28.5, 28.2, 27.8, 27.5, 27.2, 26.8, 26.5, 26.2, 25.8, 25.5, 25.2, 24.8, 24.5, 24.2, 23.8, 23.5, 23.2, 22.8, 22.5, 22.2, 21.8, 21.5, 21.2, 20.8, 20.5, 20.2, 19.8, 19.5, 19.2, 18.8, 18.5, 18.2, 17.8, 17.5, 17.2, 16.8, 16.5, 16.2, 15.8, 15.5, 15.2, 14.8, 14.5, 14.2, 13.8, 13.5, 13.2, 12.8, 12.5, 12.2, 11.8, 11.5, 11.2, 10.8, 10.5, 10.2, 9.8, 9.5, 9.2, 8.8, 8.5, 8.2, 7.8, 7.5, 7.2, 6.8, 6.5, 6.2, 5.8, 5.5, 5.2, 4.8, 4.5, 4.2, 3.8, 3.5, 3.2, 2.8, 2.5, 2.2, 1.8, 1.5, 1.2, 0.8, 0.5, 0.2, -0.2, -0.5, -0.8, -1.2, -1.5, -1.8, -2.2, -2.5, -2.8, -3.2, -3.5, -3.8, -4.2, -4.5, -4.8, -5.2, -5.5, -5.8, -6.2, -6.5, -6.8, -7.2, -7.5, -7.8, -8.2, -8.5, -8.8, -9.2, -9.5, -9.8, -10.2, -10.5, -10.8, -11.2, -11.5, -11.8, -12.2, -12.5, -12.8, -13.2, -13.5, -13.8, -14.2, -14.5, -14.8, -15.2, -15.5, -15.8, -16.2, -16.5, -16.8, -17.2, -17.5, -17.8, -18.2, -18.5, -18.8, -19.2, -19.5, -19.8, -20.2, -20.5, -20.8, -21.2, -21.5, -21.8, -22.2, -22.5, -22.8, -23.2, -23.5, -23.8, -24.2, -24.5, -24.8, -25.2, -25.5, -25.8, -26.2, -26.5, -26.8, -27.2, -27.5, -27.8, -28.2, -28.5, -28.8, -29.2, -29.5, -29.8, -30.2, -30.5, -30.8, -31.2, -31.5, -31.8, -32.2, -32.5, -32.8, -33.2, -33.5, -33.8, -34.2, -34.5, -34.8, -35.2, -35.5, -35.8, -36.2, -36.5, -36.8, -37.2, -37.5, -37.8, -38.2, -38.5, -38.8, -39.2, -39.5, -39.8, -40.2, -40.5, -40.8, -41.2, -41.5, -41.8, -42.2, -42.5, -42.8, -43.2, -43.5, -43.8, -44.2, -44.5, -44.8, -45.2, -45.5, -45.8, -46.2, -46.5, -46.8, -47.2, -47.5, -47.8, -48.2, -48.5, -48.8, -49.2, -49.5, -49.8, -50.2, -50.5, -50.8, -51.2, -51.5, -51.8, -52.2, -52.5, -52.8, -53.2, -53.5, -53.8, -54.2, -54.5, -54.8, -55.2, -55.5, -55.8, -56.2, -56.5, -56.8, -57.2, -57.5, -57.8, -58.2, -58.5, -58.8, -59.2, -59.5, -59.8, -60.2, -60.5, -60.8, -61.2, -61.5, -61.8, -62.2, -62.5, -62.8, -63.2, -63.5, -63.8, -64.2, -64.5, -64.8, -65.2, -65.5, -65.8, -66.2, -66.5, -66.8, -67.2, -67.5, -67.8, -68.2, -68.5, -68.8, -69.2, -69.5, -69.8, -70.2, -70.5, -70.8, -71.2, -71.5, -71.8, -72.2, -72.5, -72.8, -73.2, -73.5, -73.8, -74.2, -74.5, -74.8, -75.2, -75.5, -75.8, -76.2, -76.5, -76.8, -77.2, -77.5, -77.8, -78.2, -78.5, -78.8, -79.2, -79.5, -79.8, -80.2, -80.5, -80.8, -81.2, -81.5, -81.8, -82.2, -82.5, -82.8, -83.2, -83.5, -83.8, -84.2, -84.5, -84.8, -85.2, -85.5, -85.8, -86.2, -86.5, -86.8, -87.2, -87.5, -87.8, -88.2, -88.5, -88.8, -89.2, -89.5, -89.8, -90.2, -90.5, -90.8, -91.2, -91.5, -91.8, -92.2, -92.5, -92.8, -93.2, -93.5, -93.8, -94.2, -94.5, -94.8, -95.2, -95.5, -95.8, -96.2, -96.5, -96.8, -97.2, -97.5, -97.8, -98.2, -98.5, -98.8, -99.2, -99.5, -99.8, -100.2, -100.5, -100.8, -101.2, -101.5, -101.8, -102.2, -102.5, -102.8, -103.2, -103.5, -103.8, -104.2, -104.5, -104.8, -105.2, -105.5, -105.8, -106.2, -106.5, -106.8, -107.2, -107.5, -107.8, -108.2, -108.5, -108.8, -109.2, -109.5, -109.8, -110.2, -110.5, -110.8, -111.2, -111.5, -111.8, -112.2, -112.5, -112.8, -113.2, -113.5, -113.8, -114.2, -114.5, -114.8, -115.2, -115.5, -115.8, -116.2, -116.5, -116.8, -117.2, -117.5, -117.8, -118.2, -118.5, -118.8, -119.2, -119.5, -119.8, -120.2, -120.5, -120.8, -121.2, -121.5, -121.8, -122.2, -122.5, -122.8, -123.2, -123.5, -123.8, -124.2, -124.5, -124.8, -125.2, -125.5, -125.8, -126.2, -126.5, -126.8, -127.2, -127.5, -127.8, -128.2, -128.5, -128.8, -129.2, -129.5, -129.8, -130.2, -130.5, -130.8, -131.2, -131.5, -131.8, -132.2, -132.5, -132.8, -133.2, -133.5, -133.8, -134.2, -134.5, -134.8, -135.2, -135.5, -135.8, -136.2, -136.5, -136.8, -137.2, -137.5, -137.8, -138.2, -138.5, -138.8, -139.2, -139.5, -139.8, -140.2, -140.5, -140.8, -141.2, -141.5, -141.8, -142.2, -142.5, -142.8, -143.2, -143.5, -143.8, -144.2, -144.5, -144.8, -145.2, -145.5, -145.8, -146.2, -146.5, -146.8, -147.2, -147.5, -147.8, -148.2, -148.5, -148.8, -149.2, -149.5, -149.8, -150.2, -150.5, -150.8, -151.2, -151.5, -151.8, -152.2, -152.5, -152.8, -153.2, -153.5, -153.8, -154.2, -154.5, -154.8, -155.2, -155.5, -155.8, -156.2, -156.5, -156.8, -157.2, -157.5, -157.8, -158.2, -158.5, -158.8, -159.2, -159.5, -159.8, -160.2, -160.5, -160.8, -161.2, -161.5, -161.8, -162.2, -162.5, -162.8, -163.2, -163.5, -163.8, -164.2, -164.5, -164.8, -165.2, -165.5, -165.8, -166.2, -166.5, -166.8, -167.2, -167.5, -167.8, -168.2, -168.5, -168.8, -169.2, -169.5, -169.8, -170.2, -170.5, -170.8, -171.2, -171.5, -171.8, -172.2, -172.5, -172.8, -173.2, -173.5, -173.8, -174.2, -174.5, -174.8, -175.2, -175.5, -175.8, -176.2, -176.5, -176.8, -177.2, -177.5, -177.8, -178.2, -178.5, -178.8, -179.2, -179.5, -179.8, -180.2, -180.5, -180.8, -181.2, -181.5, -181.8, -182.2, -182.5, -182.8, -183.2, -183.5, -183.8, -184.2, -184.5, -184.8, -185.2, -185.5, -185.8, -186.2, -186.5, -186.8, -187.2, -187.5, -187.8, -188.2, -188.5, -188.8, -189.2, -189.5, -189.8, -190.2, -190.5, -190.8, -191.2, -191.5, -191.8, -192.2, -192.5, -192.8, -193.2, -193.5, -193.8, -194.2, -194.5, -194.8, -195.2, -195.5, -195.8, -196.2, -196.5, -196.8, -197.2, -197.5, -197.8, -198.2, -198.5, -198.8, -199.2, -199.5, -199.8, -200.2, -200.5, -200.8, -201.2, -201.5, -201.8, -202.2, -202.5, -202.8, -203.2, -203.5, -203.8, -204.2, -204.5, -204.8, -205.2, -205.5, -205.8, -206.2, -206.5, -206.8, -207.2, -207.5, -207.8, -208.2, -208.5, -208.8, -209.2, -209.5, -209.8, -210.2, -210.5, -210.8, -211.2, -211.5, -211.8, -212.2, -212.5, -212.8, -213.2, -213.5, -213.8, -214.2, -214.5, -214.8, -215.2, -215.5, -215.8, -216.2, -216.5, -216.8, -217.2, -217.5, -217.8, -218.2, -218.5, -218.8, -219.2, -219.5, -219.8, -220.2, -220.5, -220.8, -221.2, -221.5, -221.8, -222.2, -222.5, -222.8, -223.2, -223.5, -223.8, -224.2, -224.5, -224.8, -225.2, -225.5, -225.8, -226.2, -226.5, -226.8, -227.2, -227.5, -227.8, -228.2, -228.5, -228.8, -229.2, -229.5, -229.8, -230.2, -230.5, -230.8, -231.2, -231.5, -231.8, -232.2, -232.5, -232.8, -233.2, -233.5, -233.8, -234.2, -234.5, -234.8, -235.2, -235.5, -235.8, -236.2, -236.5, -236.8, -237.2, -237.5, -237.8, -238.2, -238.5, -238.8, -239.2, -239.5, -239.8, -240.2, -240.5, -240.8, -241.2, -241.5, -241.8, -242.2, -242.5, -242.8, -243.2, -243.5, -243.8, -244.2, -244.5, -244.8, -245.2, -245.5, -245.8, -246.2, -246.5, -246.8, -247.2, -247.5, -247.8, -248.2, -248.5, -248.8, -249.2, -249.5, -249.8, -250.2, -250.5, -250.8, -251.2, -251.5, -251.8, -252.2, -252.5, -252.8, -253.2, -253.5, -253.8, -254.2, -254.5, -254.8, -255.2, -255.5, -255.8, -256.2, -256.5, -256.8, -257.2, -257.5, -257.8, -258.2, -258.5, -258.8, -259.2, -259.5, -259.8, -260.2, -260.5, -260.8, -261.2, -261.5, -261.8, -262.2, -262.5, -262.8, -263.2, -263.5, -263.8, -264.2, -264.5, -264.8, -265.2, -265.5, -265.8, -266.2, -266.5, -266.8, -267.2, -267.5, -267.8, -268.2, -268.5, -268.8, -269.2, -269.5, -269.8, -270.2, -270.5, -270.8, -271.2, -271.5, -271.8, -272.2, -272.5, -272.8, -273.2, -273.5, -273.8, -274.2, -274.5, -274.8, -275.2, -275.5, -275.8, -276.2, -276.5, -276.8, -277.2, -277.5, -277.8, -278.2, -278.5, -278.8, -279.2, -279.5, -279.8, -280.2, -280.5, -280.8, -281.2, -281.5, -281.8, -282.2, -282.5, -282.8, -283.2, -283.5, -283.8, -284.2, -284.5, -284.8, -285.2, -285.5, -285.8, -286.2, -286.5, -286.8, -287.2, -287.5, -287.8, -288.2, -288.5, -288.8, -289.2, -289.5, -289.8, -290.2, -290.5, -290.8, -291.2, -291.5, -291.8, -292.2, -292.5, -292.8, -293.2, -293.5, -293.8, -294.2, -294.5, -294.8, -295.2, -295.5, -295.8, -296.2, -296.5, -296.8, -297.2, -297.5, -297.8, -298.2, -298.5, -298.8, -299.2, -299.5, -299.8, -300.2, -300.5, -300.8, -301.2, -301.5, -301.8, -302.2, -302.5, -302.8, -303.2, -303.5, -303.8, -304.2, -304.5, -304.8, -305.2, -305.5, -305.8, -306.2, -306.5, -306.8, -307.2, -307.5, -307.8, -308.2, -308.5, -308.8, -309.2, -309.5, -309.8, -310.2, -310.5, -310.8, -311.2, -311.5, -311.8, -312.2, -312.5, -312.8, -313.2, -313.5, -313.8, -314.2, -314.5, -314.8, -315.2, -315.5, -315.8, -316.2, -316.5, -316.8, -317.2, -317.5, -317.8, -318.2, -318.5, -318.8, -319.2, -319.5, -319.8, -320.2, -320.5, -320.8, -321.2, -321.5, -321.8, -322.2, -322.5, -322.8, -323.2, -323.5, -323.8, -324.2, -324.5, -324.8, -325.2, -325.5, -325.8, -326.2, -326.5, -326.8, -327.2, -327.5, -327.8, -328.2, -328.5, -328.8, -329.2, -329.5, -329.8, -330.2, -330.5, -330.8, -331.2, -331.5, -331.8, -332.2, -332.5, -332.8, -333.2, -333.5, -333.8, -334.2, -334.5, -334.8, -335.2, -335.5, -335.8, -336.2, -336.5, -336.8, -337.2, -337.5, -337.8, -338.2, -338.5, -338.8, -339.2, -339.5, -339.8, -340.2, -340.5, -340.8, -341.2, -341.5, -341.8, -342.2, -342.5, -342.8, -343.2, -343.5, -343.8, -344.2, -344.5, -344.8, -345.2, -345.5, -345.8, -346.2, -346.5, -346.8, -347.2, -347.5, -347.8, -348.2, -348.5, -348.8, -349.2, -349.5, -349.8, -350.2, -350.5, -350.8, -351.2, -351.5, -351.8, -352.2, -352.5, -352.8, -353.2, -353.5, -353.8, -354.2, -354.5, -354.8, -355.2, -355.5, -355.8, -356.2, -356.5, -356.8, -357.2, -357.5, -357.8, -358.2, -358.5, -358.8, -359.2, -359.5, -359.8, -360.2, -360.5, -360.8, -361.2, -361.5, -361.8, -362.2, -362.5, -362.8, -363.2, -363.5, -363.8, -364.2, -364.5, -364.8, -365.2, -365.5, -365.8, -366.2, -366.5, -366.8, -367.2, -367.5, -367.8, -368.2, -368.5, -368.8, -369.2, -369.5, -369.8, -370.2, -370.5, -370.8, -371.2, -371.5, -371.8, -372.2, -372.5, -372.8, -373.2, -373.5, -373.8, -374.2, -374.5, -374.8, -375.2, -375.5, -375.8, -376.2, -376.5, -376.8, -377.2, -377.5, -377.8, -378.2, -378.5, -378.8, -379.2, -379.5, -379.8, -380.2, -380.5, -380.8, -381.2, -381.5, -381.8, -382.2, -382.5, -382.8, -383.2, -383.5, -383.8, -384.2, -384.5, -384.8, -385.2, -385.5, -385.8, -386.2, -386.5, -386.8, -387.2, -387.5, -387.8, -388.2, -388.5, -388.8, -389.2, -389.5, -389.8, -390.2, -390.5, -390.8, -391.2, -391.5, -391.8, -392.2, -392.5, -392.8, -393.2, -393.5, -393.8, -394.2, -394.5, -394.8, -395.2, -395.5, -395.8, -396.2, -396.5, -396.8, -397.2, -397.5, -397.8, -398.2, -398.5, -398.8, -399.2, -399.5, -399.8, -400.2, -400.5, -400.8, -401.2, -401.5, -401.8, -402.2, -402.5, -402.8, -403.2, -403.5, -403.8, -404.2, -404.5, -404.8, -405.2, -405.5, -405.8, -406.2, -406.5, -406.8, -407.2, -407.5, -407.8, -408.2, -408.5, -408.8, -409.2, -409.5, -409.8, -410.2, -410.5, -410.8, -411.2, -411.5, -411.8, -412.2, -412.5, -412.8, -413.2, -413.5, -413.8, -414.2, -414.5, -414.8, -415.2, -415.5, -415.8, -416.2, -416.5, -416.8, -417.2, -417.5, -417.8, -418.2, -418.5, -418.8, -419.2, -419.5, -419.8, -420.2, -420.5, -420.8, -421.2, -421.5, -421.8, -422.2, -422.5, -422.8, -423.2, -423.5, -423.8, -424.2, -424.5, -424.8, -425.2, -425.5, -425.8, -426.2, -426.5, -426.8, -427.2, -427.5, -427.8, -428.2, -428.5, -428.8, -429.2, -429.5, -429.8, -430.2, -430.5, -430.8, -431.2, -431.5, -431.8, -432.2, -432.5, -432.8, -433.2, -433.5, -433.8, -434.2, -434.5, -434.8, -435.2, -435.5, -435.8, -436.

y 10c, To a solution of **68** (15 mg, 0.02 mmol) in anhydrous DCM (0.3 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (4.1 μ l, 0.64 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (450 mg). The mixture **15** 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 10:1. 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 compound **69** (14 mg, yield: 86%). ¹H NMR (CDCl₃, 300 MHz) δ : 8.89 (d, 1H, J = 10.5 Hz), 7.45 (m, 1H), 6.87-6.71 (m, 2H), 6.53 (d, 1H, J = 9.6 Hz), 5.75 (m, 2H), 5.60-5.57 (m, 2H), 4.81 (m, 1H), 4.40-4.37 (m, 2H), 4.19 (dd, 1H, J = 9.3, 9.5 Hz), 3.66 (s, 3H), 3.06 (m, 1H), 2.40-2.30 (m, 5H), 2.15-2.08 (m, 1H), 2.07 (s, 3H), 1.17 (d, 3H, J = 4.2 Hz), 1.04 (s, 9H). ¹³C NMR (CDCl₃, 75.5 MHz) δ : 168.1, 165.9, 161.4, 157.7, 145.2, 138.3, 135.2, 132.0, 125.9, 124.5, 122.3, 121.8, 108.1, 105.2, 81.4, 75.1, 60.7, 55.4, 36.1, 35.0, 32.9, 30.8, 26.7, 26.3, 21.0, 17.0. **EXAMPLE 14** Scheme 14 provides the synthesis of several compounds of the 5 invention 000CONH2 NO 72HNI I Scheme 14 117 Synthesis of compound 70 0 0 - OTBS



To a solution of **9** (40 mg, 0.113 mmol) in DMF/Et₃N (1 ml and 0.19 ml) at -20°C, Pd(Ph₃P)₂Cl₂ (7.9 mg, 0.113 mmol) and CuI (6.5 mg, 0.034 mmol) were added. Then, **22b** (50 mg, 0.113 mmol in 0.4 ml DMF) was added and the reaction was stirred at -20 °C to room temperature for 3 hours. The crude mixture was quenched with H₂O and extracted with Ethyl acetate. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (Ethyl acetate/hexanes mixture) to afforded pure **64b** (40 mg, yield: 54%).

¹H NMR (CDCl₃, 300 MHz) δ : 7.77 (d, 1H, J = 11.4 Hz), 6.75 (t, 1H, J = 10.2 Hz), 6.41-6.36 (m, 2H), 5.64-5.56 (m, 3H), 5.46 (d, 1H, J = 11.7 Hz), 4.86 (q, 1H, J = 8.1 Hz), 4.31 (dd, 1H, J = 8.4; 6.6 Hz), 4.25-4.16 (m, 1H), 3.84-3.76 (m, 1H), 3.65 (s, 3H), 2.92-2.81 (m, 1H), 2.44-2.39 (m, 2H), 2.22-2.12 (m, 5H), 2.10 (s, 3H), 2.03 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 0.99 (dd, 6H, J = 9.3; 6.9 Hz), 0.89 (s, 9H), 0.0080 (s, 3H), 0.0064 (s, 3H).

20 Synthesis of compound 65a

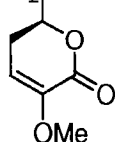
0 5 To a solution of alkenylstannane 37 (94 mg, 0.112 mmol) and 9 (47 mg, 0.135 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1.1 mL) at 0C, Copper thiophenecarboxylate (CuTC) (32.2 mg, 0.168 mmol) was added. The reaction was stirred at 0C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, 10 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 by column chromatography (Hexane/EtOAc 2:1 to 1:1) to give triene 70 (81.4 mg, yield 79%) as an oil. 15 ¹H NMR (CDCl₃, 300 MHz) δ: 7.74 (d, 1H, J = 10.5 Hz), 7.66-7.64 (m, 4H), 7.44-7.38 (m, 6H), 7.22 (dd, 1H, J= 12.3, 11.4 Hz), 6.86 (dd, 1H, J = 11.7, 11.4 Hz), 6.70 (dd, 1H, J= 9.9, 9.3 Hz), 6.40 (d, 1H, J= 9.3 Hz), 6.17 (d, 1H, J= 11.4 Hz), 5.66 (d, 1H, J= 11.4 Hz), 5.60 (dd, 1H, J= 20.5, 3.9 Hz), 5.26 (d, 1H, J= 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, J= 9.3 Hz), 4.20-4.16 (m, 1H), 3.88-3.80 (m, 1H), 3.64 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 3H), 2.28-2.20 (m, 3H), 1.91 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H, J= 6.9 Hz), 1.02 (s, 9H), 0.86 (s, 9H). 118 0 To a solution of 70 (77.2 mg, 0.106 mmol) in anhydrous THF (7.5 mL) under N₂ and at room temperature, TBAF 1M in THF (0.2 mL, 0.25 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 1:2) to give alcohol 71 (15 mg, 0.022 mmol) in anhydrous THF (0.5 mL). 8: ¹H NMR (CDCl₃, 300 MHz) δ: 8.79 (d, 1H, J= 9.6 Hz), 7.28-7.22 (m, 1H), 6.85 (t, 1H, J= 11.7 Hz), 6.73 (t, 1H, J= 9.6 Hz), 6.58 (d, 1H, J= 8.7 Hz), 6.12 (d, 1H, J= 11.4 Hz), 5.68-5.65 (m, 2H), 5.26 (d, 1H, J= 9.9 Hz), 4.86 (m, 1H), 4.38 (d, 1H, J= 9.3 Hz), 4.20-4.18 (m, 1H), 3.78-3.76 (m, 1H), 3.64 (s, 3H), 3.10 (br s, 1H), 2.86-2.70 (m, 1H), 2.41-2.34 (m, 3H), 1.82 (s, 3H), 1.14 (d, 3H, J= 6.6 Hz), 1.02 (s, 9H).

10 alcohol **65a** (5 mg; yield: 42 %).

¹H NMR (CDCl₃, 300 MHz) δ: 8.78 (d, 1H, J = 9.6 Hz), 6.77 (t, 1H, J = 9.0 Hz), 6.57 (d, 1H J = 9.0 Hz), 6.38 (d, 1H, J = 12.3 Hz), 5.60 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 4.90 (q, 1H, J = 8.7 Hz), 4.29 (d, 1H, J = 9.6 Hz), 4.23 (m, 1H), 3.80 (m, 1H), 3.65 (s, 3H), 2.86 (m, 1H), 2.66 (bs, 1H), 15 2.40 (m, 2H), 2.21 (m, 4H), 2.07 (s, 3H), 2.04 (s, 3H), 1.15 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H).

Synthesis of compound 65b

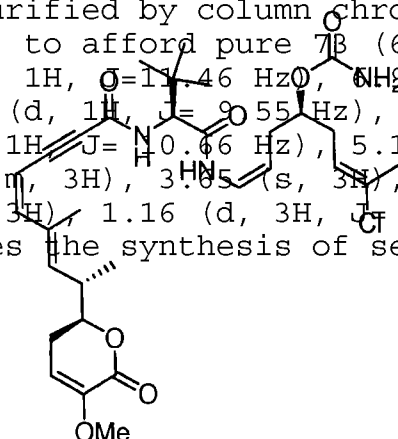
To a solution of **71** (21.6 mg, 0.0443 mmol) in anhydrous DCM (3.1 mL) at 0°C, trichloroacetyl isocyanate (TCAI) (6.4 μ L, 0.053 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium 119 oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column 5 chromatography (Hexane/EtOAc 1:2). Compound **72** (19.1 mg, yield: 76%) was obtained as a white solid. ^1H -NMR (CDCl₃, 500 MHz) δ : 8.61 (d, 1H, J = 11.4 Hz), 7.27 (t, 1H, J = 11.4 Hz), 6.92-6.78 (m, 2H), 6.52 (d, 1H, J = 9.6 Hz), 5.15 (d, 1H, J = 11.4 Hz), 5.69 (d, 1H, J = 11.4 Hz), 5.62-5.61 (m, 1H), 5.45 (br s, 2H), 5.28 (d, 1H, J = 9.6 Hz), 4.87-4.78 (m, 1H), 4.55-4.45 (m, 1H), 4.42 (d, 1H, J = 9.6 Hz), 4.25-4.20 (m, 1H), 3.64 (s, 3H), 2.87-2.80 (m, 1H), 2.44-2.17 (m, 6H), 1.81 (s, 6H), 1.16 (d, 3H, J = 6.5 Hz), 1.04 (s, 9H). EXAMPLE 15 Scheme 15 provides the synthesis of compound **73**. MeO



- To a solution of **64b** (40 mg, 0.06 mmol) in anhydrous THF (0.9 ml) under N₂ and at room temperature, TBAF 1M in THF (0.12 ml, 0.067 mmol) was added. The reaction was stirred at room temperature for 16 hours and then quenched with NH₄Cl and extracted with CH₂Cl₂. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (Ethyl acetate/hexanes mixture) afforded pure **65b** (15 mg, yield: 45%).
- ^1H NMR (CDCl₃, 300 MHz) δ : 8.95 (d, 1H, J = 10.2 Hz), 6.77 (t, 1H, J = 9.3 Hz), 6.60 (d, 1H, J = 9.0 Hz), 6.38 (d, 1H, J = 12.6 Hz), 5.64-5.60 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 4.88 (q, 1H, J = 8.4 Hz), 4.34 (dd, 1H, J = 8.7; 7.2 Hz), 4.27-4.20 (m, 1H), 3.82-3.74 (m, 1H), 3.65 (s, 3H), 2.92-2.82 (m, 1H), 2.45-2.38 (m, 2H), 2.11-2.04 (m, 5H), 1.57-1.45 (m, 6H), 1.28-1.23 (m, 3H), 1.15 (d, 6H, J = 6.6 Hz).

