

ANTITUMORAL COMPOUNDS

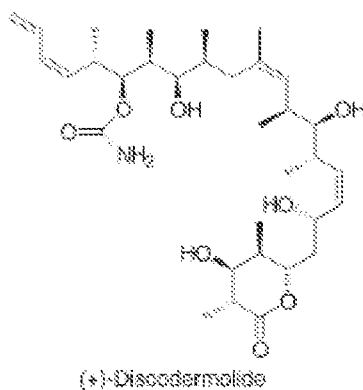
FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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).

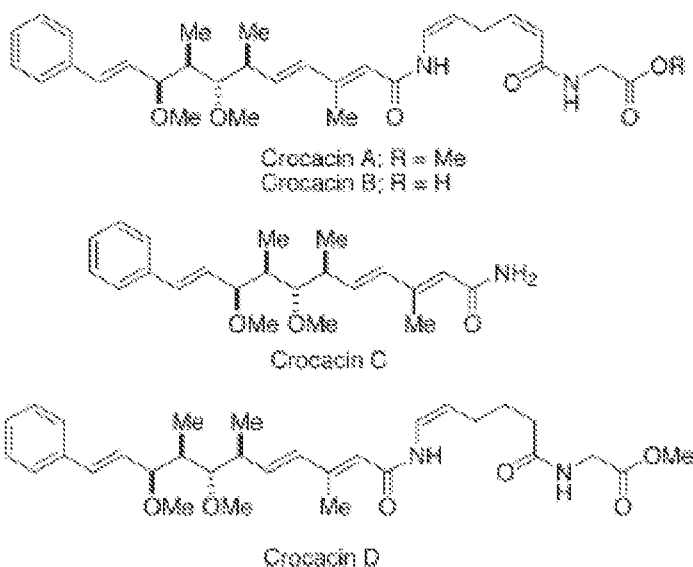


15

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

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

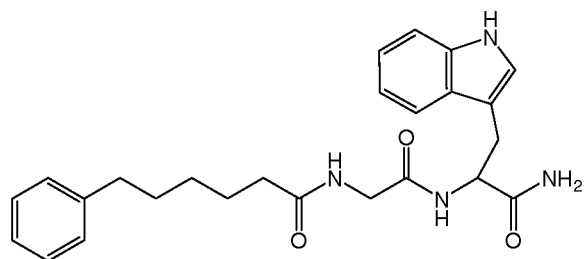


Crocacins A-D moderately inhibit the growth of a few Gram-
10 positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. The most active is crocacin D which showed a MIC of 1.4 ng/mL against the fungus *Saccharomyces cerevisiae* and strong toxicity (IC₅₀ of 0.06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

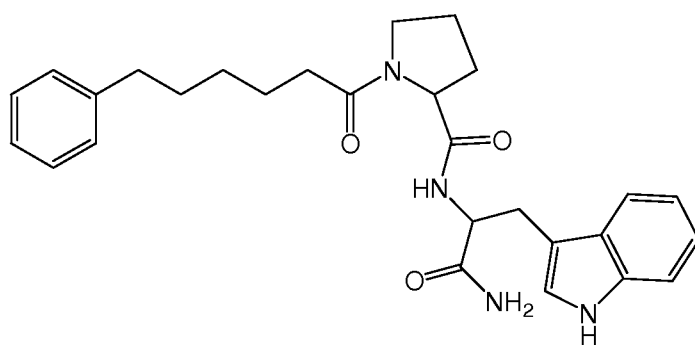
15

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:



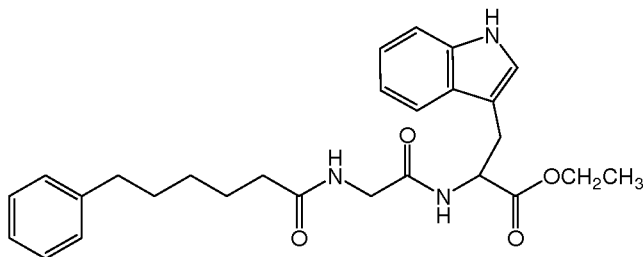
Compound R



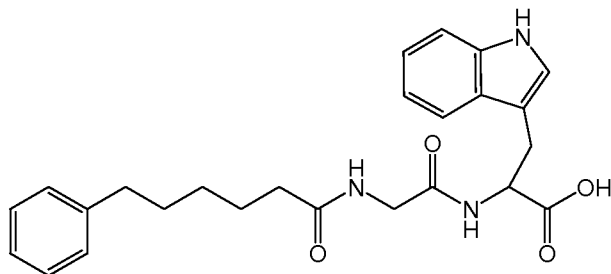
Compound U

5

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



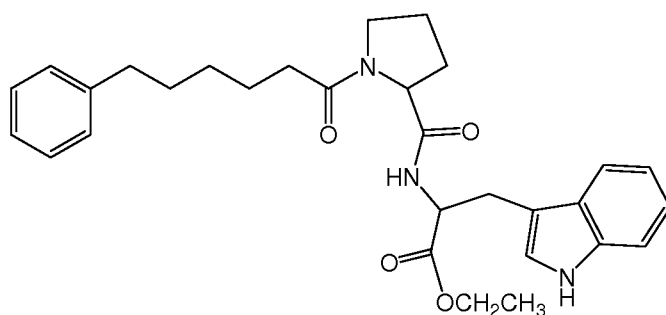
Compound S



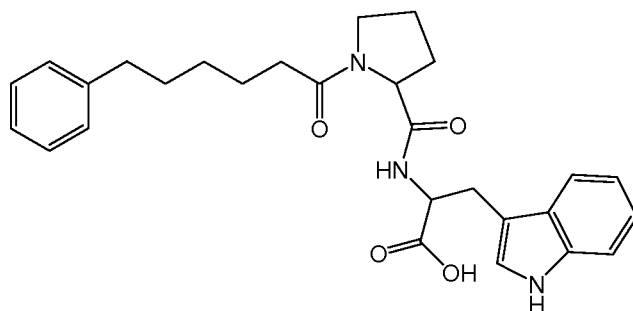
Compound T

10

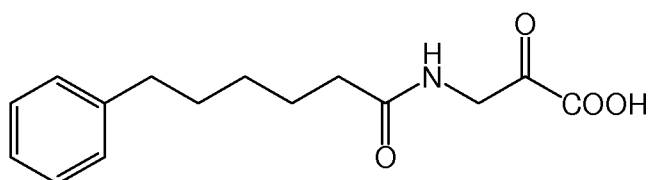
4



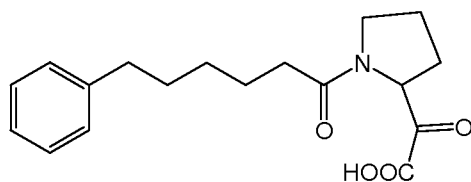
Compound V



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

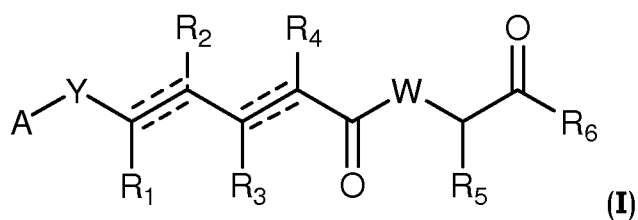
10 provide compounds that are useful in the treatment of cancer.

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



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

5

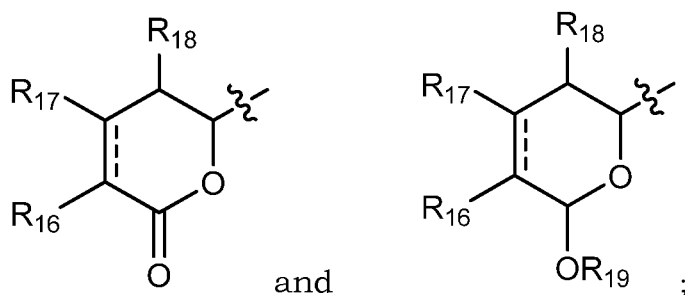
each R_{ay} , R_{by} , and R_{cy} is independently selected from hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

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

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

15

A is selected from



20 W is selected from O and NR_7 ;

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, or R_7 and R_5

together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

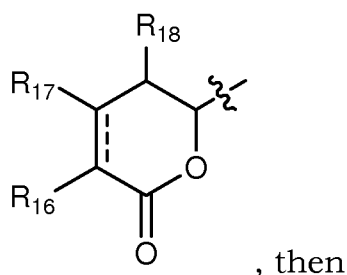
R_8 is selected from hydrogen, COR_a , $COOR_a$, substituted or
 5 unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, and substituted or unsubstituted C_4-C_{12} alkenynyl;

R_{10} is selected from hydrogen, substituted or unsubstituted C_1-C_{12}
 10 alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl;

each dotted line represents an optional additional bond, but when a triple bond exists between the C atoms to which R_1 and R_2 are attached,
 15 R_1 and R_2 are absent, and when a triple bond exists between the C atoms to which R_3 and R_4 are attached, R_3 and R_4 are absent;

and

20 when A is

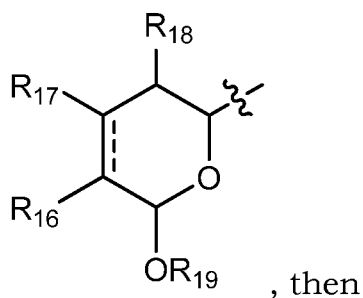


R_9 is selected from hydrogen, COR_a , $COOR_a$, substituted or
 unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12}
 25 alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, and substituted or unsubstituted C_4-C_{12} alkenynyl, with the proviso that when Y is $-CHR_{ay}-CHR_{by}-CHR_{cy}-$ or $-CHR_{ay}-CR_{by}=CR_{cy}-$ and a single or a double

bond exists between the C atoms to which R_3 and R_4 are attached then R_9 is substituted or unsubstituted C_4 - C_{12} alkenynyl; and

when A is

5



R_9 is selected from hydrogen, COR_a , $COOR_a$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, and substituted or unsubstituted C_4 - C_{12} alkenynyl;

each R_{16} , R_{17} and R_{18} 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 C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl;

R_{19} is selected from hydrogen, COR_a , $COOR_a$, $CONR_aR_b$, $S(O)R_a$, SO_2R_a , $P(O)(R_a)OR_b$, $SiR_aR_bR_c$, 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; 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 or unsubstituted aryl and substituted or unsubstituted heterocyclic group.

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.

In another aspect, the present invention is directed to pharmaceutical compositions comprising a compound of formula **I**, or a

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 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.

We define alkenynyl group as an alkyl group containing one or more double bonds and one or more triple bonds, and preferred alkenynyl groups are those having from 4 to about 12 carbon atoms. One more preferred class of alkenynyl groups has from 6 to about 10
5 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
10 groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Preferably aryl groups contain from 6 to about 10 carbon ring atoms. Specially preferred aryl groups include substituted 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
20 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 one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl,
25 isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl,
30 benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or

three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidyl, 5 oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridyl, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexyl, 3-10 azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinoliziny.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', 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. All these

5 references are incorporated by reference in their entirety. Examples of such protected OH include ethers, silyl ethers, esters, sulfonates, sulfenates and sulfinates, carbonates and carbamates. In the case of ethers the protecting group for the OH can be selected from methyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl,

10 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-

15 cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *o*-bis(2-acetoxyethoxy)methyl, tetrahydropyranyl, fluoros tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxide,

20 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*a*,4,5,6,7,7*a*-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-hydroxyethyl, 2-bromoethyl, 1-[2-

25 (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'-

30 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-

dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, pentadienylnitrobenzyl, pentadienylnitropiperonyl, halobenzyl, 2,6-dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluorous benzyl, 4-fluorousalkoxybenzyl, trimethylsilylxylyl, *p*-phenylbenzyl, 2-phenyl-

5 2-propyl, *p*-acylaminobenzyl, *p*-azidobenzyl, 4-azido-3-chlorobenzyl, 2-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, *p*-(methylsulfinyl)benzyl, *p*-siletanylbenzyl, 4-acetoxybenzyl, 4-(2-trimethylsilyl)ethoxymethoxybenzyl, 2-naphthylmethyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, 2-quinolinylmethyl, 6-methoxy-2-(4-methylphenyl-4-quinolinemethyl, 1-