Synthesis of compound 66a

930 73 20Scheme 15 Synthesis of compound 73 120 To a solution of 30
 (40mg, 0.076 mmol) and 9 (31 mg, 0.09 mmol) in NMP (0.8 ml) at 0C, Copper
 thiophenecarboxylate (CuTC, 22 mg, 0.115 mmol) was added. The reaction was
 stirred at 0 C for 45 min and an hour at room temperature. Then, the crude
 mixture was filtered through a plug of neutral alumina, washing with
 EtOAc/Ether 50:50 (20 ml) and the combined filtrates were washed with HCl
 0.5N (3x10 ml). After drying and evaporating the solvent under reduced
 pressure 10 the crude was purified by column chromatography (Ethyl
 acetate/hexanes, 5:1 to 2:1) to afford pure 7B (6 mg, yield:17%). ¹H NMR
 (CDCl₃, 300 MHz) δ: 7.27 (t, 1H, J = 11.46 Hz), 7.00 (t, 1H, J = 11.52Hz),
 6.16 (d, 1H, J= 11.7), 6.03 (d, 1H, J= 9.55 Hz), 5.84-5.70 (m, 15 1H),
 5.67-5.60 (m, 2H), 5.28 (d, 1H, J= 10.66 Hz), 5.14-5.06 (m, 2H), 4.53 (d,
 1H, J= 9.41 Hz), 4.22-4.10 (m, 3H), 3.85 (s, 3H), 2.91-2.81 (m, 1H),
 2.47-2.34 (m, 4H), 1.84 (s, 3H), 1.16 (d, 3H, J= 6.65Hz), 0.99 (s, 9H). 20
 EXAMPLE 16 Scheme 16 provides the synthesis of several compounds of this
 invention. 25

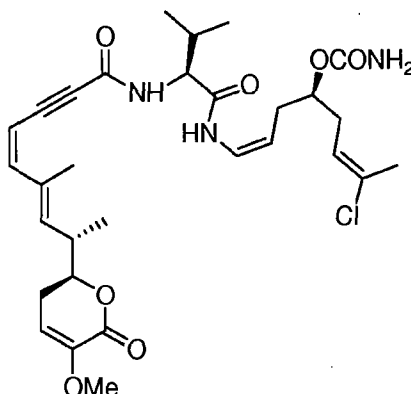


To a solution of **65a** (3.5 mg, 0.0062 mmol) in anhydrous DCM (0.45
 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (1 µl, 0.0075
 5 mmol) was added. The reaction was stirred at room temperature for 30
 min and then neutral aluminium oxide was added (100 mg). The
 mixture was stirred for 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
 10 product which was purified by column chromatography (Hexane/EtOAc
 2:1 to 1:2) affording compound **66a** (2.5 mg, yield: 70%).
¹H NMR (CDCl₃, 500 MHz) δ: 8.72 (d, 1H, J = 10.5 Hz), 6.84 (t, 1H, J =
 9.0 Hz), 6.66 (d, 1H J = 10.0 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.60 (m,
 3H), 5.46 (d, 1H, J = 12.0 Hz), 4.82 (q, 1H, J = 8.0 Hz), 4.42 (m, 2H),
 15 4.22 (m, 1H), 3.65 (s, 3H), 2.88 (m, 1H), 2.44-2.32 (m, 6H), 2.10 (s, 3H),
 2.06 (s, 3H), 1.15 (d, 3H, J = 7.0 Hz), 1.05 (s, 9H).
 MS (ES) (*m/z*) 604.2 [M+1]⁺, 626.2 (M+Na⁺).

Synthesis of compound 66b

74 R=TB DPS, Y=CI 75 R=TB DPS, Y=HTBAF 76 R=OH, Y=H ,TCAI, Al2O3 77 R=OCONH2, Y=H 78 R=TB DPS, Y=CI 79 R=TB DPS,Y=H 80 R=OH, Y=H 81 R=OCONH2,Y=H Scheme 16 5 Synthesis of compound 74 OTB DPS N OCI 122

112



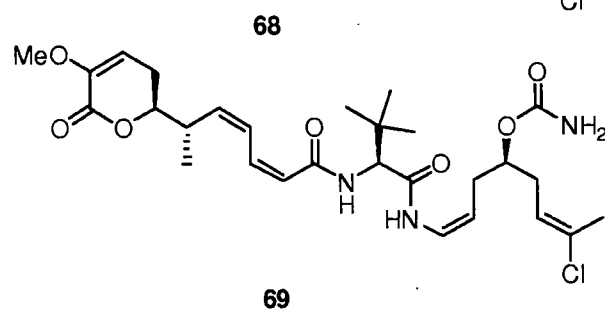
To a solution of **65b** (32 mg, 0.06 mmol) in CH₂Cl₂ (4.2 ml) at r.t, trichloroacetyl isocyanate (TCAI) (8.5 μ l, 0.072 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral Alumina was added (450 mg) while stirring for additional 30 min. The reaction mixture was filtered over alumina using a mixture of CH₂Cl₂ /MeOH 1:1 and after evaporation of the filtrate at reduced pressure the product was purified by column chromatography (Hexane/EOAc mixtures) to afford pure **66b** (12 mg, yield: 35%).

¹H NMR (CDCl₃, 300 MHz) δ : 8.90 (d, 1H, J = 10.8 Hz), 6.84 (t, 1H, J = 9.0 Hz), 6.74 (d, 1H, J = 8.7 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.64-5.58 (m, 3H), 5.45 (d, 1H, J = 12.0 Hz), 5.38 (br s, 2H), 4.86-4.78 (m, 1H), 4.44-4.39 (m, 2H), 4.27-4.19 (m, 1H), 3.65 (s, 3H), 2.96-2.84 (m, 1H), 2.51-2.39 (m, 2H), 2.37-2.30 (m, 5H), 2.18-2.04 (m, 6H), 1.15 (d, 3H, J = 6.6 Hz), 1.00-0.96 (m, 6H).

EXAMPLE 13

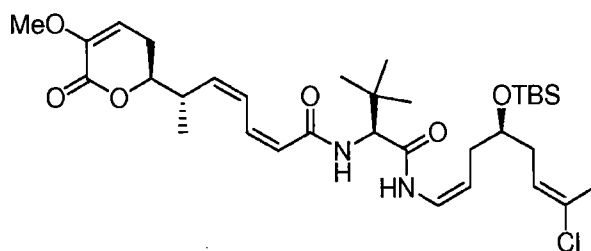
Scheme 13 provides the synthesis of several compounds of the invention.

To a solution of **40** (2.7 g, 5.12 mmol) and propiolic acid (0.41 mL, 6.66 mmol) in anhydrous DCM (51 mL) at 0 °C, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride EDC (1.23 g, 6.4 mmol) was added. The reaction was stirred at 0 °C for 30 min and 2 hours at room temperature. Then, the crude mixture was quenched with water and extracted with dichloromethane. The combined filtrates were washed with H₂O. After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (EtOAc/hexanes mixture) to afford pure compound **74** (2.25 g, 85% yield) as a white solid. NMR (CDCl₃, 300 MHz) δ : 7.66 (m, 4H), 7.47-7.36 (m, 6H), 6.86 (d, 1H, J = 10.5 Hz), 6.66 (m, 1H, J = 9.2 Hz), 6.62 (t, 1H, J = 8.9 Hz), 5.52 (d, 1H, J = 7.4 Hz), 4.79 (q, 1H, J = 8.6 Hz), 4.27 (d, 1H, J = 9.4 Hz), 3.82 (m, 1H), 2.82 (s, 1H), 2.19-2.04 (m, 4H), 1.87 (s, 3H), 1.05 (s, 9H), 0.99 (s, 9H). Synthesis of intermediate **75** To a solution of propiolic acid (45.1 mL, 0.726 mmol), amine **62** (275 mg, 0.56 mmol) in anhydrous DCM (5.6 mL) was cooled to 0 °C under argon and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC (134 mg, 0.7 mmol) was added. The reaction mixture was stirred 25 at 0 °C for 10 min and then at 23 °C for 3 hours. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried (anhydrous Na₂SO₄), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:10 to 3:1) to afford **75** (260 mg, 85% yield) as a colourless foam solid. ¹H NMR (CDCl₃, 300 MHz) δ : 7.69-7.67 (m, 4H), 7.44-7.36 (m, 6H), 7.08 (d, 1H, J = 10.2 Hz), 6.67-6.61 (m, 2H), 5.53-5.45 (m, 1H), 5.35-5.26 (m, 1H), 4.92-4.84 (m, 1H), 4.26 (d, 1H, J = 9.6 Hz), 3.89-3.82 (m, 1H), 2.80 (s, 1H), 2.26-2.05 (m, 4H), 1.44 (d, 3H, J = 7.8 Hz), 1.05 (s, 9H), 0.97 (s, 9H). Synthesis of intermediate **76** OH To a solution of **75** (244.3 mg, 0.45 mmol) in anhydrous THF (5 mL)



Scheme 13

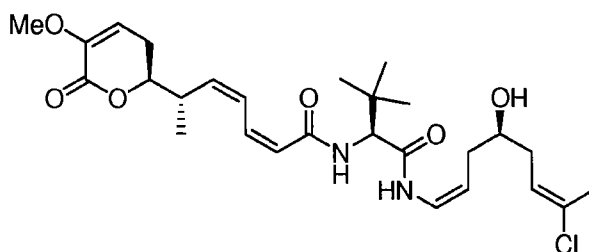
5 Synthesis of compound **67**



To a solution of alkenylstannane **21a** (50 mg, 0.07 mmol) and iodide **27** (24.8 mg, 0.08 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1 mL) at 0 °C,

under N₂ and at 0 °C, TBAF 1M in THF (0.54 mL, 0.54 mmol) was added. The reaction was stirred at room temperature for 3 hours and 15 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 4:1 to 1:2) to give alcohol **76** (94.1 mg, 69% yield) as a pale yellow oil. 20 ¹H NMR (CDCl₃, 300 MHz) δ: 9.02 (d, 1H, J = 9.9 Hz), 7.09 (d, 1H, J = 9.3 Hz), 6.74 (t, 1H, J = 9.9 Hz), 5.65-5.57 (m, 1H), 5.43-5.35 (m, 1H), 4.93-4.85 (m, 1H), 4.44 (d, 1H, J = 9.3 Hz), 3.78-3.70 (m, 1H), 2.87 (s, 1H), 2.32-2.12 (m, 4H), 1.61 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H). 25 ¹³C NMR (CDCl₃, 75 MHz) δ: 167.7, 152.4, 127.7, 126.0, 123.5, 109.4, 77.3, 74.9, 72.1, 61.9, 55.4, 51.7, 39.2, 20.8, 19.9. Synthesis of intermediate **77** To a solution of **76** (48.6 mg, 0.159 mmol) in anhydrous DCM (1.6 mL) 5 at room temperature, trichloroacetyl isocyanate (TCAI) (23.0 iii, 0.15 mmol) was added. The mixture was stirred for 30 min and then neutral aluminium oxide was added (250 mg). The mixture was dried and evaporated to give the crude product which was purified by column chromatography (hexane/EtOAc 10:1 to 6:1) to give triene **67** (19 mg, yield: 44%) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.73 (d, 1H, J = 10.5 Hz), 7.41 (dd, 1H, J = 9.6 Hz), 7.12 (bs, 1H), 7.04 (d, 1H, J = 9.6 Hz), 6.77-6.68 (m, 2H), 6.37 (d, 1H, J = 9.3 Hz), 5.74 (d, 1H, J = 9.6 Hz), 5.42-5.33 (m, 1H), 4.86 (q, 1H, J = 8.3 Hz), 4.48-4.30 (m, 1H), 4.39 (d, 1H, J = 9.6 Hz), 2.87 (s, 1H), 2.46-2.43 (m, 1H), 2.35-2.30 (m, 2H), 2.18-2.11 (m, 1H), 1.61 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). 15

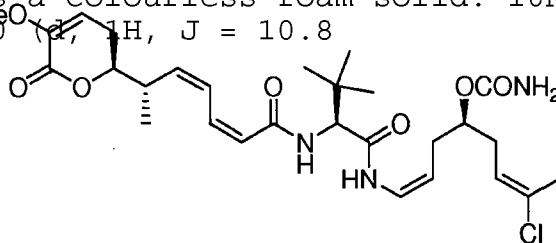
Synthesis of compound **68**



- 20 To a solution of **67** (18 mg, 0.03 mmol) in anhydrous THF (0.42 mL) under N₂ and at room temperature, TBAF 1M in 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 extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was 25 purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **68** (16 mg, yield: 80 %) as an oil.

125 OMe To a solution of iodo compound **9** (300 mg, 0.86 mmol) in diisopropylamine (4.3 mL) under N₂ at room temperature, Pd(Ph₃P)₄ (20 mg, 0.017 mmol) and CuI (6.4 mg, 0.034 mmol) were added. Then, **5** compound **74** (500 mg, 0.86 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 2 hours. The crude was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (Hexane/EtOAc 3:1 to 1:1) afforded pure compound **78** (580 mg, yield: 85%) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ: 8.90 (d, 1H, J = 10.5 Hz), 7.42 (dd, 1H, J = 11.7, 11.1 Hz), 7.37 (m, 1H), 7.25 (d, 1H, J = 10.5 Hz), 6.78-6.69 (m, 2H), 6.59 (d, 1H, J = 9.3 Hz), 6.46 (d, 1H, J = 9.2 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.64-5.48 (m, 3H), 5.43 (d, 1H, J = 12.1 Hz), 5.04-5.53 (m, 3H), 4.88-4.80 (m, 1H), 4.37 (d, 1H, J = 9.3 Hz), 4.20 (m, 1H), 3.82 (m, 1H), 3.65 (s, 3H), 3.77-3.69 (m, 1H), 3.64 (s, 3H), 3.11-3.01 (m, 4H), 2.09 (s, 3H), 1.86 (s, 3H), 1.15 (d, 3H, J = 6.8 Hz), 1.05 (s, 9H), 0.99 (s, 9H). ¹³C NMR (CDCl₃, 75.5 MHz) δ: 168.1, 165.9, 161.4, 157.7, 145.2, 138.3, 135.2, 132.0, 125.9, 124.5, 122.3, 121.8, 108.1, 105.2, 81.4, 75.1, 60.7, 55.4, 36.1, 35.0, 32.9, 30.8, 26.7, 26.3, 21.0, 17.0.

Synthesis of compound 69
68 (113 mg, 0.325 mmol) in DIPA (1.6 ml) at 23 °C, Pd(Ph₃P)₄ (7 mg, 0.006 mmol) and CuI (2.5 mg, 0.013 mmol) were added. Then **75** (195 mg, 0.358 mmol) was added and the reaction was stirred at 23 °C for 3 hours. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:3 to 1:1) to afford pure **79** (180 mg, 70 % yield) as a colourless foam solid. ¹H NMR (CDCl₃, 300 MHz) δ: 7.67-7.64 (m, 4H), 7.60 (d, 1H, J = 10.8



10

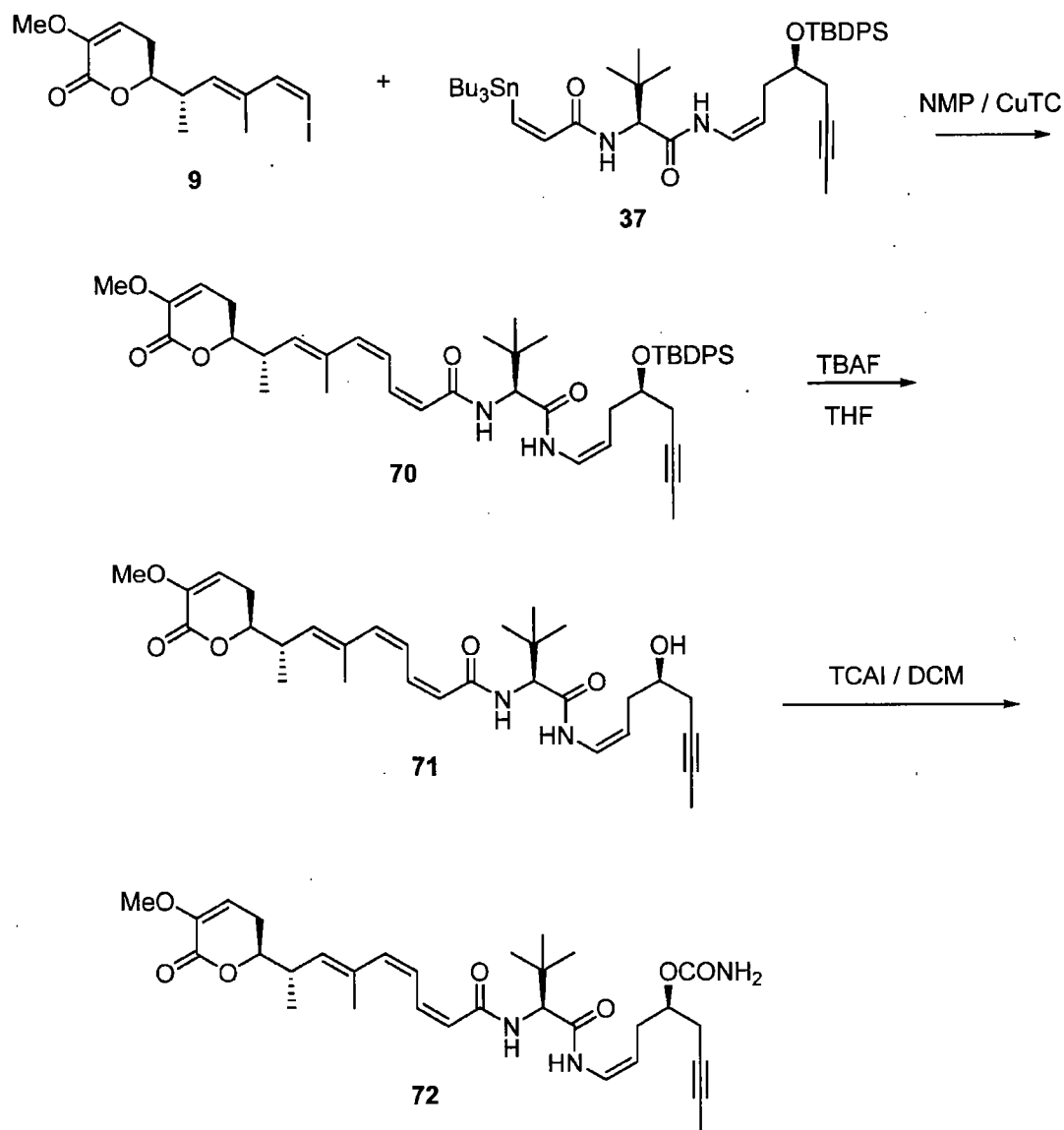
To a solution of **68** (15 mg, 0.02 mmol) in anhydrous DCM (0.3 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (4.1 µl, 0.64 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (450 mg). The mixture was stirred for 30 min and 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 compound **69** (14 mg, yield: 86%).

¹H NMR (CDCl₃, 300 MHz) δ: 8.89 (d, 1H, J = 10.5 Hz), 7.45 (m, 1H), 6.87-6.71 (m, 2H), 6.53 (d, 1H, J = 9.6 Hz), 5.75 (m, 2H), 5.60-5.57 (m, 2H), 4.81 (m, 1H), 4.40-4.37 (m, 2H), 4.19 (dd, 1H, J = 9.3, 9.5 Hz), 3.66 (s, 3H), 3.06 (m, 1H), 2.40-2.30 (m, 5H), 2.15-2.08 (m, 1H), 2.07 (s, 3H), 1.17 (d, 3H, J = 4.2 Hz), 1.04 (s, 9H).

¹³C NMR (CDCl₃, 75.5 MHz) δ: 168.1, 165.9, 161.4, 157.7, 145.2, 138.3, 135.2, 132.0, 125.9, 124.5, 122.3, 121.8, 108.1, 105.2, 81.4, 75.1, 60.7, 55.4, 36.1, 35.0, 32.9, 30.8, 26.7, 26.3, 21.0, 17.0

Hz), 7.46-7.35 (m, 6H), 6.66 (t, 1H, J = 9.6 Hz), 6.59 (dd, 1H, J = 9.9 Hz), 6.31 (d, 1H, J = 12.6 Hz), 5.62-5.54 (m, 2H), 5.42-5.37 (m, 1H), 5.32 (d, 1H, J=12.0 Hz), 5.30-5.23 (m, 1H), 4.92-4.84 (m, 1H), 4.42 (d, 1H, J = 9.6 Hz), 4.23-4.15 (m, 1H), 3.86-3.78 (m, 1H), 3.63 (s, 3H), 15 2.88-2.80 (m, 1H), 2.41-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.06 (s, 3H), 1.39 (d, 3H, J= 6.9 Hz), 1.13 (d, 3H, J= 6.6 Hz), 1.03 (s, 9H), 0.96 (s, 9H). 20 27.2, 26.7, 26.6, 19.5, 16.4, 15.5, 13.1. (One Csp2 not located). Synthesis of compound 80

0?N0 HN 127 To a solution of 9 (52 mg, 0.15 mmol) in DIPA (0.6 ml) at 23 C, Pd(Ph3P)4 (3.5 mg, 0.003 mmol) and CuI (1.14 mg, 0.006 mmol) were added. Then, 76 (45.5 mg, 0.15 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 C for 120 min. The crude mixture was 5 quenched with H2O and extracted with EtOAc. The organic phase was dried (anhydrous Na2SO4) and evaporated under reduced pressure. The residue was purified by ~~inversion~~ chromatography (dichloromethane /MeOH



Scheme 14

100:1 to 20:1) to afford pure 80. (59.5 mg, 75% yield) as a colourless oil. 10 ¹H NMR (CDCl₃, 300 MHz) δ: 8.94 (d, 1H, J = 9.9 Hz), 6.75 (t, 1H, J = 9.3 Hz), 6.69 (d, 1H, J = 9.0 Hz), 6.37 (d, 1H, J = 12.0 Hz), 5.68-5.57 (m, 3H), 5.44 (d, 1H, J = 12.0 Hz), 5.43-5.35 (m, 1H), 4.95-4.87 (m, 1H), 4.34 (d, 1H, J = 9.3 Hz), 4.24-4.17 (m, 1H), 3.76 (m, 1H), 3.64 (s, 3H), 2.91-2.78 (m, 1H), 2.63 (bs, 1H), 2.43-2.38 (m, 2H), 2.32-2.11 (m, 4H), 1.52 (s, 3H), 1.62 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.6 Hz), 1.01 (s, 9H). 13C NMR (CDCl₃, 125 MHz) δ: 167.5, 161.5, 153.2, 147.9, 145.1, 137.8, 135.4, 127.8, 125.3, 123.6, 109.0, 108.3, 103.0, 88.0, 84.7, 81.4, 72.0, 61.1, 55.4, 37.0, 35.2, 34.5, 32.8, 26.6, 26.4, 16.2, 15.3, 13.0. 20 To a solution of 9 (43 mg, 0.123 mmol) in DIPA (0.6 ml) at 23 °C, Pd(Ph₃P)₄ (2.8 mg, 0.0025 mmol) and CuI (1.0 mg, 0.005 mmol) were added. Then, 77 (43 mg, 0.123 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 120 min. The crude mixture was quenched with EtOAc and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane / MeOH 100:1 to 20:1) to afford pure 81 (38 mg, 54% yield) as a colourless oil. 10 ¹H NMR (CDCl₃, 300 MHz) δ: 9.00 (d, 1H, J = 10.8 Hz), 6.81 (t, 1H, J = 9.6 Hz), 6.73 (d, 1H, J = 9.6 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.63-5.56 (m, 5H), 5.45 (d, 1H, J = 11.7 Hz), 5.43-5.36 (m, 1H), 4.90-4.81 (m, 1H), 4.40 (d, 1H, J = 9.3 Hz), 4.40-4.33 (m, 1H), 4.24-4.17 (m, 1H), 3.64 (s, 3H), 2.90-2.82 (m, 1H), 2.42-2.31 (m, 5H), 2.18-2.09 (m, 1H), 2.09 (s, 15 3H), 1.62 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 6.6 Hz), 1.01 (s, 9H). Scheme 17 provides the synthesis of several compounds of thiophenecarboxylate (CuTC). To a solution of alkenylstannane 1a (1.1 g, 1.47 mmol) and 9 (0.62 g, 1.77 mmol) in 1-methyl-2-pyrrolidinone (NMP) (14.7 mL) at 0 °C, Copper thiophenecarboxylate (CuTC) (422 mg, 2.2 mmol) was added. 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 10 evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 2:1 to 1:1) to give triene 70 (81.4 mg, 66%) as an oil. 1H NMR (CDCl₃, 300 MHz) δ: 7.89 (d, 1H, J = 10.8 Hz), 7.22 (dd, 1H, J = 12.3, 11.4 Hz), 6.86 (dd, 1H, J = 11.7, 11.4 Hz), 6.70 (dd, 1H, J = 9.9, 9.3 Hz), 6.40 (d, 1H, J = 9.3 Hz), 6.17 (d, 1H, J = 11.4 Hz), 5.66 (d, 1H, J = 11.4 Hz), 5.60 (dd, 1H, J = 5.4, 3.9 Hz), 5.26 (d, 1H, J = 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, J = 9.3 Hz), 4.20-4.16 (m, 1H), 3.88-3.80 (m, 1H), 3.64 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 3H), 2.28-2.20 (m, 3H), 1.91 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz), 1.02 (s, 9H), 0.86 (s, 9H). yield: 79%) as an oil.

15

¹H NMR (CDCl₃, 300 MHz) δ: 7.74 (d, 1H, J = 10.5 Hz), 7.66-7.64 (m, 4H), 7.44-7.38 (m, 6H), 7.22 (dd, 1H, J = 12.3, 11.4 Hz), 6.86 (dd, 1H, J = 11.7, 11.4 Hz), 6.70 (dd, 1H, J = 9.9, 9.3 Hz), 6.40 (d, 1H, J = 9.3 Hz), 6.17 (d, 1H, J = 11.4 Hz), 5.66 (d, 1H, J = 11.4 Hz), 5.60 (dd, 1H, J = 5.4, 3.9 Hz), 5.26 (d, 1H, J = 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, J = 9.3 Hz), 4.20-4.16 (m, 1H), 3.88-3.80 (m, 1H), 3.64 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 3H), 2.28-2.20 (m, 3H), 1.91 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz), 1.02 (s, 9H), 0.86 (s, 9H).

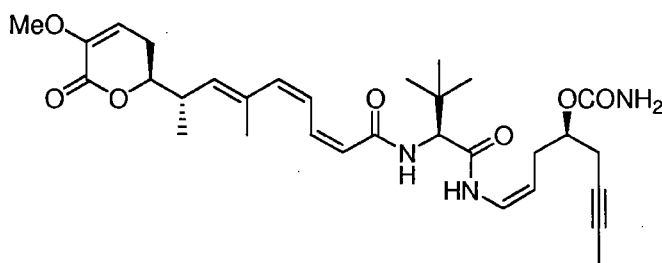
25 Synthesis of compound 71

15 9.3 Hz), 6.35 (d, 1H, J= 9.3 Hz), 6.13 (d, 1H, J= 11.4 Hz), 5.66 (d, 1H, J= 11.4 Hz), 5.60 (dd, 1H, J= 5.4, 3.9 Hz), 5.55 (br t, 1H, J= 7.8 Hz), 5.26 (d, 1H, J= 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, J= 9.3 Hz), 4.20-4.16 (m, 1H), 3.77-3.69 (m, 1H), 3.63 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 2H), 2.19-2.13 (m, 4H), 2.00 (s, 3H), 1.82 (s, 3H), 1.13 (d, 20 25 Synthesis of compound 83 131 118 To a solution of 82 (275 mg, 0.41 mmol) in anhydrous THF (6 mL) under N₂ and at room temperature, TBAF 1M in THF (0.82 mL, 0.82 5 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give 10 alcohol 83 (175 mg; yield: 76 %) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ: 9.00 (d, 1H, J= 10.2 Hz), 7.25 (dd, 1H, J= 12.0, 11.4 Hz), 6.86 (dd, 1H, J= 11.7, 11.4 Hz), 6.72 (dd, 1H, J= 9.6, 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 6.13 (d, 1H, J= 11.7 Hz), 5.68 (d, 1H, J= 11.4 Hz), 5.63-5.58 (m, 2H), 5.27 (d, 1H, J= 10.2 Hz), 4.85-4.76 (m, 15 1H), 4.42 (d, 1H, J= 9.3 Hz), 4.25-4.17 (m, 1H), 3.70-3.69 (m, 1H), 3.63 (s, 3H), 3.48 (br s, 1H), 2.89-2.75 (m, 1H), 2.42-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.04 (s, 3H), 1.82 (s, 3H), 1.14 (d, 3H, J= 6.6 Hz), 1.02 (s, 9H). 10 15 20 MeO 0 0 0 5

5 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 1:2) to give alcohol **71** (25 mg, yield: 44 %) as an oil.

¹H NMR (CDCl₃, 300 MHz) δ: 8.79 (d, 1H, J= 9.6 Hz), 7.28-7.22 (m, 1H), 6.85 (t, 1H, J= 11.7 Hz), 6.73 (t, 1H, J= 9.6 Hz), 6.58 (d, 1H, J= 8.7 Hz), 6.12 (d, 1H, J= 11.4 Hz), 5.68-5.61 (m, 2H), 5.26 (d, 1H, J= 9.9 Hz), 4.86 (q, 1H, J= 8.1 Hz), 4.38 (d, 1H, J= 9.3 Hz), 4.20-4.18 (m, 1H), 15 3.78-3.76 (m, 1H), 3.64 (s, 3H), 3.10 (br s, 1H), 2.86-2.79 (m, 1H), 2.41-2.14 (m, 6H), 1.82 (s, 6H), 1.14 (d, 3H, J= 6.6 Hz), 1.02 (s, 9H).

Synthesis of compound 72



20

To a solution of **71** (21.6 mg, 0.0443 mmol) in anhydrous DCM (3.1 mL) at 0°C, trichloroacetyl isocyanate (TCAI) (6.4 µl, 0.053 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium

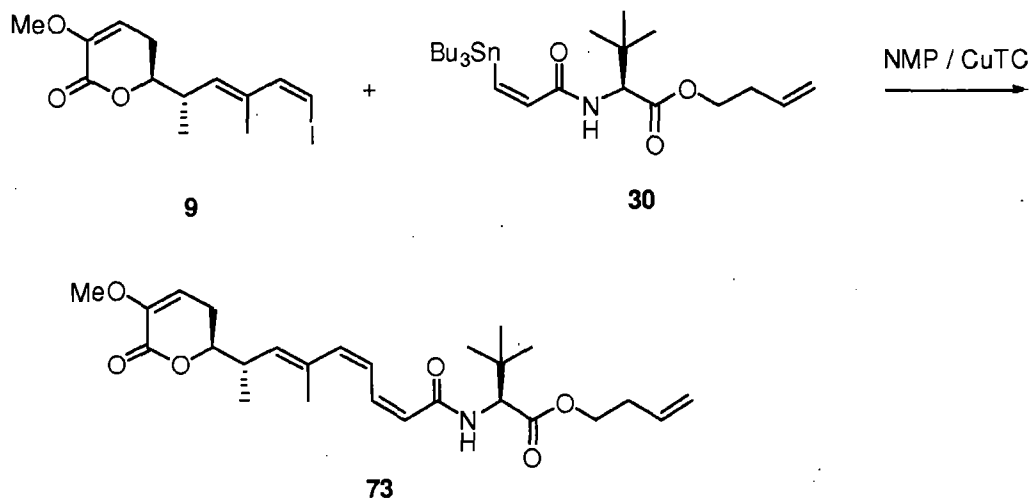
0 Nr HN CI To a solution of 83 (300 mg, 0.53 mmol) in anhydrous DCM (7.5 mL) at 0C, trichloroacetyl isocyanate (TCAI) (76 pi, 0.64 mmol) was added. The reaction was stirred at 0 C for 30 min and then neutral aluminium 132 oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 2:1 to 1:2) to give compound 84 (0.26 g, yield: 81%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ: 8.78 (d, 1H, J = 10.8 Hz), 7.30 (dd, 1H, J = 11.6, 11.6 Hz), 6.91 (dd, 1H, J = 11.6, 11.6 Hz), 6.84 (br dd, 1H, J = 10.8, 9.7 Hz), 6.51 (d, 1H, J = 9.5 Hz), 6.17 (d, 1H, J = 11.6 Hz), 5.70 (d, 10 1H, J = 11.6 Hz), 5.63 (using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 1:2) Compound, 72 (0.91 mg, 2 yield: 76%) was obtained as a white solid.

¹H NMR (CDCl₃, 500 MHz) δ: 8.61 (d, 1H, J = 11.1 Hz), 7.27 (t, 1H, J = 11.4 Hz), 6.92-6.78 (m, 2H), 6.52 (d, 1H, J = 9.3 Hz), 6.15 (d, 1H, J = 11.4 Hz), 5.69 (d, 1H, J = 11.4 Hz), 5.62-5.61 (m, 1H), 5.45 (br s, 2H), 10 5.28 (d, 1H, J = 9.6 Hz), 4.87-4.78 (m, 1H), 4.53-4.45 (m, 1H), 4.42 (d, 1H, J = 9.6 Hz), 4.25-4.20 (m, 1H), 3.64 (s, 3H), 2.87-2.80 (m, 1H), 2.44-2.17 (m, 6H), 1.81 (s, 6H), 1.16 (d, 3H, J = 6.5 Hz), 1.04 (s, 9H).

EXAMPLE 15

15

Scheme 15 provides the synthesis of compound 73.



20

Scheme 15

Synthesis of compound 73

Over a -78 C cooled solution of compound 84 (10 mg, 0.016 mmol) in anhydrous dichloromethane (0.3 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (0.02 mL, 0.02 mol) 133 was added and the mixture was stirred at -78 C. After 2 hours the reaction was quenched with a saturated aqueous solution of NH₄Cl and diluted with dichloromethane (2 mL). This mixture was stirred for 0.5 h at room temperature and then the organic layer was decanted. The 5 aqueous residue was extracted with additional dichloromethane (2 x 4 mL) and the combined organic layers were dried (anhydrous Na₂SO₄) and the solvent was evaporated. The crude was purified by column chromatography (hexane/EtOAc 2:1 to 1:2) to give compound 85 (5 mg, 58% yield) as a colourless oil. 10 ¹H NMR (CDCl₃, 300 MHz) δ : 8.57 (d, 1H, J=11.3 Hz), 7.19 (t, 1H, J=11.3 Hz), 6.92 (t, 1H, J=11.4 Hz), 6.82 (t, 1H, J=9.3 Hz), 6.38 (d, 1H, J=9.5 Hz), 6.18 (d, 1H, J=11.5 Hz), 5.64 (d, 1H, J=11.2 Hz), 5.60 (m, 1H), 5.35 (d, 1H, J=10.0 Hz), 5.27 (d, 1H, J=3.1 Hz), 4.81 (m, 2H), 4.46 (m, 1H), 4.40 (d, 1H, J=9.5 Hz), 3.85 (m, 1H), 3.57 (s, 3H), 3.21 (d, 1H, J=3.1 Hz), 2.61 (m, 1H), 2.46-2.29 (m, 3H), 2.14-2.08 (m, 3H), 2.06 (s, 3H), 1.81 (s, 3H). To a solution of 30 (40 mg, 0.076 mmol) and 9 (31 mg, 0.09 mmol) in NMP (0.8 mL) at 0 °C, Copper(I) phenylcarboxylate (CuPC, 22 mg, 0.11 mmol) was added. The reaction was stirred at 0 °C for 45 min and an

hour at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washing with EtOAc/Ether 50:50 (20 ml) and the combined filtrates were washed with HCl 0.5N (3x10 ml). After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes, 5:1 to 2:1) to afford pure **73** (6 mg, yield:17%).

¹H NMR (CDCl₃, 300 MHz) δ : 7.27 (t, 1H, J=11.46 Hz), 6.90 (t, 1H, J=11.52Hz), 6.16 (d, 1H, J=11.7), 6.03 (d, 1H, J=9.55 Hz), 5.84-5.70 (m, 1H), 5.67-5.60 (m, 2H), 5.28 (d, 1H, J=10.66 Hz), 5.14-5.06 (m, 2H), 4.53 (d, 1H, J=9.41 Hz), 4.22-4.10 (m, 3H), 3.65 (s, 3H), 2.91-2.81 (m, 1H), 2.47-2.34 (m, 4H), 1.84 (s, 3H), 1.16 (d, 3H, J=6.65Hz), 0.99 (s, 9H).

20 EXAMPLE 16

Scheme 16 provides the synthesis of several compounds of this invention.

5 Synthesis of compound 86 135 To a solution of alkenylstannane 63 (780.4 mg, 0.904 mmol) and 9 (377.4 mg, 1.085 mmol) in NMP (9 mL) at 0 C, Copper 5 thiophenecarboxylate (258.5 mg, 1.36 mmol) was added. The reaction was stirred at 0 C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3 x 10 mL). The organic solution was dried and 10 evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene 86 (450.7 mg, yield: 66%) as an oil. ¹H NMR (CDCl₃, 300 MHz) 6: 7.66-7.64 (m, 4H), 7.43-7.32 (m, 7H), 7.23 (t, 1H, J= 11.7 Hz), 6.85 (t, 1H, J= 11.7 Hz), 6.62 (dd, 1H, J= 10.5, 9.3 Hz), 6.41 (d, 1H, J= 9.3 Hz), 6.11 (d, 1H, J= 11.7 Hz), 5.66 (d, 1H, J= 11.4 Hz), 5.60 (dd, 1H, J= 5.7, 5.1 Hz), 5.49-5.41 (m, 1H), 5.32-5.27 (m, 1H), 5.25 (d, 1H, J= 9.9 Hz), 4.83-4.75 (m, 1H), 4.32 (d, 1H, J= 9.3 Hz), 4.22-4.15 (m, 1H), 3.83-3.78 (m, 1H), 3.62 (s, 3H), 2.86-2.78 (m, 1H), 2.40-2.35 (m, 2H), 2.20-2.04 (m, 4H), 1.81 (s, 3H), 1.40 (d, 3H, J= 20.6, 9 Hz), 1.13 (d, 3H, J= 6.9 Hz), 1.03 (s, 9H), 0.97 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) 8: 168.3, 166.3, 161.8, 145.4, 140.2, 137.3, 133.7, 131.3, 129.7, 128.1, 127.3, 126.8, 126.3, 125.8, 125.3, 124.8, 124.3, 123.8, 123.3, 122.8, 122.3, 121.8, 121.3, 120.8, 120.3, 119.8, 119.3, 118.8, 118.3, 117.8, 117.3, 116.8, 116.3, 115.8, 115.3, 114.8, 114.3, 113.8, 113.3, 112.8, 112.3, 111.8, 111.3, 110.8, 110.3, 109.8, 109.3, 108.8, 108.3, 107.8, 107.3, 106.8, 106.3, 105.8, 105.3, 104.8, 104.3, 103.8, 103.3, 102.8, 102.3, 101.8, 101.3, 100.8, 100.3, 99.8, 99.3, 98.8, 98.3, 97.8, 97.3, 96.8, 96.3, 95.8, 95.3, 94.8, 94.3, 93.8, 93.3, 92.8, 92.3, 91.8, 91.3, 90.8, 90.3, 89.8, 89.3, 88.8, 88.3, 87.8, 87.3, 86.8, 86.3, 85.8, 85.3, 84.8, 84.3, 83.8, 83.3, 82.8, 82.3, 81.8, 81.3, 80.8, 80.3, 79.8, 79.3, 78.8, 78.3, 77.8, 77.3, 76.8, 76.3, 75.8, 75.3, 74.8, 74.3, 73.8, 73.3, 72.8, 72.3, 71.8, 71.3, 70.8, 70.3, 69.8, 69.3, 68.8, 68.3, 67.8, 67.3, 66.8, 66.3, 65.8, 65.3, 64.8, 64.3, 63.8, 63.3, 62.8, 62.3, 61.8, 61.3, 60.8, 60.3, 59.8, 59.3, 58.8, 58.3, 57.8, 57.3, 56.8, 56.3, 55.8, 55.3, 54.8, 54.3, 53.8, 53.3, 52.8, 52.3, 51.8, 51.3, 50.8, 50.3, 49.8, 49.3, 48.8, 48.3, 47.8, 47.3, 46.8, 46.3, 45.8, 45.3, 44.8, 44.3, 43.8, 43.3, 42.8, 42.3, 41.8, 41.3, 40.8, 40.3, 39.8, 39.3, 38.8, 38.3, 37.8, 37.3, 36.8, 36.3, 35.8, 35.3, 34.8, 34.3, 33.8, 33.3, 32.8, 32.3, 31.8, 31.3, 30.8, 30.3, 29.8, 29.3, 28.8, 28.3, 27.8, 27.3, 26.8, 26.3, 25.8, 25.3, 24.8, 24.3, 23.8, 23.3, 22.8, 22.3, 21.8, 21.3, 20.8, 20.3, 19.8, 19.3, 18.8, 18.3, 17.8, 17.3, 16.8, 16.3, 15.8, 15.3, 14.8, 14.3, 13.8, 13.3, 12.8, 12.3, 11.8, 11.3, 10.8, 10.3, 9.8, 9.3, 8.8, 8.3, 7.8, 7.3, 6.8, 6.3, 5.8, 5.3, 4.8, 4.3, 3.8, 3.3, 2.8, 2.3, 1.8, 1.3, 0.8, 0.3, -0.2, -0.7, -1.2, -1.7, -2.2, -2.7, -3.2, -3.7, -4.2, -4.7, -5.2, -5.7, -6.2, -6.7, -7.2, -7.7, -8.2, -8.7, -9.2, -9.7, -10.2, -10.7, -11.2, -11.7, -12.2, -12.7, -13.2, -13.7, -14.2, -14.7, -15.2, -15.7, -16.2, -16.7, -17.2, -17.7, -18.2, -18.7, -19.2, -19.7, -20.2, -20.7, -21.2, -21.7, -22.2, -22.7, -23.2, -23.7, -24.2, -24.7, -25.2, -25.7, -26.2, -26.7, -27.2, -27.7, -28.2, -28.7, -29.2, -29.7, -30.2, -30.7, -31.2, -31.7, -32.2, -32.7, -33.2, -33.7, -34.2, -34.7, -35.2, -35.7, -36.2, -36.7, -37.2, -37.7, -38.2, -38.7, -39.2, -39.7, -40.2, -40.7, -41.2, -41.7, -42.2, -42.7, -43.2, -43.7, -44.2, -44.7, -45.2, -45.7, -46.2, -46.7, -47.2, -47.7, -48.2, -48.7, -49.2, -49.7, -50.2, -50.7, -51.2, -51.7, -52.2, -52.7, -53.2, -53.7, -54.2, -54.7, -55.2, -55.7, -56.2, -56.7, -57.2, -57.7, -58.2, -58.7, -59.2, -59.7, -60.2, -60.7, -61.2, -61.7, -62.2, -62.7, -63.2, -63.7, -64.2, -64.7, -65.2, -65.7, -66.2, -66.7, -67.2, -67.7, -68.2, -68.7, -69.2, -69.7, -70.2, -70.7, -71.2, -71.7, -72.2, -72.7, -73.2, -73.7, -74.2, -74.7, -75.2, -75.7, -76.2, -76.7, -77.2, -77.7, -78.2, -78.7, -79.2, -79.7, -80.2, -80.7, -81.2, -81.7, -82.2, -82.7, -83.2, -83.7, -84.2, -84.7, -85.2, -85.7, -86.2, -86.7, -87.2, -87.7, -88.2, -88.7, -89.2, -89.7, -90.2, -90.7, -91.2, -91.7, -92.2, -92.7, -93.2, -93.7, -94.2, -94.7, -95.2, -95.7, -96.2, -96.7, -97.2, -97.7, -98.2, -98.7, -99.2, -99.7, -100.2, -100.7, -101.2, -101.7, -102.2, -102.7, -103.2, -103.7, -104.2, -104.7, -105.2, -105.7, -106.2, -106.7, -107.2, -107.7, -108.2, -108.7, -109.2, -109.7, -110.2, -110.7, -111.2, -111.7, -112.2, -112.7, -113.2, -113.7, -114.2, -114.7, -115.2, -115.7, -116.2, -116.7, -117.2, -117.7, -118.2, -118.7, -119.2, -119.7, -120.2, -120.7, -121.2, -121.7, -122.2, -122.7, -123.2, -123.7, -124.2, -124.7, -125.2, -125.7, -126.2, -126.7, -127.2, -127.7, -128.2, -128.7, -129.2, -129.7, -130.2, -130.7, -131.2, -131.7, -132.2, -132.7, -133.2, -133.7, -134.2, -134.7, -135.2, -135.7, -136.2, -136.7, -137.2, -137.7, -138.2, -138.7, -139.2, -139.7, -140.2, -140.7, -141.2, -141.7, -142.2, -142.7, -143.2, -143.7, -144.2, -144.7, -145.2, -145.7, -146.2, -146.7, -147.2, -147.7, -148.2, -148.7, -149.2, -149.7, -150.2, -150.7, -151.2, -151.7, -152.2, -152.7, -153.2, -153.7, -154.2, -154.7, -155.2, -155.7, -156.2, -156.7, -157.2, -157.7, -158.2, -158.7, -159.2, -159.7, -160.2, -160.7, -161.2, -161.7, -162.2, -162.7, -163.2, -163.7, -164.2, -164.7, -165.2, -165.7, -166.2, -166.7, -167.2, -167.7, -168.2, -168.7, -169.2, -169.7, -170.2, -170.7, -171.2, -171.7, -172.2, -172.7, -173.2, -173.7, -174.2, -174.7, -175.2, -175.7, -176.2, -176.7, -177.2, -177.7, -178.2, -178.7, -179.2, -179.7, -180.2, -180.7, -181.2, -181.7, -182.2, -182.7, -183.2, -183.7, -184.2, -184.7, -185.2, -185.7, -186.2, -186.7, -187.2, -187.7, -188.2, -188.7, -189.2, -189.7, -190.2, -190.7, -191.2, -191.7, -192.2, -192.7, -193.2, -193.7, -194.2, -194.7, -195.2, -195.7, -196.2, -196.7, -197.2, -197.7, -198.2, -198.7, -199.2, -199.7, -200.2, -200.7, -201.2, -201.7, -202.2, -202.7, -203.2, -203.7, -204.2, -204.7, -205.2, -205.7, -206.2, -206.7, -207.2, -207.7, -208.2, -208.7, -209.2, -209.7, -210.2, -210.7, -211.2, -211.7, -212.2, -212.7, -213.2, -213.7, -214.2, -214.7, -215.2, -215.7, -216.2, -216.7, -217.2, -217.7, -218.2, -218.7, -219.2, -219.7, -220.2, -220.7, -221.2, -221.7, -222.2, -222.7, -223.2, -223.7, -224.2, -224.7, -225.2, -225.7, -226.2, -226.7, -227.2, -227.7, -228.2, -228.7, -229.2, -229.7, -230.2, -230.7, -231.2, -231.7, -232.2, -232.7, -233.2, -233.7, -234.2, -234.7, -235.2, -235.7, -236.2, -236.7, -237.2, -237.7, -238.2, -238.7, -239.2, -239.7, -240.2, -240.7, -241.2, -241.7, -242.2, -242.7, -243.2, -243.7, -244.2, -244.7, -245.2, -245.7, -246.2, -246.7, -247.2, -247.7, -248.2, -248.7, -249.2, -249.7, -250.2, -250.7, -251.2, -251.7, -252.2, -252.7, -253.2, -253.7, -254.2, -254.7, -255.2, -255.7, -256.2, -256.7, -257.2, -257.7, -258.2, -258.7, -259.2, -259.7, -260.2, -260.7, -261.2, -261.7, -262.2, -262.7, -263.2, -263.7, -264.2, -264.7, -265.2, -265.7, -266.2, -266.7, -267.2, -267.7, -268.2, -268.7, -269.2, -269.7, -270.2, -270.7, -271.2, -271.7, -272.2, -272.7, -273.2, -273.7, -274.2, -274.7, -275.2, -275.7, -276.2, -276.7, -277.2, -277.7, -278.2, -278.7, -279.2, -279.7, -280.2, -280.7, -281.2, -281.7, -282.2, -282.7, -283.2, -283.7, -284.2, -284.7, -285.2, -285.7, -286.2, -286.7, -287.2, -287.7, -288.2, -288.7, -289.2, -289.7, -290.2, -290.7, -291.2, -291.7, -292.2, -292.7, -293.2, -293.7, -294.2, -294.7, -295.2, -295.7, -296.2, -296.7, -297.2, -297.7, -298.2, -298.7, -299.2, -299.7, -300.2, -300.7, -301.2, -301.7, -302.2, -302.7, -303.2, -303.7, -304.2, -304.7, -305.2, -305.7, -306.2, -306.7, -307.2, -307.7, -308.2, -308.7, -309.2, -309.7, -310.2, -310.7, -311.2, -311.7, -312.2, -312.7, -313.2, -313.7, -314.2, -314.7, -315.2, -315.7, -316.2, -316.7, -317.2, -317.7, -318.2, -318.7, -319.2, -319.7, -320.2, -320.7, -321.2, -321.7, -322.2, -322.7, -323.2, -323.7, -324.2, -324.7, -325.2, -325.7, -326.2, -326.7, -327.2, -327.7, -328.2, -328.7, -329.2, -329.7, -330.2, -330.7, -331.2, -331.7, -332.2, -332.7, -333.2, -333.7, -334.2, -334.7, -335.2, -335.7, -336.2, -336.7, -337.2, -337.7, -338.2, -338.7, -339.2, -339.7, -340.2, -340.7, -341.2, -341.7, -342.2, -342.7, -343.2, -343.7, -344.2, -344.7, -345.2, -345.7, -346.2, -346.7, -347.2, -347.7, -348.2, -348.7, -349.2, -349.7, -350.2, -350.7, -351.2, -351.7, -352.2, -352.7, -353.2, -353.7, -354.2, -354.7, -355.2, -355.7, -356.2, -356.7, -357.2, -357.7, -358.2, -358.7, -359.2, -359.7, -360.2, -360.7, -361.2, -361.7, -362.2, -362.7, -363.2, -363.7, -364.2, -364.7, -365.2, -365.7, -366.2, -366.7, -367.2, -367.7, -368.2, -368.7, -369.2, -369.7, -370.2, -370.7, -371.2, -371.7, -372.2, -372.7, -373.2, -373.7, -374.2, -374.7, -375.2, -375.7, -376.2, -376.7, -377.2, -377.7, -378.2, -378.7, -379.2, -379.7, -380.2, -380.7, -381.2, -381.7, -382.2, -382.7, -383.2, -383.7, -384.2, -384.7, -385.2, -385.7, -386.2, -386.7, -387.2, -387.7, -388.2, -388.7, -389.2, -389.7, -390.2, -390.7, -391.2, -391.7, -392.2, -392.7, -393.2, -393.7, -394.2, -394.7, -395.2, -395.7, -396.2, -396.7, -397.2, -397.7, -398.2, -398.7, -399.2, -399.7, -400.2, -400.7, -401.2, -401.7, -402.2, -402.7, -403.2, -403.7, -404.2, -404.7, -405.2, -405.7, -406.2, -406.7, -407.2, -407.7, -408.2, -408.7, -409.2, -409.7, -410.2, -410.7, -411.2, -411.7, -412.2, -412.7, -413.2, -413.7, -414.2, -414.7, -415.2, -415.7, -416.2, -416.7, -417.2, -417.7, -418.2, -418.7, -419.2, -419.7, -420.2, -420.7, -421.2, -421.7, -422.2, -422.7, -423.2, -423.7, -424.2, -424.7, -425.2, -425.7, -426.2, -426.7, -427.2, -427.7, -428.2, -428.7, -429.2, -429.7, -430.2, -430.7, -431.2, -431.7, -432.2, -432.7, -433.2, -433.7, -434.2, -434.7, -435.2, -435.7, -436.2, -436.7, -437.2, -437.7, -438.2, -438.7, -439.2, -439.7, -440.2, -440.7, -441.2, -441.7, -442.2, -442.7, -443.2, -443.7, -444.2, -444.7, -445.2, -445.7, -446.2, -446.7, -447.2, -447.7, -448.2, -448.7, -449.2, -449.7, -450.2, -450.7, -451.2, -451.7, -452.2, -452.7, -453.2, -453.7, -454.2, -454.7, -455.2, -455.7, -456.2, -456.7, -457.2, -457.7, -458.2, -458.7, -459.2, -459.7, -460.2, -460.7, -461.2, -461.7, -462.2, -462.7, -463.2, -463.7, -464.2, -464.7, -465.2, -465.7, -466.2, -466.7, -467.2, -467.7, -468.2, -468.7, -469.2, -469.7, -470.2, -470.7, -471.2, -471.7, -472.2, -472.7, -473.2, -473.7, -474.2, -474.7, -475.2, -475.7, -476.2, -476.7, -477.2, -477.7, -478.2, -478.7, -479.2, -479.7, -480.2, -480.7, -481.2, -481.7, -482.2, -482.7, -483.2, -483.7, -484.2, -484.7, -485.2, -485.7, -486.2, -486.7, -487.2, -487.7, -488.2, -488.7, -489.2, -489.7, -490.2, -490.7, -491.2, -491.7, -492.2, -492.7, -493.2, -493.7, -494.2, -494.7, -495.2, -495.7, -496.2, -496.7, -497.2, -497.7, -498.2, -498.7, -499.2, -499.7, -500.2, -500.7, -501.2, -501.7, -502.2, -502.7, -503.2, -503.7, -504.2, -504.7, -505.2, -505.7, -506.2, -506.7, -507.2, -507.7, -508.2, -508.7, -509.2, -509.7, -510.2, -510.7, -511.2, -511.7, -512.2, -512.7, -513.2, -513.7, -514.2, -514.7, -515.2, -515.7, -516.2, -516.7, -517.2, -517.7, -518.2, -518.7, -519.2, -519.7, -520.2, -520.7, -521.2, -521.7, -522.2, -522.7, -523.2, -523.7, -524.2, -524.7, -525.2, -525.7, -526.2, -526.7, -527.2, -527.7, -528.2, -528.7, -529.2, -529.7, -530.2, -530.7, -531.2, -531.7, -532.2, -532.7, -533.2, -533.7, -534.2, -534.7, -535.2, -535.7, -536.2, -536.7, -537.2, -537.7, -538.2, -538.7, -539.2, -539.7, -540.2, -540.7, -541.2, -541.7, -542.2, -542.7, -543.2, -543.7, -544.2, -544.7, -545.2, -545.7, -546.2, -546.7, -547.2, -547.7, -548.2, -548.7, -549.2, -549.7, -550.2, -550.7, -551.2, -551.7, -552.2, -552.7, -553.2, -553.7, -554.2, -554.7, -555.2, -555.7, -556.2, -556.7, -557.2, -557.7, -558.2, -558.7, -559.2, -559.7, -560.2, -560.7, -561.2, -561.7, -562.2, -562.7, -563.2, -563.7, -564.2, -564.7, -565.2, -565.7, -566.2, -566.7, -567.2, -567.7, -568.2, -568.7, -569.2, -569.7, -570.2, -570.7, -571.2, -571.7, -572.2, -572.7, -573.2, -573.7, -574.2, -574.7, -575.2, -575.7, -576.2, -576.7, -577.2, -577.7, -578.2, -578.7, -579.2, -579.7, -580.2, -580.7, -581.2, -581.7, -582.2, -582.7, -583.2, -583.7, -584.2, -584.7, -585.2, -585.7, -586.2, -586.7, -587.2, -587.7, -588.2, -588.7, -589.2, -589.7, -590.2, -590.7, -591.2, -591.7, -592.2, -592.7, -593.2, -593.7, -594.2, -594.7, -595.2, -595.7, -596.2, -596.7, -597.2, -597.7, -598.2, -598.7, -599.2, -599.7, -600.2, -600.7, -601.2, -601.7, -602.2, -602.7, -603.2, -603.7, -604.2, -604.7, -605.2, -605.7, -606.2, -606.7, -607.2, -607.7, -608.2, -608.7, -609.2, -609.7, -610.2, -610.7, -611.2, -611.7, -612.2, -612.7, -613.2, -613.7, -614.2, -614.7, -615.2, -615.7, -616.2, -616.7, -617.2, -617.7, -618.2, -618.7, -619.2, -619.7, -620.2, -620.7, -621.2, -621.7, -622.2, -622.7, -623.2, -623.7, -624.2, -624.7, -625.2, -625.7, -626.2, -626.7, -627.2, -627.7, -628.2, -628.7, -629.2, -629.7, -630.2, -630.7, -631.2, -631.7, -632.2, -632.7, -633.2, -633.7, -634.2, -634.7, -635.2, -635.7, -636.2, -636.7, -637.2, -637.7, -638.2, -638.7, -639.2, -639.7, -640.2, -640.7, -641.2, -641.7, -642.2, -642.7, -643.2, -643.7, -644.2, -644.7, -645.2, -645.7, -646.2, -646.7, -647.2, -647.7, -648.2, -648.7, -649.2, -649.7, -650.2, -650.7, -651.2, -651.7, -652.2, -652.7, -653.2, -653.7, -654.2, -654.7, -655.2, -655.7, -656.2, -656.7, -657.2, -657.7, -658.2, -658.7, -659.2, -659.7, -660.2, -660.7, -661.2, -661.7, -662.2, -662.7, -663.2, -663.7, -664.2, -664.7, -665.2, -665.7, -666.2, -666.7, -667.2, -667.7, -668.2, -668.7, -669.2, -669.7, -670.2, -670.7, -671.2, -671.7, -672.2, -672.7, -673.2, -673.7, -674.2, -674.7, -675.2, -675.7, -676.2, -676.7, -677.2, -677.7, -678.2, -678.7, -679.2, -679.7, -680.2, -680.7, -681.2, -681.7, -682.2, -682.7, -683.2, -683.7, -684.2, -684.7, -685.2, -685.7, -686.2, -686.7, -687.2, -687.7, -688.2, -688.7, -689.2, -689.7, -690.2, -690.7, -691.2, -691.7, -692.2, -692.7, -693.2, -693.7, -694.2, -694.7, -695.2, -695.7, -696.2, -696.7, -697.2, -697.7, -698.2, -698.7, -699.2, -699.7, -700.2, -700.7, -701.2, -701.7, -702.2, -702.7, -703.2, -703.7, -704.2, -704.7, -705.2, -705.7, -706.2, -706.7, -707.2, -707.7, -708.2, -708.7, -709.2, -709.7, -710.2, -710.7, -711.2, -711.7, -712.2, -712.7, -713.2, -713.7, -714.2, -714.7, -715.2, -715.7, -716.2, -716.7, -717.2, -717.7, -718.2, -718.7, -719.2, -719.7, -720.2, -720.7, -721.2, -721.7, -722.2, -722.7, -723.2, -723.7, -724.2, -724.7, -725.2, -725.7, -726.2, -726.7, -727.2, -7