10 pyrenylmethyl, diphenylmethyl, 4-methoxydiphenylmethyl, 4-phenyldiphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, tris(4-*t*-butylphenyl)methyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl,

15 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 4,4'-dimethoxy-3''-[*N*-(imidazolylmethyl)]trityl, 4,4'-dimethoxy-3''-[*N*-(imidazolethyl)carbamoyl]trityl, bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenz[*a,c,g,i*]fluorenylmethyl)-4,4''-dimethoxytrityl, 9-anthrlyl, 9-(9-

20 phenyl)xanthenyl, 9-phenylthioxanthyl, 9-(9-phenyl-10-oxo)anthrlyl, 1,3-benzodithiolan-2-yl, and 4,5-bis(ethoxycarbonyl)-[1,3]-dioxolan-2-yl, benzisothiazolyl *S,S*-dioxido. In the case of silyl ethers the protecting group for the OH can be selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl,

25 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*-

30 butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl. In the case of esters the protecting group for the OH can be selected from formate,

benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trichloroacetamidate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, phenylacetate, diphenylacetate, 3-phenylpropionate, bisfluorous chain type

5 propanoyl, 4-pentenoate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, 5[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]levulinate, pivaloate, 1-adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate, 4-bromobenzoate, 2,5-difluorobenzoate, *p*-nitrobenzoate, picolinate, nicotinate, 2-(azidomethyl)benzoate, 4-azidobutyrate,

10 (2-azidomethyl)phenylacetate, 2-[(tritylthio)oxy]methylbenzoate, 2-[(4-methoxytritylthio)oxy]methylbenzoate, 2-[(methyl(tritylthio)amino)methyl]benzoate, 2-[(4-methoxytrityl)thio]methylamino-methylbenzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxymethyl)benzoate, 6-(levulinyloxymethyl)-3-methoxy-2-nitrobenzoate,

15 6-(levulinyloxymethyl)-3-methoxy-4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsilyloxybutyrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2-

20 (chloroacetoxymethyl)benzoate, 2-[(2-chloroacetoxy)ethyl]benzoate, 2-[2-(benzyloxy)ethyl]benzoate, 2-[2-(4-methoxybenzyloxy)ethyl]benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-

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

30 trifluoromethylbenzenesulfonate, 4-monomethoxytritylsulfenate, alkyl 2,4-dinitrophenylsulfenate, 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate, borate, and dimethylphosphinothiolyl. In the case of carbonates the

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

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

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

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

25

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

30

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

used in this application is defined here as meaning a chemical compound having undergone a chemical derivation such as substitution or addition of a further chemical group to change (for pharmaceutical use) any of its physico-chemical properties, such as solubility or bioavailability, e.g. ester and ether derivatives of an active compound that yield the active compound per se after administration to a subject. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al., Textbook of Drugdesign and Discovery, Taylor & Francis (April 2002).

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

Furthermore, compounds referred to herein may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Specifically, the term tautomer refers to one of two or more structural isomers of a compound, that exist in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are amine-imine, amide-imide, keto-enol, lactam-lactim, etc. Additionally, any compound referred to herein is intended to represent hydrates, solvates, and polymorphs, and mixtures thereof when such forms exist in the medium. In addition, compounds referred to herein may exist in isotopically-labelled forms. All geometric isomers, tautomers, atropisomers, hydrates, solvates, polymorphs, and isotopically labelled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.

15

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

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

Particularly preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₆ alkyl, and even more preferred is hydrogen, substituted or unsubstituted methyl,

30

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

Particularly preferred R₁, R₂, R₃, R₄, and R₅ are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R₁, R₂, R₃, R₄, and R₅ are hydrogen and substituted or unsubstituted C₁-C₆ alkyl, and

even more preferred is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl and substituted or unsubstituted butyl, including substituted or unsubstituted tert-butyl, substituted or unsubstituted isobutyl and substituted or unsubstituted sec-butyl. Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, COOH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

Even more preferred substituents of the above mentioned groups are OH, SCH₃, SH, NH₂, NHC(=NH)NH₂, CONH₂, COOH, phenyl, *p*-, *m*- or *o*-hydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen, methyl, isopropyl, tert-butyl, and benzyl are the most preferred R₁, R₂, R₃, R₄, and R₅ groups.

Specifically, particularly preferred R₁, R₂, R₃, and R₄ are hydrogen. And particularly preferred R₅ are methyl, isopropyl, and tert-butyl.

Particularly preferred W is NR₇ wherein R₇ is as defined before.

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

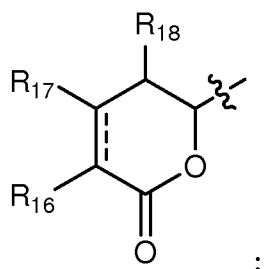
Particularly preferred R_7 and R_8 are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_7 and R_8 are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen is the most preferred.

In another embodiment, it is particularly preferred that R_7 and R_5 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. More preferred is the presence of one additional bond between the C atoms to which R_1 and R_2 are attached, and the presence of one or two additional bonds between the C atoms to which R_3 and R_4 are attached. In addition, the stereochemistry of each double bond may exist as (E) or (Z). The single isomers and mixtures of the isomers fall within the scope of the present invention.