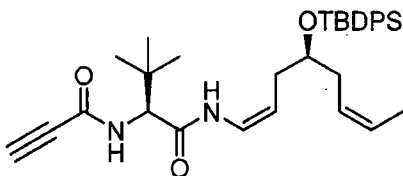
136.1, 134.8, 134.4, 134.3, 129.9, 127.8, 126.4, 126.1, 124.4, 121.7, 121.2, 108.4, 109.1, 82.0, 72.6, 60.6, 55.6, 37.5; 35.2, 32.7, 31.1, 27.2, 26.8, 26.5, 19.5, 17.4, 16.9, 13.1. 25 Synthesis of compound 87 136

122

To a solution of **40** (2.7 g, 5.12 mmol) and propiolic acid (0.41 mL, 6.66 mmol) in anhydrous DCM (51 mL) at 0 °C, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride EDC (1.23 g, 6.4 mmol) was added. The reaction was stirred at 0°C for 30 min and 2 hours at room temperature. Then, the crude mixture was quenched with water and extracted with dichloromethane. The combined filtrates were washed with H₂O. After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (EtOAc/hexanes mixture) to afford pure compound **74** (2.25 g, 85 % yield) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.47-7.36 (m, 6H), 6.96 (d, 1H, *J* = 10.5 Hz), 6.66 (d, 1H, *J* = 9.2 Hz), 6.62 (t, 1H, *J* = 8.9 Hz), 5.52 (t, 1H, *J* = 7.4 Hz), 4.79 (q, 1H, *J* = 8.6 Hz), 4.27 (d, 1H, *J* = 9.4 Hz), 3.83 (m, 1H), 2.82 (s, 1H), 2.19-2.04 (m, 4H), 1.87 (s, 3H), 1.05 (s, 9H), 0.99 (s, 9H).

Synthesis of intermediate 75



20

A solution of propiolic acid (45 μL, 0.726 mmol), amine **62** (275 mg, 0.56 mmol) in anhydrous DCM (5.6 mL) was cooled to 0 °C under argon and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC (134 mg, 0.7 mmol) was added. The reaction mixture was stirred at 0°C for 10 min and then at 23°C for 3 hours, was quenched with water and extracted with dichloromethane. The combined organic layers were dried (anhydrous Na₂SO₄), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:10 to 3:1) to afford **75** (260 mg, 85% yield) as a colourless foam solid.

To a solution of **86** (586 mg, 0.76 mmol) in anhydrous THF (7.5 mL) under N₂ and at room temperature, TBAF 1M in THF (1.53 mL, 2 mmol) **5** was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **87** **10** (320 mg, yield: 80%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ: 8.95 (d, 1H, J = 10.2 Hz), 7.25 (t, 1H, J = 12.0 Hz), 6.85 (t, 1H, J = 11.7 Hz), 6.73 (t, 1H, J = 9.6 Hz), 6.57 (d, 1H, J = 8.1 Hz), 5.61 (dd, 1H, J = 5.4, 3.9 Hz), 5.63-5.58 (m, 1H), 5.44-5.35 (m, 1H), 5.26 (d, 15 1H, J = 9.9 Hz), 4.86 (q, 1H, J = 8.1 Hz), 4.38 (d, 1H, J = 9.6 Hz), 4.24-4.16 (m, 1H), 4.92-4.84 (m, 1H), 4.26 (d, 1H, J = 9.6 Hz), 3.89-3.82 (m, 1H), 2.86-2.79 (m, 1H), 2.41-2.37 (m, 2H), 2.28-2.14 (m, 4H), 1.82 (s, 3H), 1.61 (d, 53H, J = 6.6 Hz), 1.25 (s, 9H), 0.97 (s, 137 To

a solution of **87** (56 mg, 0.105 mmol) in anhydrous DCM (1 mL) at 0°C, trichloroacetyl isocyanate (15 pL, 0.126 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was 5 soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2) to give a compound **88** (57.6 mg, yield: 96%) as a white foam. ¹⁰ ¹H NMR (CDCl₃, 300 MHz) δ: 8.69 (d, 1H, J = 10.4 Hz), 7.31 (dd, 1H, J = 11.6, 11.6 Hz), 6.90 (dd, 1H, J = 11.6, 11.6 Hz), 6.82 (ddd, 1H, J = 10.4, 9.1, 0.9 Hz), 6.53 (d, 1H, J = 9.6 Hz), 6.15 (d, 1H, J = 11.6 Hz), 5.72 (br d, 1H, J = 11.6 Hz), 5.63 (dd, 1H, J = 6.6, 2.7 Hz), 5.60 (m, 1H), 5.40 (m, 1H), 5.29 (d, 1H, J = 9.9 Hz), 4.82 (m, 1H), 4.45 (m, 1H), 4.44 (d, 15 1H, J = 9.6 Hz), 4.25 (ddd, 1H, J = 11.3, 7.0, 4.0 Hz), 3.66 (s, 3H), 2.85 (ddq, 1H, J = 9.9, 7.0, 6.7 Hz), 2.46 (m, 1H), 2.44 (m, 1H), 2.29 (m, 1H), 2.35 (m, 3H), 2.12 (ddd, 1H, J = 14.1, 8.0, 8.0 Hz), 1.82 (s, 3H), 1.63 (dd, 3H, J = 6.8, 1.0 Hz), 1.15 (d, 3H, J = 6.7 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ: 167.7, 152.4, 127.7, 126.0, 123.5, 109.4, 77.3, 74.9, 72.1, 61.3, 35.4, 34.7, 33.2, 26.8, 13.3.

Synthesis of intermediate 76
To a solution of **75** (244.3 mg, 0.45 mmol) in anhydrous THF (5 mL) under N₂ and at room temperature, TBAF 1M in THF (0.54 mL, 0.54 mmol) was added. The reaction was stirred at room temperature for 3 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 4:1 to 1:2) to give alcohol **76** (94.1 mg, 69% yield) as a pale yellow oil.

20

¹H NMR (CDCl₃, 300 MHz) δ: 9.02 (d, 1H, J = 9.9 Hz), 7.09 (d, 1H, J = 9.3 Hz), 6.74 (t, 1H, J = 9.9 Hz), 5.65-5.57 (m, 1H), 5.43-5.35 (m, 1H), 4.93-4.85 (m, 1H), 4.44 (d, 1H, J = 9.3 Hz), 3.78-3.70 (m, 1H), 2.87 (s, 1H), 2.32-2.12 (m, 4H), 1.61 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H).

25 ¹³C NMR (CDCl₃, 75 MHz) δ: 167.7, 152.4, 127.7, 126.0, 123.5, 109.4, 77.3, 74.9, 72.1, 61.3, 35.4, 34.7, 33.2, 26.8, 13.3.

Synthesis of intermediate 77

138 Diisobutylaluminum hydride (DIBAL) 1M in toluene (0.03 mL, 0.034 mol) was added and the mixture was stirred at -78 C. After 2 hours the reaction was quenched with a saturated aqueous solution of NH₄Cl and diluted with dichloromethane (2 mL). This mixture was stirred for 0.5 h at room temperature and then the organic layer was decanted. The aqueous residue was extracted with additional dichloromethane (2 x 4 mL) and the combined organic layers were dried (anhydrous Na₂SO₄) and the solvent was evaporated to give compound 89 (12 mg, 80 % yield) without further purification. ¹H NMR (CDCl₃, 500 MHz) δ: 8.67 (d, 1H, J = 10.7 Hz), 7.17 (m, 1H), 6.92 (t, 1H, J = 11.4 Hz), 6.81 (t, 1H, J = 9.6 Hz), 6.44 (d, 1H, J = 9.5 Hz), 6.18 (d, 1H, J = 11.5 Hz), 5.65 (d, 1H, J = 11.4 Hz), 5.59 (m, 1H), 5.40 (m, 1H), 5.35 (d, 1H, J = 10.0 Hz), 5.27 (s, 1H), 4.83 (q, 1H, J = 8.3 Hz), 4.80 (m, 1H), 4.46 (m, 1H), 4.40 (d, 1H, J = 9.6 Hz), 3.85 (m, 1H), 3.57 (s, 3H), 3.27 (s, 1H), 2.61 (m, 1H), 2.42 (m, 2H), 2.15-1.99 (m, 4H), 1.83 (s, 3H), 1.63 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.6 Hz), 1.04 (s, 9H). EXAMPLE 19

20 Scheme 19 provides the synthesis of several compounds of this invention 139 OR N 0-90a R=TBDPS, Y=H, 90b R=TBS, Y=Cl, MeO, \ I 0 0

- 5 To a solution of **76** (48.6 mg, 0.159 mmol) in anhydrous DCM (1.6 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (23.0 μL, 0.19 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (250 mg). The mixture was stirred for 60 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of
- 10 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 1:100) affording compound **77** (43 mg, 77% yield) as a white solid.

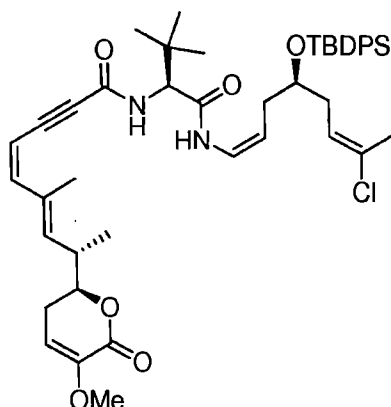
- 15 ¹H NMR (CDCl₃, 300 MHz) δ: 9.02 (d, 1H, J = 10.5 Hz), 7.12 (bs, 1H), 7.04 (d, 1H, J = 9.6 Hz), 6.98 (bs, 1H), 6.80 (t, 1H, J = 9.7 Hz), 5.63-5.53 (m, 1H), 5.42-5.33 (m, 1H), 4.86 (q, 1H, J = 8.3 Hz), 4.48-4.30 (m, 1H), 4.39 (d, 1H, J = 9.6 Hz), 2.87 (s, 1H), 2.46-2.43 (m, 1H), 2.35-2.30 (m, 2H), 2.18-2.11 (m, 1H), 1.61 (d, 3H, J = 6.0 Hz), 1.00 (s, 9H).

20

Synthesis of compound 78

(7E)-45 (7Z)-27 Pd(PPh₃)₄ CuI, iPr₂NH MeO 0 OR (7E,11E)-91a,
R=TBBDPS, Y=H (7E,11E)-91b, R=TBS, Y=Cl (7Z,11E)-91c, R=TBBDPS, Y=H
(7Z,11E)-91d, R=TBS, Y=Cl Scheme 19 Synthesis of intermediate 90a

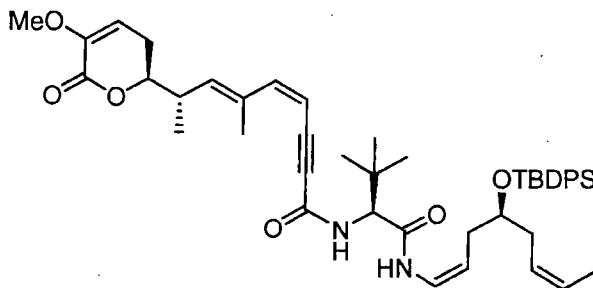
125



To a solution of iodo compound **9** (300 mg, 0.86 mmol) in diisopropylamine (4.3 mL) under N₂ at room temperature, Pd(Ph₃P)₄ (20 mg, 0.017 mmol) and CuI (6.4 mg, 0.034 mmol) were added. Then, compound **74** (500 mg, 0.86 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 2 hours. The crude was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (Hexane/EtOAc 3:1 to 1:1) afford pure compound **78** (580 mg, yield:85%) as a yellow solid.

¹H NMR (CDCl₃, 300 MHz) δ: 7.67 (m, 4H), 7.48-7.37 (m, 6H), 7.75 (d, 1H, *J* = 10.5 Hz), 6.65 (t, 1H, *J* = 10.1 Hz), 6.46 (d, 1H *J* = 9.2 Hz), 6.38 (d, 1H, *J* = 12.0 Hz), 5.64-5.48 (m, 3H), 5.43 (d, 1H, *J* = 12.1 Hz), 4.78 (q, 1H, *J* = 7.7 Hz), 4.28 (d, 1H, *J* = 9.3 Hz), 4.20 (m, 1H), 3.82 (m, 1H), 3.65 (s, 3H), 2.86 (m, 1H), 2.40 (m, 2H), 2.14 (m, 4H), 2.09 (s, 3H), 1.86 (s, 3H), 1.15 (d, 3H, *J* = 6.6 Hz), 1.05 (s, 9H), 0.99 (s, 9H).

Synthesis of compound 79

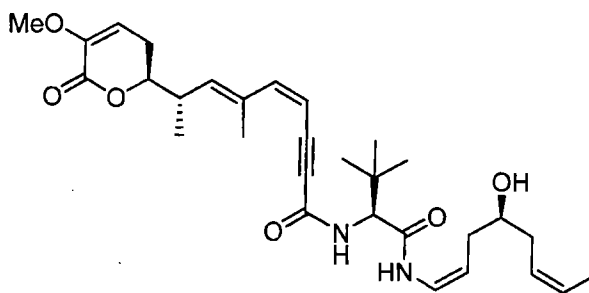


OTBDPS 140 A solution of (E)-pent-2-en-4-ynoic acid (52 mg, 0.54 mmol), amine 62 (232 mg, 0.47 mmol) in anhydrous DCM (5 mL) was cooled to 0C under argon and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC (100 mg, 0.52 mmol) was added. The reaction mixture was stirred at 0C for 10 min and then at 23C for 90 min, was quenched with a saturated aqueous solution of NH₄Cl and extracted with dichloromethane. The combined organic layers were dried (anhydrous Na₂SO₄), filtered and concentrated to afford 90a (223 mg, 83 A yield) as a colourless foam solid, which was used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ: 7.69-7.67 (m, 4H), 7.44-7.36 (m, 6H), 7.11 (d, 1H, J = 15.6 Hz), 6.72-6.60 (m, 2H), 6.42 (d, 1H, J = 8.1 Hz), 6.41 (d, 1H, J = 15.6 Hz), 5.54-5.45 (m, 1H), 5.36-5.27 (m, 1H), 4.89-4.81 (m, 1H), 4.73 (d, 1H, J = 9.3 Hz), 3.93 (m, 1H), 3.25 (bs, 1H), 2.25-2.02 (m, 4H), 1.45 (d, 3H, J = 6.3 Hz), 1.05 (s, 9H), 0.97 (s, 9H). MS (ES) [m/z] = 593.3 [M+Na]⁺. ¹³C NMR (CDCl₃, 125 MHz) δ: 167.7, 164.1, 155.8, 134.4, 123.6, 122.9, 122.7, 122.6, 122.5, 122.4, 121.4, 121.1, 109.2, 84.6, 80.5, 20.72.3, 60.7, 35.3, 33.8, 32.4, 29.7, 27.0, 26.5, 19.3, 12.9. Synthesis of intermediate 90b

Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:3 to 1:1) to afford pure **79** (180 mg, 70 % yield) as a colourless foam solid.

- 10 ¹H NMR (CDCl₃, 300 MHz) δ: 7.67-7.64 (m, 4H), 7.60 (d, 1H, J = 10.8 Hz), 7.46-7.35 (m, 6H), 6.66 (t, 1H, J = 9.6 Hz), 6.59 (dd, 1H, J = 9.9 Hz), 6.31 (d, 1H, J = 12.6 Hz), 5.62-5.54 (m, 2H), 5.42-5.37 (m, 1H), 5.32 (d, 1H, J = 12.0 Hz), 5.30-5.23 (m, 1H), 4.92-4.84 (m, 1H), 4.42 (d, 1H, J = 9.6 Hz), 4.23-4.15 (m, 1H), 3.86-3.78 (m, 1H), 3.63 (s, 3H),
- 15 2.88-2.80 (m, 1H), 2.41-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.06 (s, 3H), 1.39 (d, 3H, J = 6.9 Hz), 1.13 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H), 0.96 (s, 9H).
- ¹³C NMR (CDCl₃, 75 MHz) δ: 167.5, 161.7, 153.3, 148.2, 145.4, 138.2, 136.1, 135.7, 134.4, 129.9, 127.8, 127.8, 126.5, 126.1, 121.6, 109.5,
- 20 108.5, 103.1, 88.2, 85.1, 81.7, 72.6, 60.8, 55.6, 37.2, 35.6, 34.1, 32.6, 27.2, 26.7, 26.6, 19.5, 16.4, 15.5, 13.1. (One Csp² not located).

Synthesis of compound 80



OTBS /I\ CI N 25 To a solution of amine 20a (96.04 mg, 0.24 mmol) and (E)-pent-2-en-4-ynoic acid (27.4 mg, 0.28 mmol) in dry dichloromethane /DMF (10:1, 3.3 mL), under argon atmosphere and at 0 °C, DIPEA (0.049 mL, 0.28 mmol), HOAt (38.11 mg, 0.28 mmol), and HATU (106.4 mg, 0.28 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 dichloromethane. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (dichloromethane /MeOH 100:1 to 20:1) to afford pure **80** (59.5 mg, 75% yield) as a colourless oil.

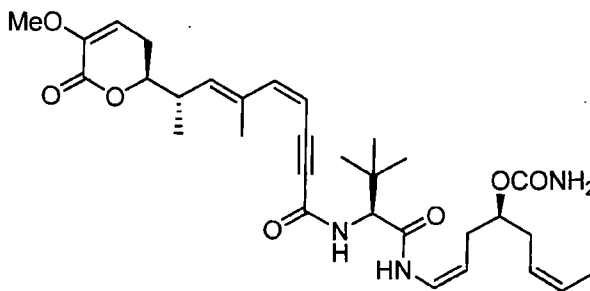
10 To a solution of **9** (52 mg, 0.15 mmol) in DIPA (0.6 mL) at 23 °C, Pd(PPh₃)₄ (0.5 mg, 0.003 mmol) and CuI (0.14 mg, 0.003 mmol) were added. Then, **76** (45.5 mg, 0.15 mmol) in 0.4 mL of DIPA was added and the reaction was stirred at 23 °C for 120 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane /MeOH 100:1 to 20:1) to afford pure **80** (59.5 mg, 75% yield) as a colourless oil.

- 10 ¹H NMR (CDCl₃, 300 MHz) δ: 8.94 (d, 1H, J = 9.9 Hz), 6.75 (t, 1H, J = 9.3 Hz), 6.69 (d, 1H, J = 9.0 Hz), 6.37 (d, 1H, J = 12.0 Hz), 5.68-5.57 (m, 3H), 5.44 (d, 1H, J = 12.0 Hz), 5.43-5.35 (m, 1H), 4.95-4.87 (m, 1H), 4.34 (d, 1H, J = 9.3 Hz), 4.24-4.17 (m, 1H), 3.76 (m, 1H), 3.64 (s, 3H), 2.91-2.78 (m, 1H), 2.63 (bs, 1H), 2.43-2.38 (m, 2H), 2.32-2.11 (m, 4H), 2.07 (s, 3H), 1.62 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.6 Hz), 1.01 (s, 9H).
- 15 ¹³C NMR (CDCl₃, 125 MHz) δ: 167.5, 161.5, 153.2, 147.9, 145.1, 137.8, 135.4, 127.8, 125.5, 123.6, 109.0, 108.3, 103.0, 88.0, 84.7, 81.4, 72.0, 61.1, 55.4, 37.0, 35.2, 34.5, 32.8, 26.6, 26.4, 16.2, 15.3, 13.0.

20

MS (ES) [m/z] = 549.2 [M+Na]⁺.

Synthesis of compound 81



OTBDPS. To a solution of 45 (56.2 mg, 0.182 mmol) in DIPA (1.6 ml) at 23°C, Pd(Ph₃P)₄ (15.7 mg, 0.014 mmol) and CuI (5.2 mg, 0.028 mmol) were added. Then, 90a (114.6 mg, 0.200 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4 to 6:1) to afford pure 91a (96 mg, 70% yield) as a colourless oil. NMR (CDCl₃, 300 MHz) δ: 7.68-7.66 (m, 4H), 7.46-7.35 (m, 6H), 7.11 (s, 1H, J = 10.8 Hz), 6.81 (dd, 1H, J = 15.3 Hz), 6.30 (dd, 1H, J = 10.2 Hz), 6.25 (d, 1H, J = 15.3 Hz), 6.15-6.32 (dd, 1H, J = 15.9, 8.4 Hz), 5.74 (d, 1H, J = 15.9 Hz), 5.72 (dd, 1H, J = 10.2 Hz), 5.55 (m, 1H), 5.30-5.27 (m, 1H), 4.84-4.82 (m, 1H), 4.30 (d, 1H, J = 9.3 Hz), 4.28-4.21 (m, 1H), 3.86-3.82 (m, 1H), 3.65 (s, 10 H), 2.68-2.62 (m, 1H), 2.43-2.36 (m, 2H), 2.22-2.04 (m, 1H), 1.04 (s, 9H), 0.96 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz) δ: 167.7, 164.3, 161.3, 145.5, 145.2, 135.2, 134.1, 131.8, 129.8, 129.7, 127.8, 126.4, 125.8, 122.2, 121.4, 115.1, 111.3, 109.1, 108.9, 85.1, 86.7, 80.8, 72.3, 60.7, 55.4, 41.5, 35.2, 33.8, 32.4, 29.7, 27.0, 26.5, 25.9, 19.3, 15.5, 12.9.

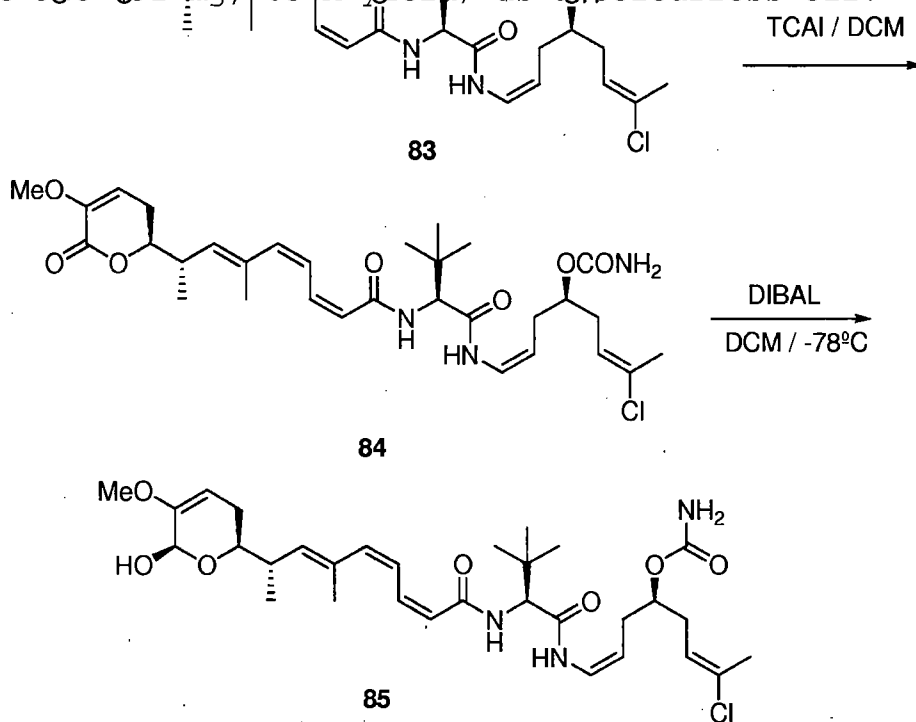
To a solution of 9 (43 mg, 0.123 mmol) in DIPA (0.6 ml) at 23 °C, Pd(Ph₃P)₄ (2.8 mg, 0.0025 mmol) and CuI (1.0 mg, 0.003 mmol) were added. Then, 77 (43 mg, 0.123 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 120 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane / MeOH, 100:1 to 20:1) to afford pure 81 (38 mg, 54% yield) as a colourless oil.

- 10 ¹H NMR (CDCl₃, 300 MHz) δ: 9.00 (d, 1H, J = 10.8 Hz), 6.81 (t, 1H, J = 9.6 Hz), 6.73 (d, 1H, J = 9.6 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.63-5.56 (m, 5H), 5.45 (d, 1H, J = 11.7 Hz), 5.43-5.36 (m, 1H), 4.90-4.81 (m, 1H), 4.40 (d, 1H, J = 9.3 Hz), 4.40-4.33 (m, 1H), 4.24-4.17 (m, 1H), 3.64 (s, 3H), 2.90-2.82 (m, 1H), 2.42-2.31 (m, 5H), 2.18-2.09 (m, 1H), 2.09 (s, 3H), 1.62 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 6.6 Hz), 1.01 (s, 9H).

EXAMPLE 17

Scheme 17 provides the synthesis of several compounds of this invention

Synthesis of compound 91b OTBS 20 To a solution of 45 (30.2 mg, 0.098 mmol) in DIPA (0.5 ml) at 23C, Pd(Ph₃P)₄ (8 mg, 0.007 mmol) and CuI (3 mg, 0.014 mmol) were added. Then, 90b (47.6 mg, 0.098 mmol) in 0.5 ml of DIPA was added and the reaction was stirred at 23 C for 90 min. The crude mixture was 25 quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4 to 1:1) to afford pure 91b (41.2 mg, 64 A) yield) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) 6.70 (d, 1H, J= 10.2 Hz), 6.82 (t, 1H, J= 15.3, 2.4 Hz), 6.72 (t, 1H, J= 9.5 Hz), 6.28 (d, 1H, J= 9.0 Hz), 6.25 (d, 1H, J= 15.3 Hz), 6.15 (dd, 1H, J= 15.9, 8.1 Hz), 5.74 (d, 1H, J= 15.9 Hz), 5.63 (dd, 1H, J= 6.3, 3.0 Hz), 5.62-5.55 (m, 1H), 4.89-4.81 (m, 1H), 5.10-4.38 (d, 1H, J= 9.6 Hz), 4.30-4.23 (m, 1H), 3.79-3.75 (m, 1H), 3.65 (s, 3H), 2.69-2.61 (m, 1H), 2.44-2.32 (m, 2H), 2.20-2.14 (m, 4H), 2.02 (s, 3H), 1.18 (d, 3H, J= 6.6 Hz), 1.02 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) 6: 168.1, 164.6, 161.5, 145.7, 145.4, 132.1, 131.2, 123.9, 122.4, 111.5, 108.9, 108.2, 95.4, 86.9, 81.0, 71.7, 61.0, 55.7, 41.7, 36.5, 35.4, 33.8, 29.9, 26.8, 26.2, 21.3, 18.3, 15.7, -4.3, -4.4. Synthesis of compound 91c 15 To a solution of 78 (11.2 mg, 0.188 mmol) in DIPA (1.6 mL) at 23C, Pd(Ph₃P)₄ (16.3 mg, 0.014 mmol) and CuI (5.3 mg, 0.028 mmol) were added. Then, 90a (11.2 mg, 0.207 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23C for 90 min. The crude mixture was 20 quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4 to 6:1) to afford pure 91c (9.2 mg, 65 A yield) as a colourless oil.



Scheme 17

5 Synthesis of compound 82

144 10.5, 9.3 Hz), 6.39 (d, 1H, J=9.0 Hz), 6.30 (d, 1H, J= 15.3 Hz), 5.88 (t, 1H, J = 10.5 Hz), 5.71 (dd, 1H, J = 10.5, 2.1 Hz), 5.69-5.61 (m, 1H), 5.53-5.47 (m, 1H), 5.35-5.30 (m, 1H), 4.88-4.80 (m, 1H), 4.31 (d, 1H, J = 9.6 Hz), 4.28-4.19 (m, 1H), 3.87-3.82 (m, 1H), 3.65 (s, 3H), 3.14-3.06 (m, 1H), 2.58-2.47 (m, 1H), 2.41-2.32 (m, 1H), 2.23-2.04 (m, 4H), 1.43 (d, 3H, J= 6.6 Hz), 1.18 (d, 3H, J= 6.9 Hz), 1.05 (s, 9H), 0.98 (s, 9H). ¹³C NMR (CDCl₃, 300 MHz) δ: 167.9, 164.5, 161.7, 145.5, 145.4, 136.1, 134.3, 132.4, 130.0, 129.9, 127.9, 127.8, 126.7, 126.1, 122.2, 121.6, 110.7, 109.4, 108.4, 93.2, 91.8, 81.0, 72.6, 61.0; 55.6, 39.6, 35.4, 34.0, 10 32.7, 29.8, 27.2, 26.8, 23.5, 19.5, 15.8, 13.2. Synthesis of compound 91d

OTBS ONM{N? H OCI 15 To a solution of 27 (26.2 mg, 0.085 mmol) in DIPEA (4 ml) at -20 °C, Pd(Ph₃P)₂Cl₂ (6 mg, 0.0085 mmol) and CuI (5mg, 0.025 mmol) were added. Then, 90b (45 mg, 0.094 mmol) was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous 20 Na₂SO₄) and evaporated under reduced pressure. Purification by column chromatography (EtOAc/hexanes 1:10 to 2:1) to afforded 91d (44.5 mg, 79% yield) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.89 (d, 1H, J= 10.8 Hz), 7.22 (dd, 1H, J= 12.3, 11.4 Hz), 6.86 (dd, 1H, J= 11.7, 11.4 Hz), 6.70 (dd, 1H, J= 9.9, 9.3 Hz), 6.35 (d, 1H, J= 9.3 Hz), 6.13 (d, 1H, J= 11.4 Hz), 5.66 (d, 1H, J= 11.4 Hz), 5.60 (dd, 1H, J= 5.4, 3.9 Hz), 5.55 (br t, 1H, J= 7.8 Hz), 5.26 (d, 1H, J= 10.2 Hz), 4.84-4.76 (m, 1H), 4.3 (d, 1H, J= 9.3 Hz), 4.20-4.16 (m, 1H), 3.77-3.69 (m, 1H), 3.63 (s, 3H), 2.89-2.77 (m, 1H), 2.41-2.33 (m, 2H), 2.19-2.13 (m, 4H), 2.00 (s, 3H), 1.82 (s, 3H), 1.13 (d, 3H, J= 6.9 Hz), 1.02 (s, 9H), 0.86 (s, 9H), 0.4 (s, 3H), 0.03 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ: 168.5, 166.4, 161.8, 145.4, 140.3, 137.3, 134.4, 134.3, 131.0, 124.3, 124.1, 122.4, 121.2, 108.7, 108.4, 82.0, 71.6, 60.6, 55.6, 37.5, 36.5, 35.1, 33.8, 26.5, 26.0, 21.3, 18.3, 17.4, 16.9, -4.3, -4.4.

5 thiophenecarboxylate (CuTCF) (422 mg, 2.2 mmol) was added. The reaction was stirred at 0 °C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3x15 mL). The organic solution was dried and

10 evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene **82** (0.66 g, yield: 66%) as an oil.

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

¹³C NMR (CDCl₃, 75 MHz) δ: 168.5, 166.4, 161.8, 145.4, 140.3, 137.3, 134.4, 134.3, 131.0, 124.3, 124.1, 122.4, 121.2, 108.7, 108.4, 82.0, 71.6, 60.6, 55.6, 37.5, 36.5, 35.1, 33.8, 26.5, 26.0, 21.3, 18.3, 17.4, 16.9, -4.3, -4.4.

25

Synthesis of compound 83

To a solution of 91a (78.2 mg, 0.104 mmol) in anhydrous THF (2 mL) 10 under N₂ and at 0 °C, TBAF 1M in THF (0.2 mL, 0.208 mmol) was added. The reaction was stirred at room temperature for 3 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 4:1 to 1:2) to give alcohol 92a (17.9 mg, 34 % yield) as a pale yellow oil. ¹H NMR (CDCl₃, 500 MHz) δ: 8.89 (d, 1H, J = 10.0 Hz), 6.80 (dd, 1H, J = 15.0, 2.0 Hz), 6.75 (dd, 1H, J = 10.0, 9.0 Hz), 6.50 (d, 1H, J = 9.5 Hz), 6.28 (d, 1H, J = 15.5 Hz), 6.14 (dd, 1H, J = 15.5, 8.0 Hz), 5.74 (dd, 1H, J = 16.0, 2.5 Hz), 5.68-6.5 (m, 1H), 5.63 (dd, 1H, J = 6.5, 2.5 Hz), 5.42-5.39 (m, 1H), 4.92-4.90 (m, 1H), 4.37 (d, 1H, J = 9.0 Hz), 4.28-4.23 (m, 1H), 3.79-3.73 (m, 1H), 3.65 (s, 3H), 2.67-2.62 (m, 1H), 2.47-2.37 (m, 2H), 2.34-2.15 (m, 4H), 1.64 (d, 3H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.01 (s, 9H). 25

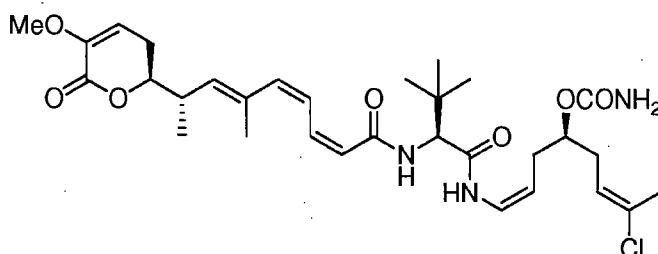
Synthesis of compound 92b To a solution of 91b (41.2 mg, 0.061 mmol) in anhydrous THF (1 mL) under N₂ and at 0 °C, TBAF 1M in THF (0.12 mL, 0.122 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1 to 1:2) to give alcohol 92b (14.7 mg, 65 % yield) as a pale yellow oil. ¹H NMR (CDCl₃, 500 MHz) δ: 6.80 (d, 1H, J = 15.6 Hz), 6.15 (dd, 1H, J = 15.9, 8.4 Hz), 5.75 (d, 1H, J = 15.9 Hz), 5.63-5.60 (m, 2H), 4.92-4.84 (m, 1H), 4.41 (d, 1H, J = 9.3 Hz), 4.29-4.23 (m, 1H), 3.79-3.76 (m, 1H), 3.65 (s, 3H), 3.10 (br s, 1H), 2.69-2.61 (m, 1H), 2.46-2.37 (m, 2H), 2.20-2.14 (m, 4H), 2.04 (s, 3H), 1.18 (d, 3H, J = 6.9 Hz), 1.02 (s, 9H). 30

10 alcohol **83** (175 mg; yield: 76 %) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ: 9.00 (d, 1H, J = 10.2 Hz), 7.25 (dd, 1H, J = 12.0, 11.4 Hz), 6.86 (dd, 1H, J = 11.7, 11.4 Hz), 6.72 (dd, 1H, J = 9.6, 8.7 Hz), 6.68 (d, 1H, J = 8.7 Hz), 6.13 (d, 1H, J = 11.7 Hz), 5.68 (d, 1H, J = 11.4 Hz), 5.63-5.58 (m, 2H), 5.27 (d, 1H, J = 10.2 Hz), 4.85-4.76 (m, 1H), 4.42 (d, 1H, J = 9.3 Hz), 4.25-4.17 (m, 1H), 3.70-3.69 (m, 1H), 3.63 (s, 3H), 3.48 (br s, 1H), 2.89-2.75 (m, 1H), 2.42-2.36 (m, 2H), 2.22-2.11 (m, 4H), 2.04 (s, 3H), 1.82 (s, 3H), 1.14 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H).

Synthesis of compound 84

20



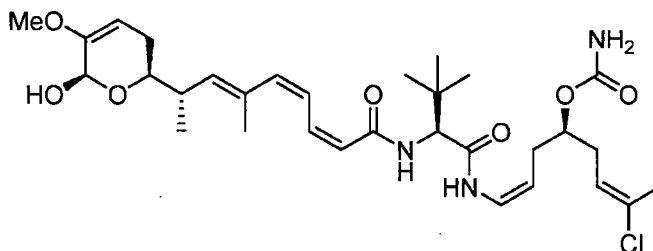
To a solution of **83** (300 mg, 0.53 mmol) in anhydrous DCM (7.5 mL) at 0 °C, trichloroacetyl isocyanate (TCAI) (76 µl, 0.64 mmol) was added. The reaction was stirred at 0 °C for 30 min and then neutral aluminium

Synthesis of compound 92c 147 added. The reaction was stirred at room temperature for 4 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 5 by flash chromatography (hexane/EtOAc 4:1 to 1:2) to give alcohol 92c (18.1 mg, 37% yield) as a pale yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ: 8.94 (d, 1H, J = 9.6 Hz), 6.83 (dd, 1H, J = 15.3, 2.1 Hz), 6.75 (t, 1H, J = 9.6 Hz), 6.57 (d, 1H, J = 9.6 Hz), 6.32 (d, 1H, J = 15.3 Hz), 5.88 (d, 1H, J = 10.2 Hz), 5.74-5.70 (m, 1H), 5.67-5.62 (m, 2H), 5.44-5.36 (m, 1H), 4.95-4.86 (m, 1H), 4.36 (dd, 1H, J = 10.8 Hz), 3.73 (dd, 1H, J = 10.8 Hz), 3.65 (s, 3H), 3.14-3.06 (m, 1H), 2.59-2.11 (m, 6H), 1.63 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.02 (s, 9H). The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (hexane/EtOAc 4:1 to 1:2) to give compound 84 (0.26 g, yield: 81%) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ: 8.78 (d, 1H, J = 10.8 Hz), 7.90 (dd, 1H, J = 11.6, 11.6 Hz), 6.91 (dd, 1H, J = 11.6, 11.6 Hz), 6.84 (br dd, 1H, J = 9.9 Hz), 6.82 (dd, 1H, J = 15.6, 1.4 Hz), 6.31 (d, 1H, J = 9.5 Hz), 6.17 (d, 1H, J = 11.6 Hz), 5.70 (d, 1H, J = 9.3 Hz), 6.33 (d, 1H, J = 9.3 Hz), 5.88 (t, 1H, J = 10.5 Hz), 5.71 (dd, 1H, J = 10.8, 10.2 Hz), 5.64 (dd, 2H, J = 6.5, 2.6 Hz), 5.61 (br Hz)H, 4.46 (d, 1H, J = 9.3 Hz), 5.29 (d, 1H, J = 9.8 Hz), 4.80 (m, 1H), 4.41 (m, 1H), 4.41 (d, 1H, J = 9.5 Hz), 4.24 (ddd, 1H, J = 11.5, 7.1, 4.1 Hz), 3.66 (s, 3H), 2.85 (ddq, 1H, J = 9.8, 7.1, 6.7 Hz), 2.46 (m, 1H), 2.45 (ddd, 1H, J = 17.3, 11.5, 2.6 Hz), 2.37 (ddd, 1H, J = 17.3, 6.5, 4.1 Hz), 2.33 (m, 2H), 2.09 (ddd, 1H, J = 14.1, 8.4, 8.1 Hz), 2.06 (s, 3H), 1.82 (s, 3H), 1.15 (d, 3H, J = 6.7 Hz), 1.04 (s, 9H).

¹³C NMR (CDCl₃, 75 MHz) δ: 168.2, 166.3, 161.6, 157.2, 145.2, 140.2, 137.6, 134.1, 133.7, 132.0, 124.6, 124.5, 122.4, 120.7, 108.2, 105.0, 81.9, 74.9, 60.8, 55.4, 37.1, 34.7, 33.0, 30.7, 26.7, 26.1, 21.0, 17.1, 16.3.

Synthesis of compound 85



25

Over a -78 °C cooled solution of compound **84** (10 mg, 0.016 mmol) in anhydrous dichloromethane (0.3 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (0.02 mL, 0.02 mol)

5 4.28-4.20 (m, 1H), 3.72 (m, 1H), 3.64 (s, 3H), 3.13-3.06 (m, 2H), 2.58-
2.47 (m, 1H), 2.41-2.33 (m, 1H), 2.31-2.15 (m, 4H), 2.05 (s, 3H), 1.18 (d,
3H, $J = 6.9$ Hz), 1.02 (s, 9H). EXAMPLE 20 10

133

was added and the mixture was stirred at -78 °C. After 2 hours the
reaction was quenched with a saturated aqueous solution of NH_4Cl and
diluted with dichloromethane (2 mL). This mixture was stirred for 0.5 h
at room temperature and then the organic layer was decanted. The
5 aqueous residue was extracted with additional dichloromethane (2 x 4
mL) and the combined organic layers were dried (anhydrous Na_2SO_4)
and the solvent was evaporated. The crude was purified by column
chromatography (hexane/EtOAc 2:1 to 1:2) to give compound **85** (5 mg,
50% yield) as a colourless oil.

10

^1H NMR (CDCl_3 , 300 MHz) δ : 8.57 (d, 1H, $J = 10.9$ Hz), 7.19 (t, 1H, $J =$
11.3 Hz), 6.92 (t, 1H, $J = 11.4$ Hz), 6.82 (t, 1H, $J = 9.3$ Hz), 6.38 (d, 1H,
 $J = 9.5$ Hz), 6.18 (d, 1H, $J = 11.5$ Hz), 5.64 (d, 1H, $J = 11.2$ Hz), 5.60 (m,
1H), 5.35 (d, 1H, $J = 10.0$ Hz), 5.27 (d, 1H, $J = 3.1$ Hz), 4.81 (m, 2H),
15 4.46 (m, 1H), 4.40 (d, 1H, $J = 9.5$ Hz), 3.85 (m, 1H), 3.57 (s, 3H), 3.21
(d, 1H, $J = 3.1$ Hz), 2.61 (m, 1H), 2.46-2.29 (m, 3H), 2.14-2.08 (m, 3H),
2.06 (s, 3H), 1.81 (s, 3H), 1.08 (d, 3H, $J = 6.7$ Hz), 1.05 (s, 9H).