25 In compounds wherein A is



When Y is a) $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$, or $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$; or b) $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$ or $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$, and a triple bond exists between the C atoms to which R_3 and R_4 are attached, then particularly preferred R_9 is hydrogen, substituted or unsubstituted

5 $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl. More preferably is hydrogen, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl. The

10 preferred substituted alkyl, 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 even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On

15 the other hand, more preferred alkenyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-dienyl, octa-1,4-dienyl, octa-1,3-dienyl, nona-1,7-dienyl, nona-1,6-dienyl, nona-1,5-dienyl, nona-1,4-dienyl, nona-1,3-dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-

20 dienyl are the most preferred alkenyl groups. On the other hand, more preferred alkynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-7-ynyl, oct-6-ynyl, oct-5-ynyl, oct-4-ynyl, oct-3-ynyl, oct-2-ynyl, oct-1-ynyl, non-8-ynyl, non-7-ynyl, non-6-ynyl, non-5-ynyl, non-4-ynyl, non-3-

25 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-

30 1-en-5-ynyl, oct-1-en-4-ynyl, oct-1-en-3-ynyl, non-1-en-8-ynyl, non-1-en-7-ynyl, non-1-en-6-ynyl, non-1-en-5-ynyl, non-1-en-4-ynyl, non-1-en-3-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, and

hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said 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',

5 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

10 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

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-

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
 5 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-
 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 -CHR_{ay}-CHR_{by}-CHR_{cy}- or -CHR_{ay}-CR_{by}=CR_{cy}- 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', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR',
 30 COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted

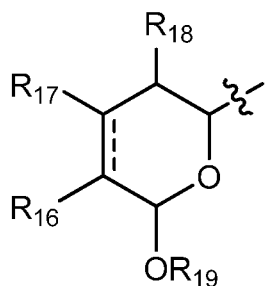
or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, COOH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. More preferred substituents for the above mentioned 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 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,

triphenylsilyl, diphenylmethysilyl, di-*t*-butylmethysilyl, 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.

Particularly preferred R_{16} is hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R_{16} groups.

Particularly preferred R_{17} and R_{18} are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_{17} and R_{18} are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, and even more preferred are hydrogen.

On the other hand, in compounds wherein A is



Particularly preferred R_9 is hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, and substituted or unsubstituted C_4 - C_{12} alkenynyl, and 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, 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 even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-dienyl, octa-1,4-dienyl, octa-1,3-dienyl, nona-1,7-dienyl, nona-1,6-dienyl, nona-1,5-dienyl, nona-1,4-dienyl, nona-1,3-dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-dienyl are the most preferred alkenyl groups. On the other hand, more preferred alkynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-7-ynyl, oct-6-ynyl, oct-5-ynyl, oct-4-ynyl, oct-3-ynyl, oct-2-ynyl, oct-1-ynyl, non-8-ynyl, non-7-ynyl, non-6-ynyl, non-5-ynyl, non-4-ynyl, non-3-ynyl, non-2-ynyl, non-1-ynyl, hept-6-ynyl, hept-5-ynyl, hept-4-ynyl, hept-3-ynyl, hept-2-ynyl, and hept-1-ynyl are the most preferred alkynyl groups. On the other hand, more preferred alkenynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Oct-1-en-7-ynyl, oct-1-en-6-ynyl, oct-1-en-5-ynyl, oct-1-en-4-ynyl, oct-1-en-3-ynyl, non-1-en-8-ynyl, non-1-en-7-ynyl, non-1-en-6-ynyl, non-1-en-5-ynyl, non-1-en-4-ynyl, non-1-en-3-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, and hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said 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 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, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl, are the most preferred substituents for these alkyl, alkenyl, alkynyl and alkenynyl groups.

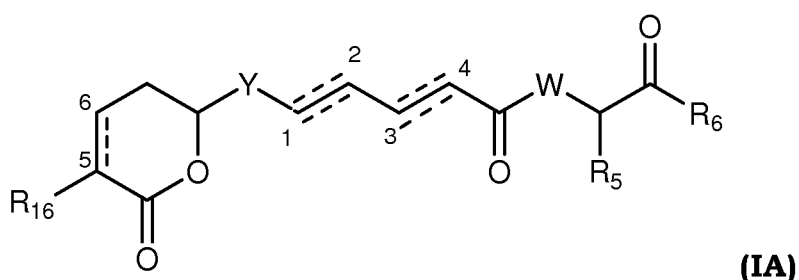
10 Particular preferred R_{16} is hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH
15 and methoxy are the most preferred R_{16} groups.

Particularly preferred R_{17} and R_{18} are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl and particularly preferred R_{19} is hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl and COR_a , wherein R_a is a
20 substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_{17} and R_{18} are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl and more preferred R_{19} are hydrogen, substituted or unsubstituted C_1 - C_6 alkyl and COR_a , wherein R_a is a substituted or unsubstituted C_1 - C_6 alkyl. Particularly preferred R_a is methyl, ethyl, propyl, isopropyl and butyl,
25 including tert-butyl. Even more preferred R_{17} , R_{18} and R_{19} are hydrogen.

Particularly preferred is the presence of one or more additional bonds in the places indicated with a dotted line. More preferred is the
30 presence of one additional bond between the C atoms to which R_1 and R_2 are attached, and the presence of one or two additional bonds between the C atoms to which R_3 and R_4 are attached. In addition, the

stereochemistry of each double bond may exist as (E) or (Z). The single isomers and mixtures of the isomers fall within the scope of the present invention.

- 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

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,
 15 substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

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

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

W is selected from O and NR_7 ;

25

R_7 is selected from hydrogen, COR_a , COOR_a , substituted or
 unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$

alkenyl, and substituted or unsubstituted 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 each R₈ and R₉ are independently 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
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
15 unsubstituted C₂-C₁₂ alkynyl;

- R₁₆ is 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
20 unsubstituted C₂-C₁₂ alkynyl; and

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

each dotted line represents an optional additional bond.

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

Particularly preferred R_{ay} , R_{by} , and R_{cy} are hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_{ay} , R_{by} , and R_{cy} are hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, and even more preferred is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, and substituted or unsubstituted butyl, including substituted or unsubstituted tert-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted sec-butyl. Preferred substituents of said groups are OR' , $=O$, SR' , SOR' , SO_2R' , NO_2 , NHR' , $NR'R'$, $=N-R'$, $NHCOR'$, $N(COR')_2$, $NHSO_2R'$, $NR'C(=NR')NR'R'$, CN , halogen, COR' , $COOR'$, $OCOR'$, $OCONHR'$, $OCONR'R'$, $CONHR'$, $CONR'R'$, protected OH , substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH , NO_2 , NH_2 , SH , CN , halogen, COH , $COalkyl$, $COOH$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list. Even more preferred substituents of the above mentioned groups are OH , SCH_3 , SH , NH_2 , $NHC(=NH)NH_2$, $CONH_2$, $COOH$, phenyl, *p*-, *m*- or *o*-hydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen and methyl are the most preferred R_{ay} , R_{by} , and R_{cy} groups. Specifically, when Y is $-CHR_{ay}-$ then particularly preferred R_{ay} is methyl, when Y is $-CR_{ay}=CR_{by}-$ then particularly preferred R_{ay} is hydrogen and particularly preferred R_{by} is methyl, and when Y is $-CHR_{ay}-CR_{by}=CR_{cy}-$ then particularly preferred

R_{ay} is hydrogen or methyl, particular preferred R_{by} is hydrogen, and particularly preferred R_{cy} is methyl.