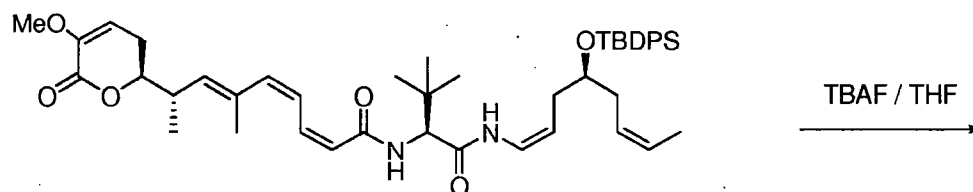
EXAMPLE 18

20

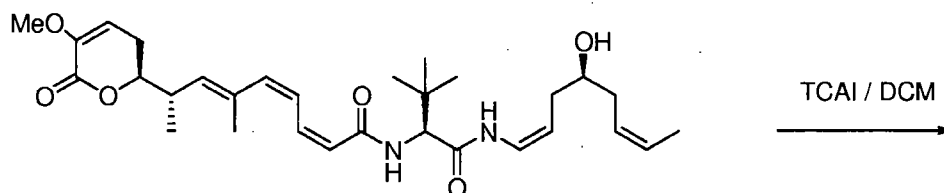
Scheme 18 provides the synthesis of several compounds of this
invention

Scheme 20 provides the synthesis of the following compound of the invention. Scheme 20 20 Synthesis of compound 93 149 To a solution of 92d (6.5 mg, 0.012 mmol) in anhydrous DCM (0.2 mL) at 23 C, trichloroacetyl isocyanate (TCAI) (1.7 ill, 0.014 mmol) was 5 added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (120 mg). 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 10 give the crude product which was purified by column chromatography (dichloromethane / MeOH 100:1 to 40:1) affording compound 93 (3 mg, 42% yield) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ : 8.83 (d, 1H, J = 10.5 Hz), 6.89-6.81 (m, 15 2H), 6.62 (d, 1H, J = 9.9 Hz), 6.32 (d, 1H, J = 15.3 Hz), 5.87 (t, 1H, J = 20 13C NMR (CDCl₃, 125 MHz) δ : 167.9, 164.3, 161.4, 157.6, 145.1, 145.0

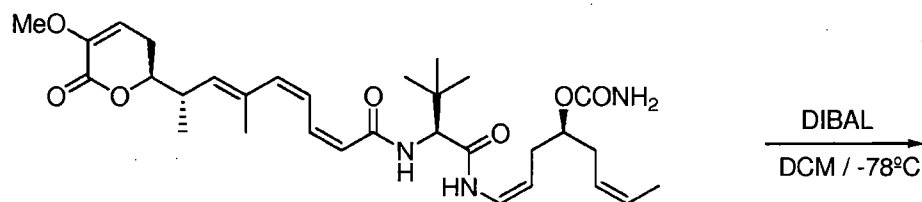
63



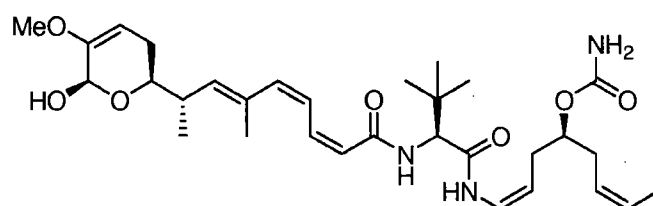
86



87



88

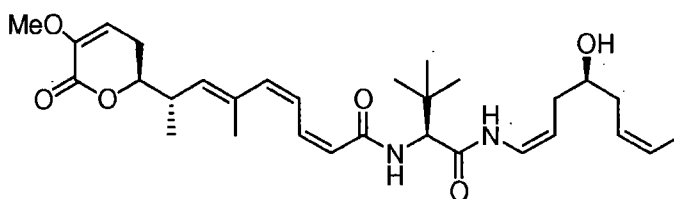


89

Scheme 18

5 Synthesis of compound 86

136

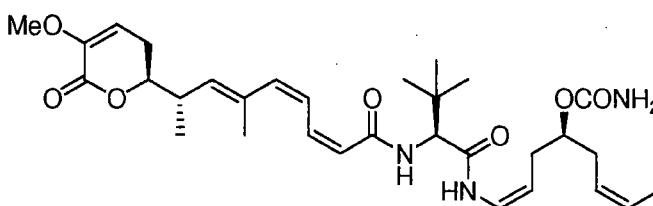


To a solution of **86** (586 mg, 0.76 mmol) in anhydrous THF (7.5 mL) under N₂ and at room temperature, TBAF 1M in THF (1.53 mL, 2 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **87** (320 mg, yield: 80%) as a white solid.

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

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

Synthesis of compound 88



13C NMR (CDCl₃, 125 MHz) δ : 167.9, 164.6, 161.7, 145.5, 136.1, 134.3, 15
 132.5, 129.9, 127.8, 126.7, 126.1, 121.7, 118.9, 116.4, 108.9, 108.4,
 104.5, 98.8, 82.8, 81.6, 72.6, 60.9, 55.7, 38.0, 35.5, 34.0, 32.7, 27.2,
 26.9, 26.5, 19.5, 17.3, 16.5, 13.1. Synthesis of compound 96 20 N OH To a
 solution of 95 (250 mg, 0.326 mmol) in THF (3.3 mL) under N₂ and at 0C,
 TBAF 1M in THF (0.65 mL, 0.65 mmol) was added. The reaction 25 was stirred
 at room temperature for 3 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, 153 (hexane/EtOAc, 4:1 to 1:3), to give
 alcohol 96 (150 mg, 87 % yield) as a colourless oil. NMR (CDCl₃, 300 MHz)
 6: 8.76 (d, 1H, J = 9.3 Hz), 6.17 (d, 1H, J = 12.0 Hz), 6.15-6.09 (m, 1H), 6.07 (d, 1H, J = 12.0 Hz),
 5.74-5.60 (m, 1H), 5.61 (dd, 1H, J = 6.3, 3.0 Hz), 5.44-5.37 (m, 1H),
 4.94-4.85 (m, 1H), 4.41 (d, 1H, J = 9.3 Hz), 4.25-4.17 (m, 1H), 3.76 (m,
 1H), 3.65 (s, 3H), 2.92-2.80 (m, 1H), 2.55-2.11 (m, 6H), 1.93 (s, 3H),
 1.62 (d, 3H, J = 6.6 Hz), 1.14 (t, 3H, J = 6.6 Hz). This mixture was stirred for 0.5 h
 at room temperature and then the organic layer was decanted. The
 aqueous residue was extracted with additional dichloromethane (2 x 4

mL) and the combined organic layers were dried (anhydrous Na₂SO₄)
 and the solvent was evaporated to give compound **89** (12 mg, 80 %
 yield) without further purification.

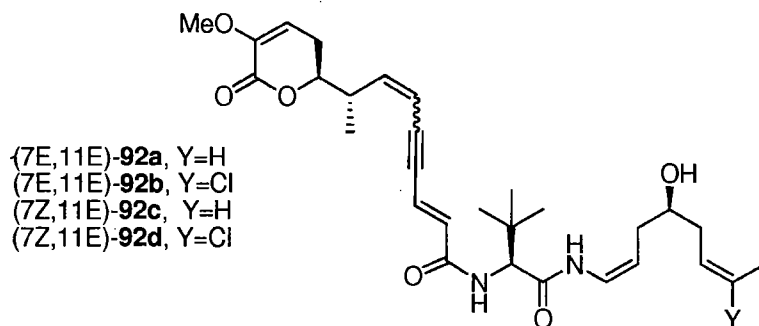
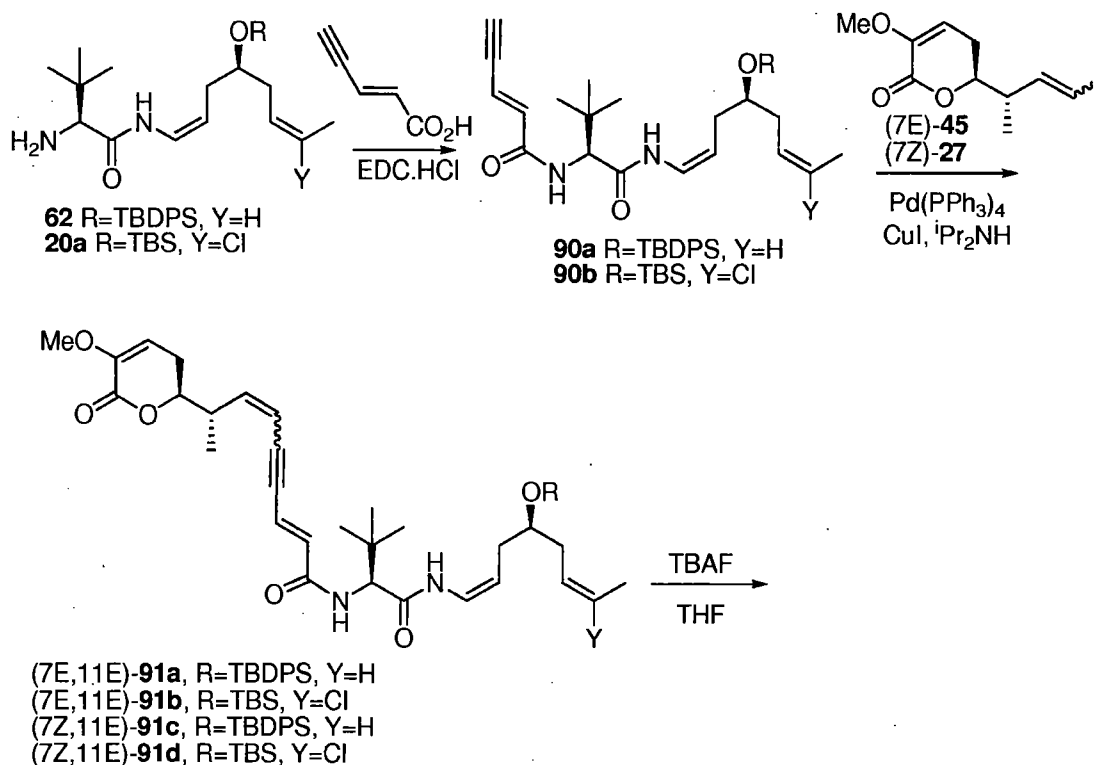
- 10 ¹H NMR (CDCl₃, 500 MHz) δ : 8.67 (d, 1H, J = 10.7 Hz), 7.17 (m, 1H),
 6.92 (t, 1H, J = 11.4 Hz), 6.81 (t, 1H, J = 9.6 Hz), 6.44 (d, 1H, J = 9.5
 Hz), 6.18 (d, 1H, J = 11.5 Hz), 5.65 (d, 1H, J = 11.4 Hz), 5.59 (m, 1H),
 5.40 (m, 1H), 5.35 (d, 1H, J = 10.0 Hz), 5.27 (s, 1H), 4.83 (q, 1H, J = 8.3
 Hz), 4.80 (m, 1H), 4.46 (m, 1H), 4.40 (d, 1H, J = 9.6 Hz), 3.85 (m, 1H),
 15 3.57 (s, 3H), 3.27 (s, 1H), 2.61 (m, 1H), 2.42 (m, 2H), 2.15-1.99 (m, 4H),
 1.83 (s, 3H), 1.63 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.6 Hz), 1.04 (s,
 9H).

EXAMPLE 19

- 20 Scheme 19 provides the synthesis of several compounds of this
 invention

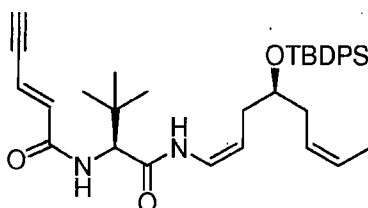
10 Hz), 1.01 (s, 9H). EXAMPLE 22 Scheme 22 provides the synthesis of several compounds of the 15 invention. 0 OMe 100 0 OMe Scheme 22 5
 Synthesis of intermediate 97 OTBDPS %r"-- 0CI

139



Scheme 19

Synthesis of intermediate 90a



To a solution of **40** (200 mg, 0.38 mmol) and 4-pentynoic acid (48 mg, 10 0.49 mmol) in anhydrous DCM (3.8 mL) at 0 °C, EDC (91 mg, 0.47 mmol) was added. The reaction was stirred at 0°C for 30 min and 2 hours at room temperature. Then, the crude mixture was hydrolyzed with water and extracted with dichloromethane (3 x 5 mL). After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (hexane/EtOAc, 6:1) to afford pure compound **97** (105 mg, 47 % yield) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.43 (m, 6H), 7.44 (d, 1H, J = 10.6 Hz), 6.65 (t, 1H, J = 9.3 Hz), 6.46 (d, 1H, J = 9.1 Hz), 5.52 (t, 1H, J = 7.2 Hz), 4.75 (q, 1H, J = 7.6 Hz), 4.29 (d, 1H, J = 9.2 Hz), 3.81 (m, 1H), 2.63-2.40 (m, 4H), 2.19-2.03 (m, 5H), 1.86 (s, 3H), 1.05 (arg), 0.00 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz) δ: 167.7, 164.1, 135.8, 134.4, 134.1, 129.7, 129.7, 127.6, 127.6, 126.4, 125.8, 121.4, 121.1, 109.2, 84.6, 80.5, 72.3, 60.7, 35.3, 33.8, 32.4, 29.7, 27.0, 26.5, 19.3, 12.9.

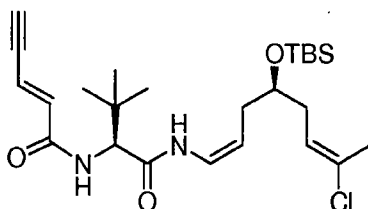
A solution of (*E*)-pent-2-en-4-ynoic acid (52 mg, 0.54 mmol), amine **62** (232 mg, 0.47 mmol) in anhydrous DCM (5 mL) was cooled to 0 °C under argon and DIPEA (0.148 mmol) in 15 diisopropylamine (0.75 mL) hydrochloride, EDC (100 mg, 0.52 mmol) was added. The reaction mixture was stirred at 0 °C for 10 min and then at 23 °C for 90 min, was quenched with a saturated aqueous solution of NH₄Cl and extracted with dichloromethane. The combined organic layers were dried with anhydrous Na₂SO₄, filtered and concentrated to afford **90a** (223 mg, 83 % yield) as a colourless foam solid, which was used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ: 7.69-7.67 (m, 4H), 7.44-7.36 (m, 6H), 7.11 (d, 1H, J = 10.8 Hz), 6.72-6.60 (m, 2H), 6.42 (d, 1H J = 8.1 Hz), 6.41 (d, 1H J = 15.6 Hz), 5.54-5.45 (m, 1H), 5.36-5.27 (m, 1H), 4.89-4.81 (m, 1H), 4.30 (d, 1H, J = 9.3 Hz), 3.89-3.79 (m, 1H), 3.25 (bs, 1H), 2.25-2.02 (m, 4H), 1.45 (d, 3H, J = 6.3 Hz), 1.05 (s, 9H), 0.97 (s, 9H).

¹H NMR (CDCl₃, 300 MHz) δ: 7.69-7.67 (m, 4H), 7.44-7.36 (m, 6H), 7.11 (d, 1H, J = 10.8 Hz), 6.72-6.60 (m, 2H), 6.42 (d, 1H J = 8.1 Hz), 6.41 (d, 1H J = 15.6 Hz), 5.54-5.45 (m, 1H), 5.36-5.27 (m, 1H), 4.89-4.81 (m, 1H), 4.30 (d, 1H, J = 9.3 Hz), 3.89-3.79 (m, 1H), 3.25 (bs, 1H), 2.25-2.02 (m, 4H), 1.45 (d, 3H, J = 6.3 Hz), 1.05 (s, 9H), 0.97 (s, 9H).

MS (ES) [m/z] = 593.3 [M+Na]⁺.

¹³C NMR (CDCl₃, 125 MHz) δ: 167.7, 164.1, 135.8, 134.4, 134.1, 129.7, 129.7, 127.6, 127.6, 126.4, 125.8, 121.4, 121.1, 109.2, 84.6, 80.5, 72.3, 60.7, 35.3, 33.8, 32.4, 29.7, 27.0, 26.5, 19.3, 12.9.

Synthesis of intermediate **90b**



25

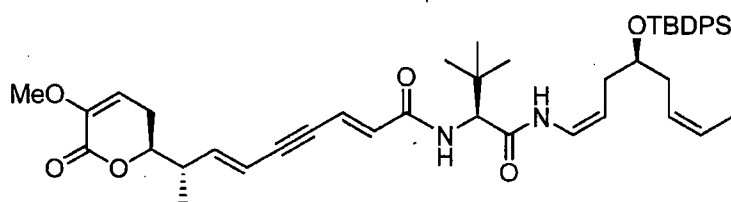
To a solution of amine **20a** (96.04 mg, 0.24 mmol) and (*E*)-pent-2-en-4-ynoic acid (27.4 mg, 0.28 mmol) in dry dichloromethane /DMF (10:1, 3.3 mL), under argon atmosphere and at 0 °C, DIPEA (0.049 mL, 0.28

156 4.74 (q, 1H, J = 8.3 Hz), 4.28 (d, 1H, J = 9.2 Hz), 4.16 (m, 1H), 3.81 (m, 1H), 3.64 (s, 3H), 2.81 (m, 1H), 2.66 (m, 2H), 2.47-2.36 (m, 4H), 2.18-2.06 (m, 4H), 2.04 (s, 3H), 1.85 (s, 3H), 1.12 (d, 3H, J = 6.6 Hz), 1.04 (s, 9H), 0.98 (s, 9H). Synthesis of compound 99 OMe 10 To a solution of 98 (75 mg, 0.09 mmol) in anhydrous THF (1.5 mL) under N₂ and at room temperature, TBAF 1M in THF (0.18 mL, 0.18 mmol) was added. The reaction was stirred at room temperature for 4 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 1:3) to give alcohol 99 (35 mg, 67 % yield) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ: 8.92 (d, 1H, J = 10.1 Hz), 8.74 (d, 1H, J = 10.1 Hz), 8.63 (d, 1H, J = 9.1 Hz), 6.06 (d, 1H, J = 12.0 Hz), 5.62 (m, 2H), 5.47 (d, 1H, J = 9.8 Hz), 5.34 (d, 1H, J = 11.9 Hz), 4.84 (q, 1H, J = 8.5 Hz), 4.32 (d, 1H, J = 9.1 Hz), 4.18 (m, 1H), 2.82 (m, 1H), 2.66 (m, 2H), 2.49-2.36 (m, 4H), 2.24-2.14 (m, 4H), 2.05 (s, 3H), 2.02 (s, 3H), 1.12 (d, 3H, J = 6.6 Hz), 1.00 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz) δ: 171.3, 161.4, 161.7, 145.1, 142.1, 135.5, 134.4, 131.7, 123.6, 123.4, 108.4, 108.2, 106.1, 94.3, 81.8, 80.2, 71.4, 157.6, 60.9, 36.7, 36.1, 35.3, 34.5, 33.0, 29.6, 26.5, 26.3, 21.0, 16.4, 16.1, 15.5. Synthesis of compound 100 5

- 10 ¹H NMR (CDCl₃, 300 MHz) δ: 7.91 (d, 1H, J = 10.2 Hz), 6.74-6.63 (m, 3H), 6.48 (d, 1H, J = 15.6 Hz), 5.58-5.53 (m, 1H), 4.89-4.81 (m, 1H), 4.48 (d, 1H, J = 9.3 Hz), 3.77-3.73 (m, 1H), 3.25 (d, 1H, J = 9.3 Hz), 2.18-2.09 (m, 4H), 2.01 (s, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).
- 15 ¹³C NMR (CDCl₃, 75 MHz) δ: 168.3, 164.4, 134.7, 131.7, 133.9, 122.5, 121.3, 109.1, 84.8, 80.8, 71.6, 61.0, 36.5, 35.4, 33.8, 26.8, 26.0, 21.2, 18.3, -4.3, -4.4.

Synthesis of compound 91a

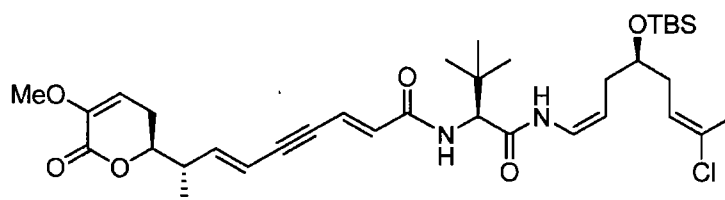
20



- To a solution of **45** (56.2 mg, 0.182 mmol) in DIPA (1.6 ml) at 23°C, Pd(Ph₃P)₄ (15.7 mg, 0.014 mmol) and CuI (5.2 mg, 0.028 mmol) were added. Then, **90a** (114.6 mg, 0.200 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The

OME To a solution of **99** (30 mg, 0.05 mmol) in anhydrous DCM (3.15 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (6 μ l, 0.06 mmol) **10** was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (375 mg). The mixture was stirred for 1 h 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) affording compound **100** (26 mg, 82 % yield) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ : 8.87 (d, 1H, J= 10.7 Hz), 6.81 (t, 1H, J= 8.8 Hz), 6.62 (d, 1H, J= 9.5 Hz), 6.06 (d, 1H, J= 12.0 Hz), 5.75 (bs, 2H), 5.61 (m, 2H), 5.45 (d, 1H, J= 10.1 Hz), 5.35 (d, 1H, J= 11.9 Hz), 4.80 (q, 1H, J= 8.4 Hz), 4.37 (m, 1H), 4.33 (d, 1H, J= 9.3 Hz), 4.18 (m, 1H), 3.64 (s, 3H), 2.83 (m, 1H), 2.66 (m, 2H), 2.50-2.27 (m, 8H), 2.05 (s, 3H), 2.03 (s, 3H), 1.12 (d, 3H, J= 6.6 Hz), 0.99 (s, 9H), 0.95 (s, 9H). **10** ¹³C NMR (CDCl₃, 125 MHz) δ : 167.7, 164.3, 161.3, 145.5, 145.2, 135.2, 134.1, 131.8, 129.8, 129.7, 127.6, 127.6, 126.4, 125.8, 122.2, 121.4, 111.3, 109.1, 108.0, 95.1, 86.7, 80.8, 72.3, 60.7, 55.4, 41.5, 35.2, 33.8, 32.4, 29.7, 27.0, 26.5, 25.9, 19.3, 15.5, 12.9.

Synthesis of compound **91b**



20

To a solution of **45** (30.2 mg, 0.098 mmol) in DIPA (0.5 ml) at 23°C, Pd(Ph₃P)₄ (8 mg, 0.007 mmol) and CuI (3 mg, 0.014 mmol) were added. Then, **90b** (47.6 mg, 0.098 mmol) in 0.5 ml of DIPA was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4 to 1:1) to afford pure **91b** (41.2 mg, 64 % yield) as a colourless oil.

25

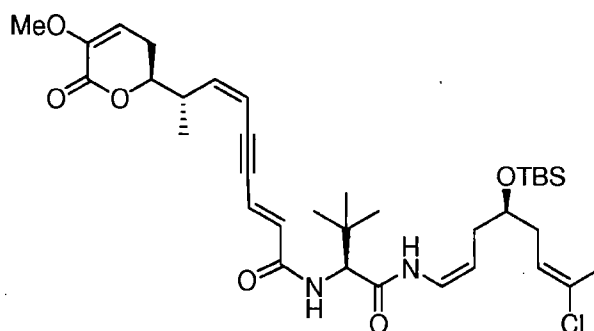
lung carcinoma (NSCLC) HT29 HTB-38 human colon colorectal adenocarcinoma MDA-MB-231 HTB-26 human breast breast adenocarcinoma 15 EVALUATION OF CYTOTOXIC ACTIVITY USING THE SBR COLORIMETRIC ASSAY A colorimetric type of assay, using sulforhodamine B (SRB) reaction has been adapted for a quantitative measurement of cell growth and viability (following the technique described by Skehan P et al. J. Natl. Cancer Inst. 1990, 82, 1107-1112). 20 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 25 human cancer, were obtained from the American Type Culture Collection (ATCC) 5.53-5.47 (m, 1H), 5.35-5.30 (m, 1H), 4.88-4.80 (m, 1H), 4.31 (d, 1H, J

= 9.6 Hz), 4.28-4.19 (m, 1H), 3.87-3.82 (m, 1H), 3.65 (s, 3H), 3.14-3.06

5 (m, 1H), 2.58-2.47 (m, 1H), 2.41-2.32 (m, 1H), 2.23-2.04 (m, 4H), 1.43 (d, 3H, J = 6.6 Hz), 1.18 (d, 3H, J = 6.9 Hz), 1.05 (s, 9H), 0.98 (s, 9H).

^{13}C NMR (CDCl_3 , 300 MHz) δ : 167.9, 164.5, 161.7, 145.5, 145.4, 136.1, 134.3, 132.4, 130.0, 129.9, 127.9, 127.8, 126.7, 126.1, 122.2, 121.6, 110.7, 109.4, 108.4, 93.2, 91.8, 81.0, 72.6, 61.0, 55.6, 39.6, 35.4, 34.0, 10 32.7, 29.8, 27.2, 26.8, 23.5, 19.5, 15.8, 13.2.