Particularly preferred R₅ is hydrogen and substituted or
5 unsubstituted C₁-C₁₂ alkyl. More preferred R₅ is hydrogen and substituted or unsubstituted C₁-C₆ alkyl, and even more preferred is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl and substituted or unsubstituted butyl,
10 including substituted or unsubstituted tert-butyl, substituted or unsubstituted isobutyl and substituted or unsubstituted sec-butyl. Preferred substituents of said groups are OR', =O, SR', SOR', SO₂R', NO₂, NHR', NR'R', =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR',
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.

Particularly preferred W is NR_7 wherein R_7 is as defined before.

Particularly preferred R_6 is NR_8R_9 , wherein R_8 and R_9 are as defined before.

5

Particularly preferred R_7 and R_8 are hydrogen and substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl. More preferred R_7 and R_8 are hydrogen and substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl; and even more preferred are hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-
10 butyl. Hydrogen is the most preferred.

In another embodiment, it is particularly preferred that R_7 and R_5 together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted heterocyclic group. In this
15 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) $-\text{CHR}_{\text{ay}}-$, $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-$, $-\text{CR}_{\text{ay}}=\text{CR}_{\text{by}}-$, $-\text{C}\equiv\text{C}-$, or $-\text{CHR}_{\text{ay}}-\text{C}\equiv\text{C}-$; or b) $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$ or $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$ and a triple bond exists between C_3 and C_4 , then particularly preferred R_9 is hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or
25 unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl. More preferably is hydrogen, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl. 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

even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-
 5 dienyl, octa-1,4-dienyl, octa-1,3-dienyl, nona-1,7-dienyl, nona-1,6-dienyl, nona-1,5-dienyl, nona-1,4-dienyl, nona-1,3-dienyl, hepta-1,5-dienyl, hepta-1,4-dienyl, hepta-1,3-dienyl are the most preferred alkenyl groups. On the other hand, more preferred alkynyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8
 10 or 9 carbon atoms. Oct-7-ynyl, oct-6-ynyl, oct-5-ynyl, oct-4-ynyl, oct-3-ynyl, oct-2-ynyl, oct-1-ynyl, non-8-ynyl, non-7-ynyl, non-6-ynyl, non-5-ynyl, non-4-ynyl, non-3-ynyl, non-2-ynyl, non-1-ynyl, hept-6-ynyl, hept-5-ynyl, hept-4-ynyl, hept-3-ynyl, hept-2-ynyl, and hept-1-ynyl are the most preferred alkynyl groups. On the other hand, more preferred
 15 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-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-
 20 en-4-ynyl, and 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,
 25 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,
 30 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',
 5 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,
 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*-
 15 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-
 20 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-
 30 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 alkenynyl groups.

When Y is $-\text{CHR}_{\text{ay}}-\text{CHR}_{\text{by}}-\text{CHR}_{\text{cy}}-$ or $-\text{CHR}_{\text{ay}}-\text{CR}_{\text{by}}=\text{CR}_{\text{cy}}-$ and a
 5 single or a double bond exists between C₃ and C₄, then R₉ is substituted or unsubstituted C₄-C₁₂ alkenynyl. 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-
 10 1-en-6-ynyl, oct-1-en-5-ynyl, oct-1-en-4-ynyl, oct-1-en-3-ynyl, non-1-en-8-ynyl, non-1-en-7-ynyl, non-1-en-6-ynyl, non-1-en-5-ynyl, non-1-en-4-ynyl, non-1-en-3-ynyl, hept-1-en-6-ynyl, hept-1-en-5-ynyl, hept-1-en-4-ynyl, and hept-1-en-3-ynyl, are the most preferred alkenynyl groups. Preferred substituents for said alkenynyl groups are OR', =O,
 15 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
 20 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
 25 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

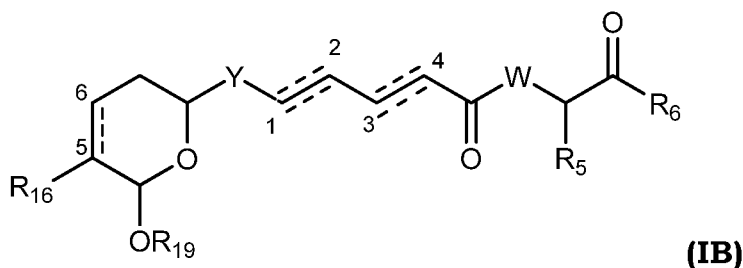
alkynyl, and substituted or unsubstituted aryl. Even more preferred substituents for these alkenynyl groups are halogen, OR', =O, OCONHR', OCONR'R', CONHR', CONR'R', and protected OH wherein the protecting group for the OH is preferably selected from trimethylsilyl, triethylsilyl, triisopropylsilyl,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

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.

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

(IB)

wherein Y is selected from -CHR_{ay}-, -CHR_{ay}-CHR_{by}-, -CR_{ay}=CR_{by}-, -C≡C-, -CHR_{ay}-CHR_{by}-CHR_{cy}-, -CHR_{ay}-CR_{by}=CR_{cy}-, and -CHR_{ay}-C≡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;

R₅ is 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;

W is selected from O and NR₇;

R₇ is selected from hydrogen, COR_a, COOR_a, 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, 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;

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, 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

or unsubstituted aryl and substituted or unsubstituted heterocyclic group; and

each dotted line represents an optional additional bond.

5

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

10 Particularly preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. More preferred R_{ay}, R_{by}, and R_{cy} are hydrogen and substituted or unsubstituted C₁-C₆ alkyl, and even more preferred is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted
 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

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

30

of the above mentioned groups are OH, SCH₃, SH, NH₂, NHC(=NH)NH₂, CONH₂, COOH, phenyl, *p*-, *m*- or *o*-hydroxyphenyl, indolyl, including 1-, 2-, and 3-indolyl, and imidazolyl, including 4- and 5-imidazolyl. Hydrogen, methyl, isopropyl, tert-butyl and benzyl are the most preferred R₅ groups, and even most preferred methyl, isopropyl, and tert-butyl.

Particularly preferred W is NR₇ wherein R₇ is as defined before.

10 Particularly preferred R₆ is NR₈R₉, wherein R₈ and R₉ are 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 substituted or unsubstituted C₁-C₆ alkyl; and even more preferred are 15 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 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

unsubstituted C₂-C₁₂ alkynyl, and substituted or unsubstituted C₄-C₁₂ alkenynyl. The preferred substituted alkyl, substituted alkenyl, substituted alkynyl and substituted alkenynyl may present not only one but two or more substituents. More preferred alkyl groups are those
 5 having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Heptyl, octyl and nonyl are the most preferred alkyl groups. On the other hand, more preferred alkenyl groups are those having from 6 to about 10 carbon atoms; and even more preferably 7, 8 or 9 carbon atoms. Octa-1,6-dienyl, octa-1,5-dienyl, octa-1,4-dienyl,
 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
 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,

triphenylsilyl, diphenylmethysilyl, di-*t*-butylmethysilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorosilyl, are the most preferred substituents for these alkyl, alkenyl, alkynyl and alkenynyl groups.

Particular preferred R_{16} is hydrogen, OR_a and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Hydrogen, OH and methoxy are the most preferred R_{16} groups.

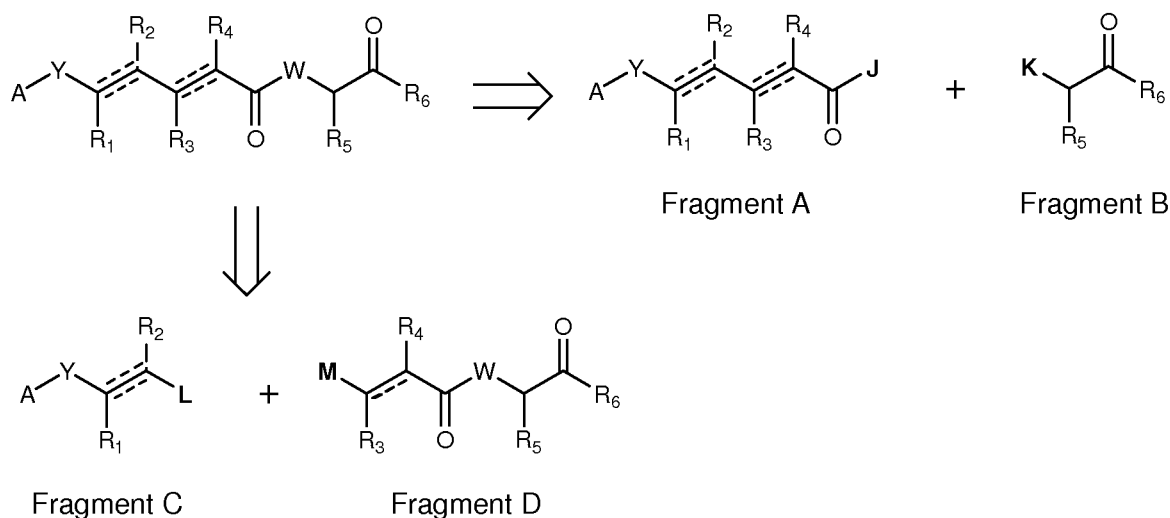
15

Particularly preferred R_{19} is hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl and COR_a , wherein R_a is a substituted or unsubstituted C_1 - C_{12} alkyl. More preferred R_{19} is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl and COR_a , wherein R_a is a substituted or unsubstituted C_1 - C_6 alkyl. Particularly preferred R_a is methyl, ethyl, propyl, isopropyl and butyl, including tert-butyl. Even more preferred R_{19} 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 C_1 and C_2 , and/or the presence of one or two additional bonds between C_3 and C_4 , and/or the presence of one additional bond between C_5 and C_6 . 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.

30

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



Scheme A

where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , 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).

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 at the appropriate stage to a desired substituent.
- 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 synthetic organic chemistry which
- 20 are known by a person skilled in the art.

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

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

With this invention we provide novel pharmaceutical compositions
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.