Synthesis of compound 91d



15 To a solution of **27** (26.2 mg, 0.085 mmol) in DIPEA (4 ml) at -20 °C, $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (6 mg, 0.0085 mmol) and CuI (5mg, 0.025 mmol) were added. Then, **90b** (45 mg, 0.094 mmol) was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H_2O and extracted with EtOAc. The organic phase was dried (anhydrous 20 Na_2SO_4) and evaporated under reduced pressure. Purification by column chromatography (EtOAc/hexanes 1:10 to 2:1) to afforded **91d** (44.5 mg, 79% yield) as a colourless oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 7.75 (d, 1H, J = 11.1 Hz), 6.81 (dd, 1H, J = 15.6, 2.4 Hz), 6.68 (t, 1H, J = 9.3 Hz), 6.37 (d, 1H, J = 9.3 Hz), 6.34 (d, 25 1H, J = 11.7 Hz), 5.87 (t, 1H, J = 10.8 Hz), 5.70 (dd, 1H, J = 10.8, 2.4 Hz), 5.62-5.57 (m, 2H), 4.85 (q, 1H, J = 8.1 Hz), 4.41 (d, 1H, J = 9.3 Hz),

160 Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS), 2mM Lglutamine, 100 U/mL penicillin and 100 U/mL streptomycin at 37C, 5% CO2 and 98% humidity. For the experiments, cells were harvested 5 from subconfluent cultures using trypsinization and resuspended in fresh medium before counting and plating. Cells were seeded in 96 well microtiter plates at 5 x 10³ cells per well in aliquots of 150 μ l, and allowed to attach to the plate surface for 10 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, 2.56-2.46 (m, 1H), 2.40-2.32 (m, 1H), 2.26-2.13 (m, 4H), 2.04 (s, 3H), 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: 1.17 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

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 5 min.

Synthesis of compound 92a 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 20 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). 25 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).

To a solution of **91a** (78.2 mg, 0.104 mmol) in anhydrous THF (2 mL) Table 1 illustrates data on the biological activity of compound **9** under N₂ atmosphere. TBAF (0.2 mL, 0.208 mmol) was added. The reaction was stirred at room temperature for 3 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

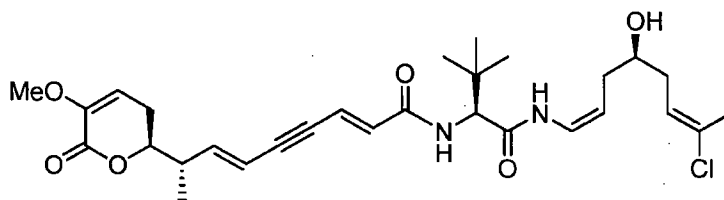
15 by flash chromatography (hexane/EtOAc 4:1 to 1:2) to give alcohol **92a** (17.9 mg, 34 % yield) as a pale yellow oil.

¹H NMR (CDCl₃, 500 MHz) δ : 8.89 (d, 1H, J = 10.0 Hz), 6.80 (dd, 1H, J = 15.0, 2.0 Hz), 6.75 (dd, 1H, J = 10.0, 9.0 Hz), 6.50 (d, 1H, J = 9.5 Hz), 6.28 (d, 1H, J = 15.5 Hz), 6.14 (dd, 1H, J = 15.5, 8.0 Hz), 5.74 (dd, 1H, J = 16.0, 2.5 Hz), 5.68-65 (m, 1H), 5.63 (dd, 1H, J = 6.5, 2.5 Hz), 5.42-5.39 (m, 1H), 4.92-4.90 (m, 1H), 4.37 (d, 1H, J = 9.0 Hz), 4.28-4.23 (m, 1H), 3.79-3.73 (m, 1H), 3.65 (s, 3H), 2.67-2.62 (m, 1H), 2.47-2.37 (m, 2H), 2.34-2.15 (m, 4H), 1.64 (d, 3H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.01 (s, 9H).

20 = 16.0, 2.5 Hz), 5.68-65 (m, 1H), 5.63 (dd, 1H, J = 6.5, 2.5 Hz), 5.42-5.39 (m, 1H), 4.92-4.90 (m, 1H), 4.37 (d, 1H, J = 9.0 Hz), 4.28-4.23 (m, 1H), 3.79-3.73 (m, 1H), 3.65 (s, 3H), 2.67-2.62 (m, 1H), 2.47-2.37 (m, 2H), 2.34-2.15 (m, 4H), 1.64 (d, 3H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.01 (s, 9H).

25 **Synthesis of compound 92b**

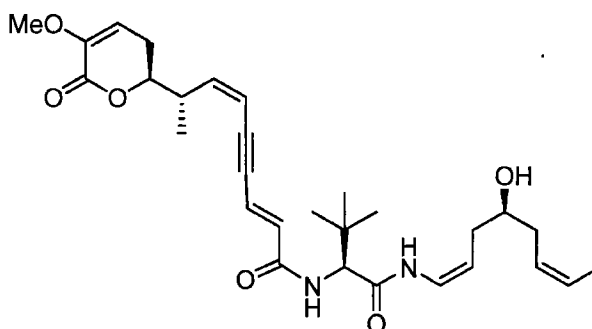
146



To a solution of **91b** (41.2 mg, 0.061 mmol) in anhydrous THF (1 mL) under N₂ and at 0 °C, TBAF 1M in THF (0.12 mL, 0.122 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1 to 1:2) to give alcohol **92b** (14.7 mg, 65 % yield) as a pale yellow oil.

¹H NMR (CDCl₃, 500 MHz) δ: 8.85 (d, 1H, *J* = 10.2 Hz), 6.84-6.73 (m, 2H), 6.61 (d, 1H, *J* = 9.3 Hz), 6.27 (d, 1H, *J* = 15.6 Hz), 6.15 (dd, 1H, *J* = 15.9, 8.4 Hz), 5.75 (d, 1H, *J* = 15.9 Hz), 5.63-5.60 (m, 2H), 4.92-4.84 (m, 1H), 4.41 (d, 1H, *J* = 9.3 Hz), 4.29-4.23 (m, 1H), 3.79-3.76 (m, 1H), 3.65 (s, 3H), 3.10 (bs, 1H), 2.69-2.61 (m, 1H), 2.46-2.37 (m, 2H), 2.20-2.14 (m, 4H), 2.04 (s, 3H), 1.18 (d, 3H, *J* = 6.9 Hz), 1.02 (s, 9H).

Synthesis of compound 92c



20

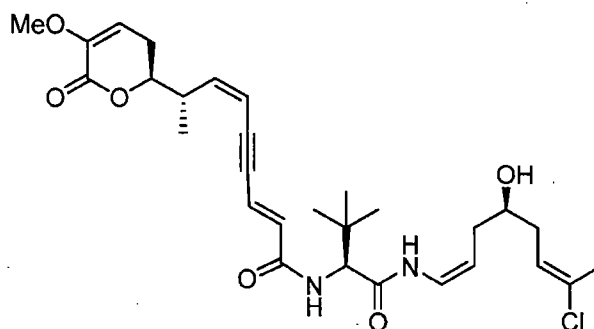
To a solution of **91c** (71.5 mg, 0.095 mmol) in anhydrous THF (2 mL) under N₂ and at 0 °C, TBAF 1M in THF (0.19 mL, 0.19 mmol) was

added. The reaction was stirred at room temperature for 4 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
5 by flash chromatography (hexane/EtOAc 4:1 to 1:2) to give alcohol **92c** (18.1 mg, 37% yield) as a pale yellow oil.

^1H NMR (CDCl_3 , 300 MHz) δ : 8.94 (d, 1H, $J = 9.6$ Hz), 6.83 (dd, 1H, $J = 15.3, 2.1$ Hz), 6.75 (t, 1H $J = 9.6$ Hz), 6.57 (d, 1H, $J = 9.6$ Hz), 6.32 (d, 1H, $J = 15.3$ Hz), 5.88 (d, 1H, $J = 10.2$ Hz), 5.74-5.70 (m, 1H), 5.67-5.62
10 m, 2H), 5.44-5.36 (m, 1H), 4.95-4.86 (m, 1H), 4.38 (d, 1H, $J = 9.3$ Hz), 4.28-4.23 (m, 1H), 3.77-3.73 (m, 1H), 3.65 (s, 3H), 3.14-3.06 (m, 1H), 2.59-2.11 (m, 6H), 1.63 (d, 3H, $J = 6.9$ Hz), 1.19 (d, 3H, $J = 6.6$ Hz), 1.02 (s, 9H).

Synthesis of compound 92d

15



To a solution of **91d** (40 mg, 0.06 mmol) in anhydrous THF (0.6 mL) under N_2 and at room temperature, TBAF 1M in THF (0.12 mL, 0.12
20 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 4:1 to 1:2) to give
25 alcohol **92d** (20 mg, 61 % yield) as a colourless oil.

>1.48E-05 1.18E-05 > 1.66E-05 >1.51E-05 HT29 G150 2.22E-06 1.78E-06
1.21E-08 4.23E-07 TGI 4.29E-06 3.03E-06 5.13E-08 6.50E-07 LC50 >1.48E-05

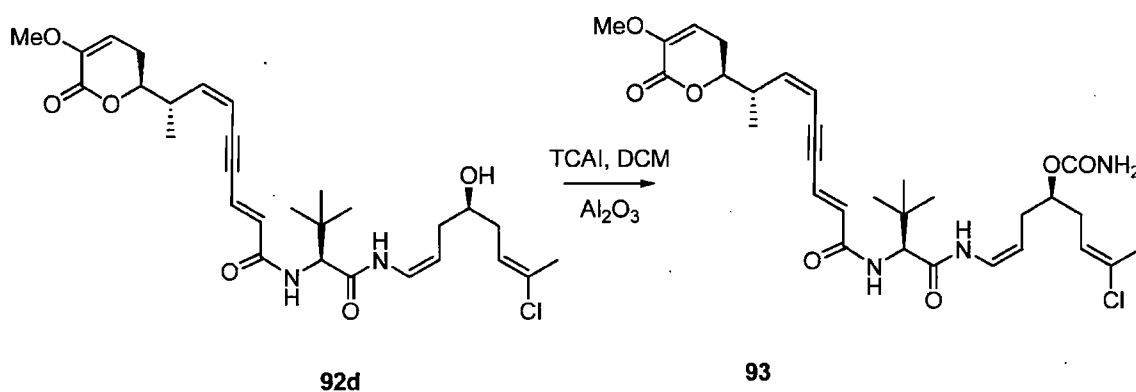
148

¹H NMR (CDCl₃, 300 MHz) δ: 8.90 (d, 1H, *J* = 9.9 Hz), 6.82 (dd, 1H, *J* = 15.6, 2.4 Hz), 6.74 (t, 1H, *J* = 9.6 Hz), 6.66 (d, 1H, *J* = 9.3 Hz), 6.33 (d, 1H, *J* = 9.3 Hz), 5.88 (t, 1H, *J* = 10.5 Hz), 5.71 (dd, 1H, *J* = 10.8, 2.4 Hz), 5.64-5.59 (m, 2H), 4.84 (q, 1H, *J* = 7.8 Hz), 4.40 (d, 1H, *J* = 9.3 Hz),
5 4.28-4.20 (m, 1H), 3.72 (m, 1H), 3.64 (s, 3H), 3.13-3.06 (m, 2H), 2.58-2.47 (m, 1H), 2.41-2.33 (m, 1H), 2.31-2.15 (m, 4H), 2.05 (s, 3H), 1.18 (d, 3H, *J* = 6.9 Hz), 1.02 (s, 9H).

EXAMPLE 20

10

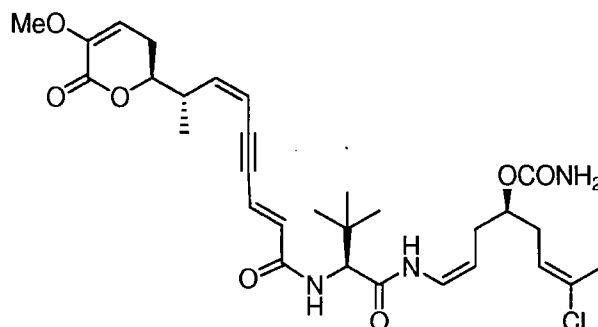
Scheme 20 provides the synthesis of the following compound of the invention.



15

Scheme 20

20 Synthesis of compound 93



To a solution of **92d** (6.5 mg, 0.012 mmol) in anhydrous DCM (0.2 mL) at 23 °C, trichloroacetyl isocyanate (TCAI) (1.7 μ l, 0.014 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (120 mg). 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 (dichloromethane /MeOH 100:1 to 40:1) affording compound **93** (3 mg, 42% yield) as a white solid.

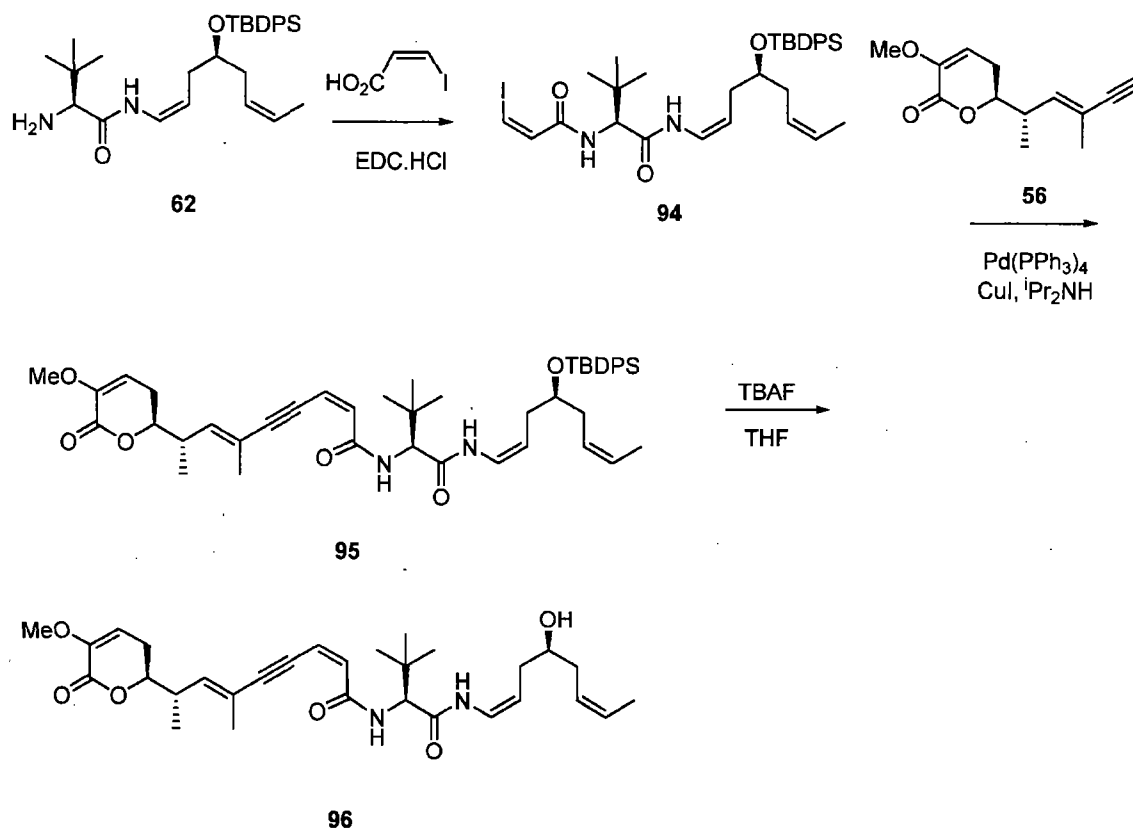
^1H NMR (CDCl_3 , 300 MHz) δ : 8.83 (d, 1H, J = 10.5 Hz), 6.89-6.81 (m, 2H), 6.62 (d, 1H, J = 9.9 Hz), 6.32 (d, 1H, J = 15.3 Hz), 5.87 (t, 1H, J = 9.0 Hz), 5.73 (dd, 1H, J = 10.5, 2.4 Hz), 5.65-5.57 (m, 2H), 5.38 (bs, 2H), 4.84-4.76 (m, 1H), 4.48 (d, 1H, J = 9.3 Hz), 4.40-4.33 (m, 1H), 4.28-4.21 (m, 1H), 3.66 (s, 3H), 3.19-3.10 (m, 1H), 2.58-2.42 (m, 3H), 2.35-2.30 (m, 2H), 2.14-2.06 (m, 1H), 2.08 (s, 3H), 1.20 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz) δ : 167.9, 164.3, 161.4, 157.6, 145.1, 145.0, 132.3, 132.0, 124.5, 122.3, 121.9, 110.6, 108.3, 104.9, 92.9, 91.7, 80.8, 75.1, 61.2, 55.5, 39.3, 35.0, 32.9, 30.9, 26.7, 26.4, 21.0, 15.9.

MS (ES) $[m/z]$ = 590.2 $[M+H]^+$.

EXAMPLE 21

Scheme 21 provides the synthesis of several compounds of the invention.

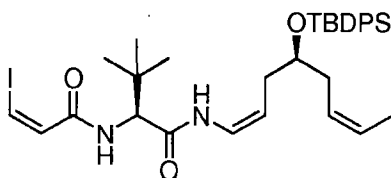


5

Scheme 21

Synthesis of intermediate 94

10



A solution of (Z)-Iodoacrylic acid (365 mg, 1.84 mmol) (prepared as described in Takeuchi, R. Tanabe, K., Tanaka, S. *J. Org. Chem.* 2000,

25 To a solution of **94** (304.4 mg, 0.45 mmol) in DIPA (5.5 ml) at 23°C, Pd(Ph₃P)₄ (39.3 mg, 0.034 mmol) and CuI (12.9 mg, 0.068 mmol) were added. Then, **56** (100 mg, 0.45 mmol) was added and the reaction was stirred at 23°C for 45 min. The crude mixture was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous

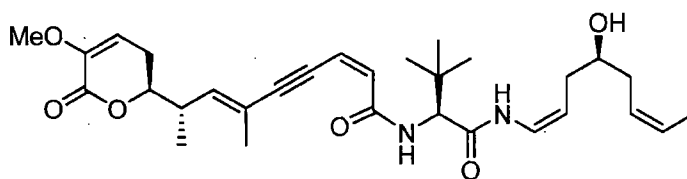
Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:4 to 3:1) to afford pure **95** (300 mg, 87 % yield) as a colourless foam solid.

5 ¹H NMR (CDCl₃, 300 MHz) δ: 7.82 (d, 1H, *J* = 9.3 Hz), 7.68-7.65 (m, 4H), 7.46-7.29 (m, 7H), 6.62 (dd, 1H, *J* = 10.2, 9.3 Hz), 6.14 (d, 1H, *J* = 12.3 Hz), 6.08 (dd, 1H, *J* = 10.5, 9.3 Hz), 6.05 (d, 1H, *J* = 12.3 Hz), 5.60 (dd, 1H, *J* = 6.3, 3.0 Hz), 5.52-5.43 (m, 1H), 5.33-5.25 (m, 1H), 4.85-4.77 (m, 1H), 4.44 (d, 1H, *J* = 9.3 Hz), 4.24-4.23 (m, 1H), 3.88-3.80 (m, 1H),
10 3.64 (s, 3H), 2.91-2.79 (m, 1H), 2.54-2.34 (m, 2H), 2.23-2.04 (m, 4H), 1.92 (s, 3H), 1.42 (d, 3H, *J* = 6.9 Hz), 1.13 (d, 3H, *J* = 6.6 Hz), 1.04 (s, 9H), 0.99 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz) δ: 167.9, 164.6, 161.7, 145.5, 136.1, 134.3,
15 132.5, 129.9, 127.8, 126.7, 126.1, 121.7, 118.9, 116.4, 108.9, 108.4, 104.5, 98.8, 82.8, 81.6, 72.6, 60.9, 55.7, 38.0, 35.5, 34.0, 32.7, 27.2, 26.9, 26.5, 19.5, 17.3, 16.5, 13.1.

Synthesis of compound 96

20



To a solution of **95** (250 mg, 0.326 mmol) in THF (3.3 mL) under N₂ and at 0°C, TBAF 1M in THF (0.65 mL, 0.65 mmol) was added. The reaction
25 was stirred at room temperature for 3 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 4:1 to 1:3) to give alcohol **96** (150 mg, 87 % yield) as a colourless oil.

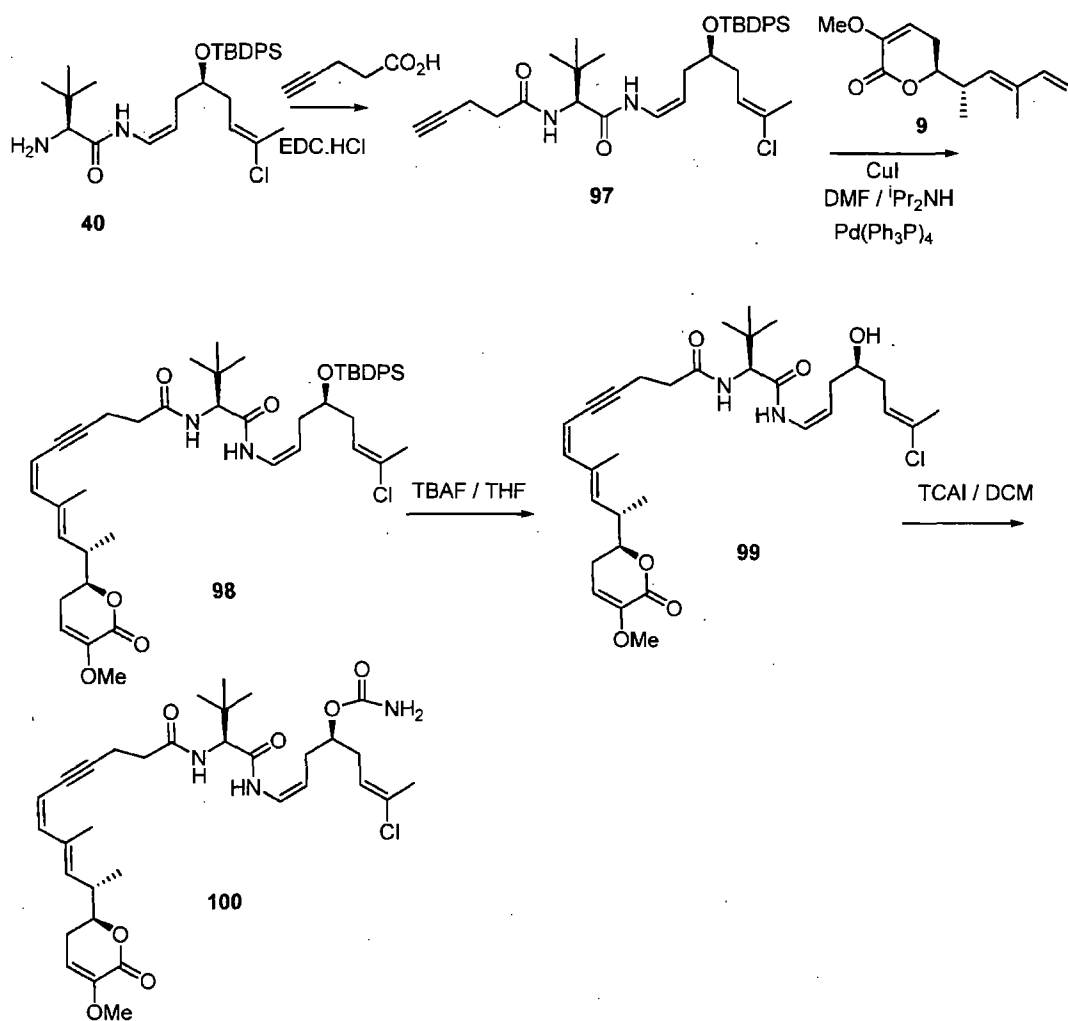
¹H NMR (CDCl₃, 300 MHz) δ : 8.76 (d, 1H, J = 9.9 Hz), 7.83 (d, 1H, J = 9.0 Hz), 6.74 (t, 1H, J = 9.3 Hz), 6.17 (d, 1H, J = 12.0 Hz), 6.15-6.09 (m, 1H), 6.07 (d, 1H, J = 12.0 Hz), 5.74-5.60 (m, 1H), 5.61 (dd, 1H, J = 6.3, 3.0 Hz), 5.44-5.37 (m, 1H), 4.94-4.85 (m, 1H), 4.41 (d, 1H, J = 9.3 Hz), 4.25-4.17 (m, 1H), 3.76 (m, 1H), 3.65 (s, 3H), 2.92-2.80 (m, 1H), 2.55-2.11 (m, 6H), 1.93 (s, 3H), 1.62 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.6 Hz), 1.01 (s, 9H).

EXAMPLE 22

Scheme 22 provides the synthesis of several compounds of the invention.

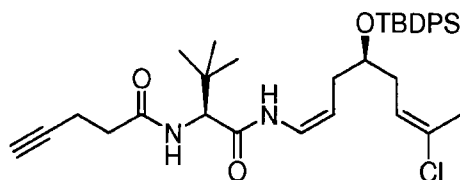
1.93E-09 LC50 8.13E-06 3.53E-06 > 1.90E-05 > 1.76E-07 A549 G150 2.30E-07
 2.09E-06 2.66E-07 1.76E-10 TGI > 1.77E-05 2.61E-06 1.84E-06 2.81E-09

154



Scheme 22

5 Synthesis of intermediate 97



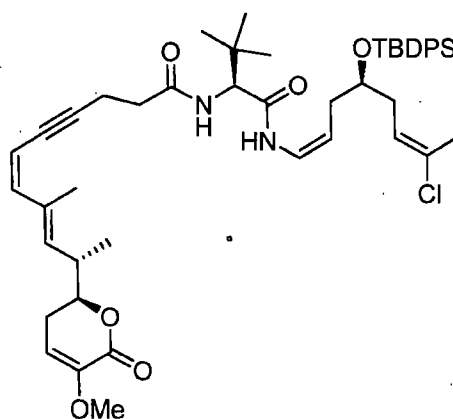
To a solution of **40** (200 mg, 0.38 mmol) and 4-pentynoic acid (48 mg, 0.49 mmol) in anhydrous DCM (3.8 ml) at 0 °C, EDC (91 mg, 0.47 mmol) was added. The reaction was stirred at 0°C for 30 min and 2 hours at room temperature. Then, the crude mixture was hydrolyzed

with water and extracted with dichloromethane (3 x 5 mL). After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (hexane/EtOAc, 6:1) to afford pure compound **97** (105 mg, 47 % yield) as a colourless oil.