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

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

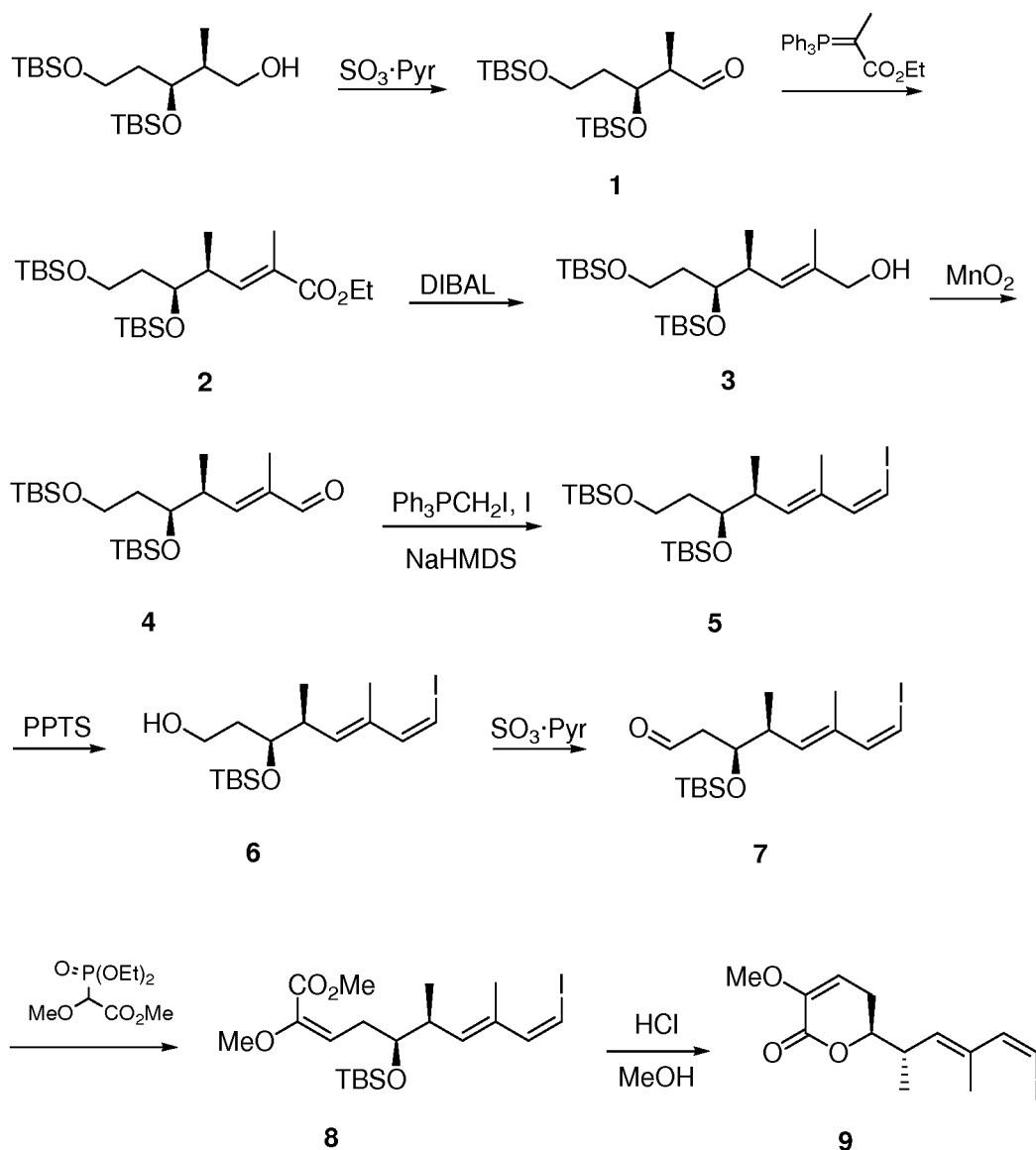
Antitumoral activities of these compounds include, but are not
15 limited to lung cancer, colon cancer, and breast cancer.

EXAMPLES

EXAMPLE 1: SYNTHESIS OF FRAGMENT 9

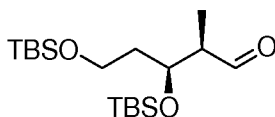
20 Scheme 1 provides an example of the synthesis of fragment 9.

51



Scheme 1

5

Synthesis of intermediate 1

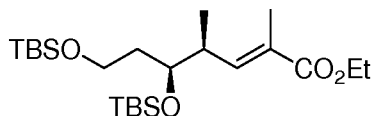
- 10 To a 0 °C solution of (2S,3S)-3,5-Bis[[(*tert*-butyl)dimethylsilyl]oxy]-2-methylpentan-1-ol (P. Phukan, S. Sasmal and M.E. Maier *Eur. J. Org. Chem.* 2003, 1733-1740) (50 g, 0.14 mol) in a mixture of

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

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

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

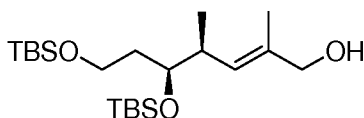
15 Synthesis of intermediate 2



Over a solution of aldehyde **1** (45 g, 0.12 mol) in toluene (625 mL)
20 Carboethoxyethylidene-triphenylphosphorane (113 g, 0.31 mol) was added and the mixture was heated at 60 °C over 17 h. Then, the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 100:0 to 10:1) affording 53.3 g (yield: 96%) of ester compound **2**.

25 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, 6.9 Hz), 0.90 (m, 18H), 0.05 (m, 12H).

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

Synthesis of intermediate 3

5

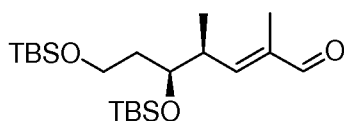
Over a -78°C cooled solution of ester **2** (46.7 g, 0.105 mol) in anhydrous THF (525 mL) under argon atmosphere, Diisobutylaluminum hydride (DIBAL) 1M in toluene (231 mL, 0.231 mol) was added over a period of 10 min and the mixture was stirred at -78°C . After 4 hours the reaction
 10 was quenched with 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
 15 Na_2SO_4 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 (CDCl_3 , 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, $J =$
 20 6.9 Hz), 0.88 (m, 18H), 0.03 (m, 12H).

^{13}C NMR (CDCl_3 , 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, MnO_2 (101 g, 1.16 mol) was added and the

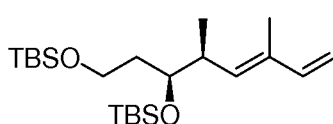
mixture was stirred at room temperature for 2 hours. This mixture was filtrated over a silica gel column eluting with EtOAc (3L) and the resulting solution was dried under reduced pressure to afford 29.1 g (yield: 94%) of aldehyde **4**.

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

¹³C NMR (CDCl₃, 75 MHz)δ: 195.4, 157.8, 138.3, 72.0, 59.5, 38.7, 37.5, 25.8, 18.2, 18.0, 14.3, 9.4, -4.4, -4.5, -5.4.

10

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**.

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

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

Synthesis of intermediate 6

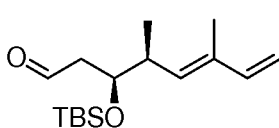


To a solution of iodide **5** (12 g, 22.9 mmol) in EtOH (114 mL) pyridinium *p*-toluenesulfonate (PPTS) (2.01 g, 8.0 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then
15 the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 10:1) affording 8.7 g (yield: 93%) of alcohol **6**.