- 5 ¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.43 (m, 6H), 7.14 (d, 1H, *J* = 10.6 Hz), 6.65 (t, 1H, *J* = 9.3 Hz), 6.40 (d, 1H, *J* = 9.1 Hz), 5.52 (t, 1H, *J* = 7.2 Hz), 4.75 (q, 1H, *J* = 7.6 Hz), 4.29 (d, 1H, *J* = 9.2 Hz), 3.81 (m, 1H), 2.63-2.40 (m, 4H), 2.19-2.03 (m, 5H), 1.86 (s, 3H), 1.05 (s, 9H), 0.98 (s, 9H).

10

Synthesis of compound 98



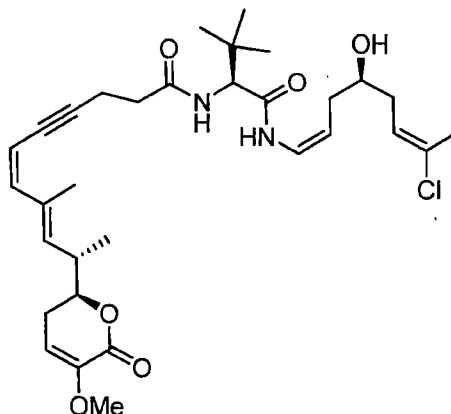
- To a solution of iodo compound **9** (52 mg, 0.148 mmol) in
15 diisopropylamine (0.75 mL) under N₂ at room temperature, Pd(Ph₃P)₄
(2.3 mg, 0.002 mmol) and CuI (1.0 mg, 0.005 mmol) were added. Then,
compound **97** (90 mg, 0.148 mmol) was added portionwise and the
reaction mixture was stirred at room temperature for 2 hours. The
crude was quenched with H₂O and extracted with EtOAc. The organic
20 phase was dried (anhydrous Na₂SO₄) and evaporated under reduced
pressure. Purification by column chromatography (hexane/EtOAc 3:1 to
1:2) afford pure compound **98** (105 mg, 86% yield) as a white solid.

- ¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.41 (m, 6H), 7.26 (d, 1H, *J* = 10.6 Hz), 6.64 (t, 1H, *J* = 10.1 Hz), 6.42 (d, 1H, *J* = 9.3 Hz), 6.06 (d,
25 1H, *J* = 12.0 Hz), 5.61 (m, 1H), 5.48 (m, 2H), 5.35 (d, 1H, *J* = 11.8 Hz),

4.74 (q, 1H, $J = 8.3$ Hz), 4.28 (d, 1H, $J = 9.2$ Hz), 4.16 (m, 1H), 3.81 (m, 1H), 3.64 (s, 3H), 2.81 (m, 1H), 2.66 (m, 2H), 2.47-2.36 (m, 4H), 2.18-2.06 (m, 4H), 2.04 (s, 3H), 1.85 (s, 3H), 1.12 (d, 3H, $J = 6.6$ Hz), 1.04 (s, 9H), 0.98 (s, 9H).

5

Synthesis of compound 99



10 To a solution of **98** (75 mg, 0.09 mmol) in anhydrous THF (1.5 mL) under N_2 and at room temperature, TBAF 1M in THF (0.18 mL, 0.18 mmol) was added. The reaction was stirred at room temperature for 4 hours and then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were dried
15 over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:1 to 1:3) to give alcohol **99** (35 mg, 67 % yield) as a white solid.

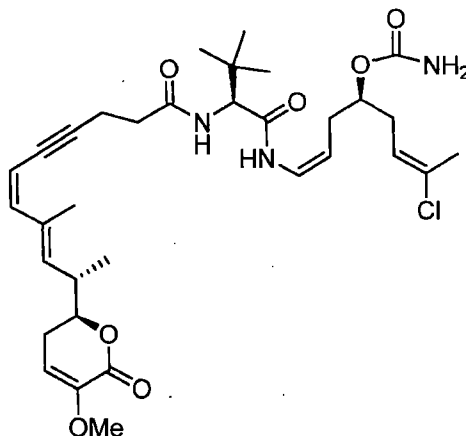
1H NMR ($CDCl_3$, 300 MHz) δ : 8.92 (d, 1H, $J = 10.1$ Hz), 6.74 (t, 1H, $J = 9.5$ Hz), 6.67 (d, 1H, $J = 9.1$ Hz), 6.06 (d, 1H, $J = 12.0$ Hz), 5.62 (m, 2H),
20 5.47 (d, 1H, $J = 9.8$ Hz), 5.34 (d, 1H, $J = 11.9$ Hz), 4.84 (q, 1H, $J = 8.5$ Hz), 4.32 (d, 1H, $J = 9.1$ Hz), 4.18 (m, 1H), 3.73 (m, 1H), 3.64 (s, 3H), 3.20 (d, 1H, $J = 4.0$ Hz), 2.82 (m, 1H), 2.66 (m, 2H), 2.49-2.36 (m, 4H), 2.24-2.14 (m, 4H), 2.05 (s, 3H), 2.02 (s, 3H), 1.12 (d, 3H, $J = 6.6$ Hz), 1.00 (s, 9H).

25 ^{13}C NMR($CDCl_3$, 75 MHz) δ : 171.3, 168.4, 161.7, 145.1, 142.1, 135.5, 134.4, 131.7, 123.6, 123.4, 108.4, 108.2, 106.1, 94.3, 81.8, 80.2, 71.4,

60.9, 36.7, 36.1, 35.3, 34.5, 33.0, 29.6, 26.5, 26.3, 21.0, 16.4, 16.1, 15.5.

Synthesis of compound 100

5



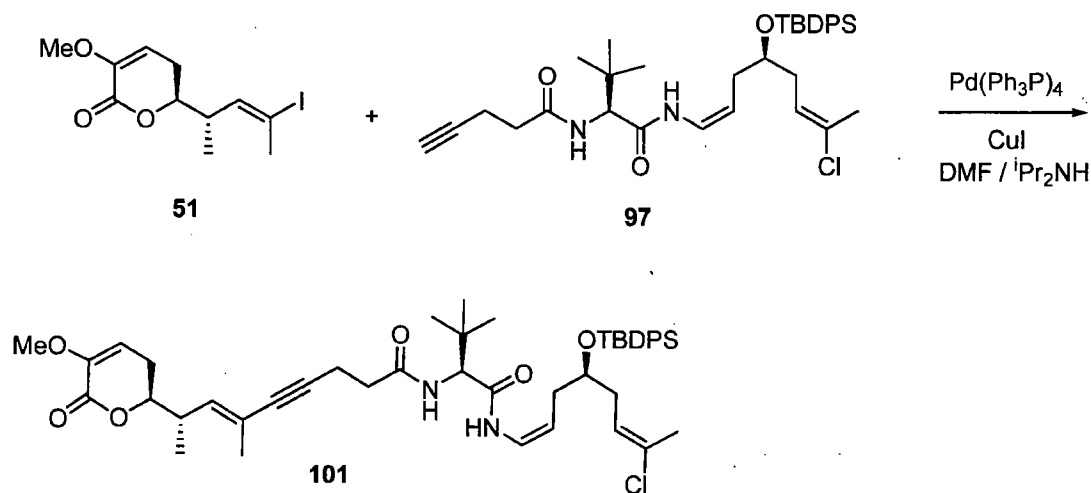
To a solution of **99** (30 mg, 0.05 mmol) in anhydrous DCM (3.15 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (6 μ l, 0.06 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (375 mg). The mixture was stirred for 1 h and then 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) affording compound **100** (26 mg, 82 % yield) as a white solid.

^1H NMR (CDCl_3 , 300 MHz) δ : 8.87 (d, 1H, J = 10.7 Hz), 6.81 (t, 1H, J = 9.8 Hz), 6.62 (d, 1H, J = 9.5 Hz), 6.06 (d, 1H, J = 12.0 Hz), 5.75 (bs, 2H), 5.61 (m, 2H), 5.45 (d, 1H, J = 10.1 Hz), 5.35 (d, 1H, J = 11.9 Hz), 4.80 (q, 1H, J = 8.4 Hz), 4.37 (m, 1H), 4.33 (d, 1H, J = 9.3 Hz), 4.18 (m, 1H), 3.64 (s, 3H), 2.83 (m, 1H), 2.66 (m, 2H), 2.50-2.27 (m, 8H), 2.05 (s, 3H), 2.03 (s, 3H), 1.12 (d, 3H, J = 6.6 Hz), 0.99 (s, 9H).

25 EXAMPLE 23

Scheme 23 provides the synthesis of several compounds of the invention.

5



Scheme 23

10

Synthesis of compound 101

To a solution of iodo compound **51** (70 mg, 0.217 mmol) in diisopropylamine (1.1 mL) under N₂ at room temperature, Pd(Ph₃P)₄ (5
15 mg, 0.004 mmol) and CuI (1.7 mg, 0.008 mmol) were added. Then, compound **97** (132 mg, 0.217 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 2 hours. The crude was quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced
20 pressure. Purification by column chromatography (hexane/EtOAc 3:1 to 1:2) afforded pure compound **101** (80 mg, 50 % yield) as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.41 (m, 6H), 7.25 (d, 1H, *J* = 10.6 Hz), 6.65 (t, 1H, *J* = 10.1 Hz), 6.44 (d, 1H *J* = 9.3 Hz), 5.63- 5.48 (m, 3H), 4.78 (q, 1H, *J* = 8.3 Hz), 4.32 (d, 1H, *J* = 9.2 Hz), 4.14 (m, 1H),
25 3.81 (m, 1H), 3.64 (s, 3H), 2.81 (m, 1H), 2.62 (m, 2H), 2.46-2.33 (m,

4H), 2.18-2.05 (m, 4H), 2.02 (s, 3H), 1.85 (s, 3H), 1.12 (d, 3H, $J = 6.6$ Hz), 1.04 (s, 9H), 0.98 (s, 9H).

5 EXAMPLE 24: 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
10 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

15 **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).

20

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
25 human cancer, were obtained from the American Type Culture Collection (ATCC).

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
5 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
10 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
15 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
20 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).

25 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
30 that produces 50% net cell killing (cytotoxic effect).

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

Table 1. Cytotoxicity assay - Activity Data (Molar)

		Compound 64a	Compound 65a	Compound 66a	Compound 64b
MDA- MB-231	GI ₅₀	4.89E-06	3.56E-06	4.47E-08	1.33E-06
	TGI	>1.48E-05	9.98E-06	7.78E-07	>1.51E-05
	LC ₅₀	>1.48E-05	>1.78E-05	>1.66E-05	>1.51E-05
A549	GI ₅₀	4.44E-06	3.39E-06	3.31E-08	6.80E-07
	TGI	>1.48E-05	6.24E-06	3.97E-07	3.33E-06
	LC ₅₀	>1.48E-05	1.18E-05	> 1.66E-05	>1.51E-05
HT29	GI ₅₀	2.22E-06	1.78E-06	1.21E-08	4.23E-07
	TGI	4.29E-06	3.03E-06	5.13E-08	6.50E-07
	LC ₅₀	>1.48E-05	7.31E-06	2.81E-06	2.42E-06

5

Table 1. (cont.)

		Compound 65b	Compound 66b	Compound 67	Compound 68
MDA- MB-231	GI ₅₀	5.48E-07	2.71E-08	9.10E-07	7.84E-07
	TGI	>1.83E-05	3.73E-07	1.04E-06	1.49E-06
	LC ₅₀	>1.83E-05	4.58E-06	1.21E-06	6.50E-06
A549	GI ₅₀	3.11E-07	2.54E-08	1.57E-06	1.47E-06
	TGI	1.81E-06	8.13E-08	2.82E-06	4.21E-06
	LC ₅₀	> 1.83E-05	> 1.69E-05	4.86E-06	> 1.91E-05
HT29	GI ₅₀	1.83E-07	2.20E-08	1.88E-06	4.59E-07
	TGI	4.94E-07	2.88E-08	2.35E-06	7.07E-07
	LC ₅₀	> 1.83E-05	4.24E-08	3.14E-06	> 1.91E-05

>1.21E-5 1.32E-5 A549 G150 1.38E-10 7.78E-6 1.11E-7 3.06E-6 TGI 2.79E-10
 >1.90E-5 4.95E-7 6.62E-6 LC50 8.19E-10 >1.90E-5 >1.21E-5

162

Table 1. (cont.)

		Compound 69	Compound 70	Compound 71	Compound 72
MDA- MB-231	GI50	3.36E-07	1.70E-06	2.09E-07	2.46E-10
	TGI	1.63E-06	2.48E-06	2.85E-06	1.93E-09
	LC50	8.13E-06	3.53E-06	> 1.90E-05	> 1.76E-07
A549	GI50	2.30E-07	2.09E-06	2.66E-07	1.76E-10
	TGI	> 1.77E-05	2.61E-06	1.84E-06	2.81E-09
	LC50	> 1.77E-05	3.27E-06	8.54E-06	> 1.76E-07
HT29	GI50	1.73E-07	1.96E-06	5.89E-08	5.79E-11
	TGI	4.24E-07	2.74E-06	1.75E-07	1.25E-10
	LC50	> 1.77E-05	4.05E-06	> 1.90E-05	> 1.76E-07

Table 1. (cont.)

		Compound 78	Compound 79	Compound 80	Compound 81	Compound 85
MDA- MB- 231	GI ₅₀	>1.25E-5	>1.31E-5	1.52E-7	2.98E-6	1.02E-9
	TGI	>1.25E-5	>1.31E-5	>1.90E-5	>1.76E-5	1.81E-9
	LC ₅₀	>1.25E-5	>1.31E-5	>1.90E-5	>1.76E-5	>1.64E-8
A549	GI ₅₀	>1.25E-5	>1.31E-5	9.30E-8	2.28E-6	7.23E-10
	TGI	>1.25E-5	>1.31E-5	3.04E-7	8.43E-6	1.64E-9
	LC ₅₀	>1.25E-5	>1.31E-5	>1.90E-5	>1.76E-5	>1.64E-8
HT29	GI ₅₀	>1.25E-5	5.10E-6	4.94E-8	1.26E-6	3.45E-10
	TGI	>1.25E-5	>1.31E-5	9.49E-8	2.98E-6	6.25E-10
	LC ₅₀	>1.25E-5	>1.31E-5	>1.90E-5	>1.76E-5	1.97E-9

1.22E-5 HT29 GI50 8.02E-11 5.89E-6 5.32E-8 9.00E-7 TOT 1.27E-10 8.92E-6
 7.01E-8 2.21E-6 LC50 2.27E-10 >1.90E-5 1.69E-7 5.77E-6

Table 1. (cont.)

		Compound 89	Compound 96	Compound 98	Compound 99
MDA- MB-231	GI50	2.96E-10	1.31E-5	1.04E-7	2.72E-6
	TGI	>1.74E-9	>1.90E-5	1.81E-7	6.11E-6
	LC50	>1.74E-9	>1.90E-5	>1.21E-5	1.32E-5
A549	GI50	1.38E-10	7.78E-6	1.11E-7	3.06E-6
	TGI	2.79E-10	>1.90E-5	4.95E-7	6.62E-6
	LC50	8.19E-10	>1.90E-5	>1.21E-5	1.22E-5
HT29	GI50	8.02E-11	5.89E-6	5.32E-8	9.00E-7
	TGI	1.27E-10	8.92E-6	7.01E-8	2.21E-6
	LC50	2.27E-10	>1.90E-5	1.69E-7	5.77E-6

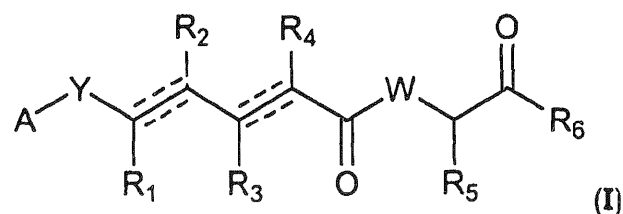
5

Table 1. (cont.)

		Compound 100
MDA- MB-231	GI ₅₀	3.48E-7
	TGI	>1.58E-5
	LC ₅₀	>1.58E-5
A549	GI ₅₀	3.95E-7
	TGI	2.21E-6
	LC ₅₀	>1.58E-5
HT29	GI ₅₀	5.38E-8
	TGI	3.01E-7
	LC ₅₀	7.59E-6

CLAIMS

1. A compound of general formula I



5

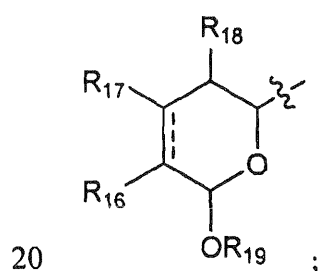
wherein Y is selected from $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$, $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, 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 C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl;

each R_1 , R_2 , R_3 , R_4 , and R_5 is independently selected from hydrogen,
substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted
15 C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl;

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

A is



20

W is selected from O and NR_7 ;

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or
25 unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl,

and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅ together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

- 5 R₈ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;
- 10 R₁₀ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each dotted line represents an optional additional bond, but when a
 15 triple bond 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
 20 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl;

each R₁₆, R₁₇ and R₁₈ are independently selected from hydrogen, OR_a,
 25 OCOR_a, OCOOR_a, NR_aR_b, NR_aCOR_b, and NR_aC(=NR_a)NR_aR_b, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl;

- R₁₉ is selected from hydrogen, COR_a, COOR_a, CONR_aR_b, S(O)R_a, SO₂R_a,
 30 P(O)(R_a)OR_b, SiR_aR_bR_c, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl; and

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

a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

10 2. A compound according to claim 1, wherein R_{19} is selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl and COR_a , and wherein R_a is a substituted or unsubstituted C_1 - C_6 alkyl.

3. A compound according to claim 2, wherein R_{19} is hydrogen.

15

4. A compound according to any one of the preceding claims, wherein R_{16} is selected from hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.

20 5. A compound according to claim 4, wherein R_{16} is selected from hydrogen, OH and methoxy.

6. A compound according to any one of the preceding claims, wherein one additional bond is present between the C atoms to which R_{16} and
25 R_{17} are attached.

7. A compound according to any one of the preceding claims, wherein R_{17} and R_{18} are hydrogen.

30 8. A compound according to any one of the preceding claims, 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.

9. A compound according to claim 8 wherein R_1 , R_2 , R_3 and R_4 are hydrogen.
- 5 10. A compound according to any one of the preceding claims, wherein Y is selected from $-\text{CHR}_{\text{ay}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$ and $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, and wherein R_{ay} , R_{by} and R_{cy} are independently selected from hydrogen and substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl.
- 10 11. A compound according to claim 10, wherein R_{ay} , R_{by} and R_{cy} are independently selected from hydrogen and methyl.
12. A compound according to any one of the preceding claims, wherein R_5 is selected from hydrogen and a substituted or unsubstituted $\text{C}_1\text{-C}_6$
15 alkyl.
13. A compound according to claim 12, wherein R_5 is selected from methyl, isopropyl and tert-butyl.
- 20 14. A compound according to any one of the preceding claims, wherein W is NR_7 and wherein R_7 is as defined in claim 1.
15. A compound according to claim 14, wherein R_7 is hydrogen.
- 25 16. A compound according to any one of claims 1 to 11, 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.
- 30 17. A compound according to any one of the preceding claims, wherein R_6 is NR_8R_9 and wherein R_8 is hydrogen and R_9 is selected from hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or

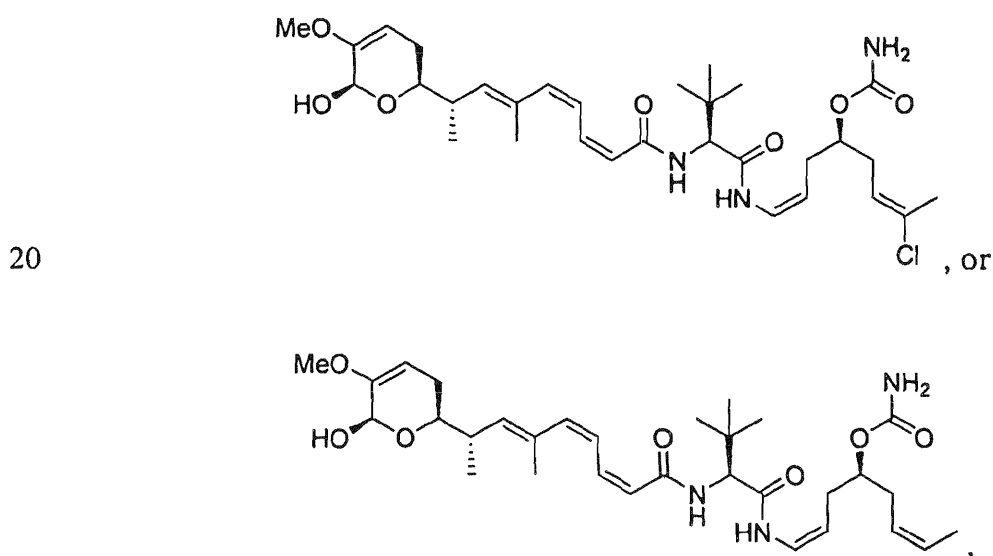
- 168 -

unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl.

18. A compound according to claim 17, wherein R₉ is selected from a
 5 substituted C₂-C₁₂ alkenyl and a substituted C₄-C₁₂ alkenynyl that are
 substituted in one or more positions with halogen, OR', =O, OCOR',
 OCONHR', OCONR'R', CONHR', CONR'R' and protected OH, wherein
 each of the R' groups is independently selected from hydrogen,
 substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted
 10 C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl and
 substituted or unsubstituted aryl.

19. A compound according to any one of the preceding claims, wherein
 one additional bond is present between the C atoms to which R₁ and R₂
 15 are attached and one or two additional bonds are present between the C
 atoms to which R₃ and R₄ are attached.

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



or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

25

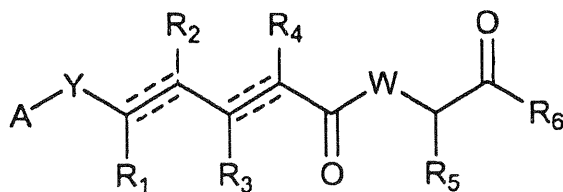
21. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and a pharmaceutically acceptable diluent or carrier.

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

23. A compound according to any one of claims 1 to 20, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, for use as a medicament for treating cancer,

24. Use of a compound according to any of claims 1 to 20, or pharmaceutically acceptable salts, tautomers, or stereoisomers thereof, in the preparation of a medicament for the treatment of cancer.

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

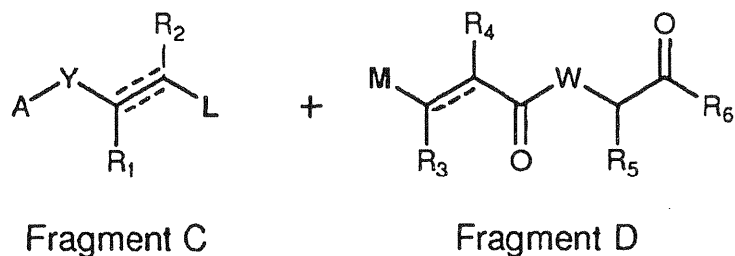


- 170 -

as defined in any one of claims 1 to 20 wherein A, Y, W, R₁, R₂, R₃, R₄, R₅ and R₆ are also as defined in any one of claims 1 to 20

comprising the coupling of Fragments C and D

5



wherein R₁, R₂, R₃, R₄, R₅, R₆, A, Y and W are the desired groups as defined in the compound of formula I or an appropriate protecting group as needed, and L and M are the appropriate reacting or leaving groups.

10

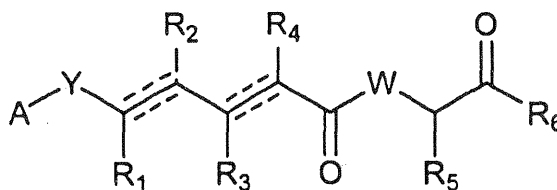
26. A process according to claim 25, wherein the compound of formula I is any one of the compounds defined in claim 20.

27. A process according to claim 25 or claim 26 wherein leaving group

15 "L" is iodide.

28. A process according to any one of claims 25 to 27 wherein reacting group "M" is tributyl tin.

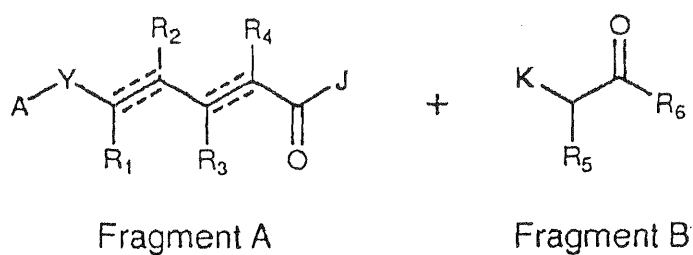
20 29. A process for the preparation of a compound according to formula I



- 171 -

as defined in any one of claims 1 to 20 wherein A, Y, W, R₁, R₂, R₃, R₄, R₅ and R₆ are also as defined in any one of claims 1 to 20

comprising the coupling of Fragments A and B



5

wherein R₁, R₂, R₃, R₄, R₅, R₆, A and Y are the desired groups or an appropriate protecting group as needed, and J and K are the appropriate reacting or leaving groups.

10 30. A process according to claim 29, wherein the compound of formula I is any one of the compounds defined in claim 20.

31. A compound when prepared according to the process of claim 25 or claim 29.