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

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

25 Synthesis of intermediate 7

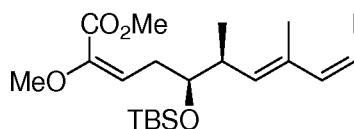


To a 0 °C solution of alcohol **6** (8.7 g, 21.2 mmol) in a mixture of Dichloromethane/DMSO (50.9 mL/22.9mL), Et₃N (14.8 mL, 106 mmol) was added via addition funnel. After 10 min, SO₃·Pyr (8.43 g, 53.0 mol) was added portionwise and the solution was stirred for another 2h at 0 °C. Then, it was diluted with Dichloromethane (800 mL) and quenched with HCl (0.5N, 50 mL). The organic layer was decanted, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (hexane/EtOAc 10:1) afforded 6.9 g (yield: 80%) of aldehyde **7**.

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

¹³C 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

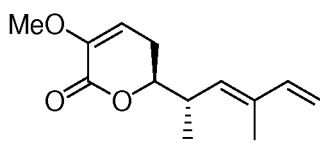
To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (5.51 g, 14.45 mmol) and 18-crown-6 (11.5 g, 43.34 mmol) in anhydrous THF (390 mL) stirred under argon atmosphere at -78 °C, a 0.5 M Potassium bis(trimethylsilyl)amide solution (KHMDs) (43.34 mL, 21.67 mmol) was added dropwise. After 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.

Purification by column chromatography (hexane/Et₂O 20:1) afforded pure 4.2 g (59%) of (**E**)-**8**.

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

¹³C 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, 18.1, 16.5, 15.7, -4.3, -4.5.

10 Synthesis of intermediate 9



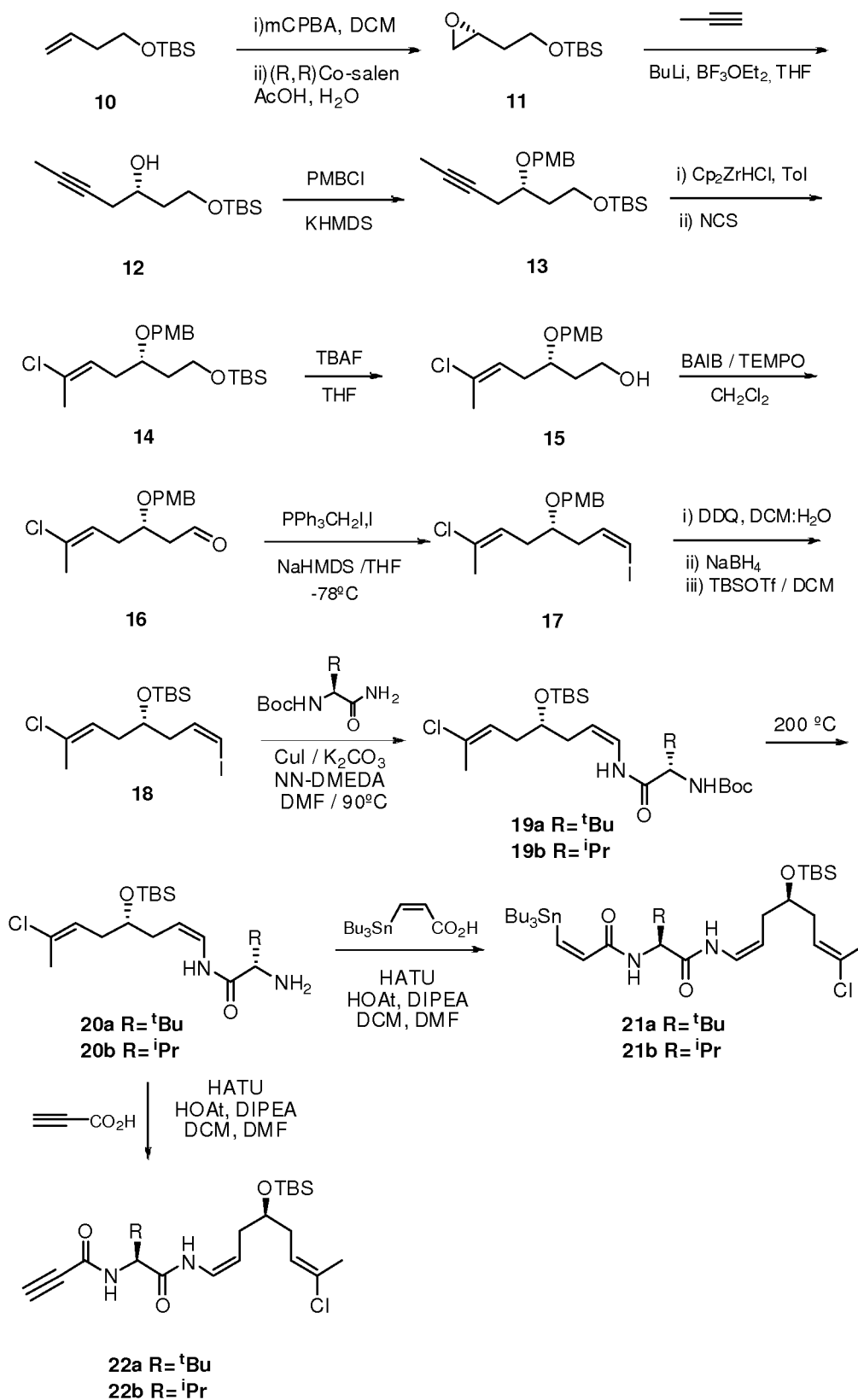
To a solution of ester **8** (4.15 g, 8.39 mmol) in MeOH (125 mL) at room
15 temperature, HCl 37% (1.04 mL) was added and the reaction mixture
was stirred for 6 hours. Then the mixture was neutralized with a
saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent
was evaporated under reduced pressure. The resulting suspension was
20 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,
25 12.0, 15.0, 18.0 Hz), 1.87 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz).

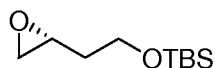
¹³C NMR (125 MHz, CDCl₃)δ: 161.6, 145.2, 141.8, 134.4, 132.7, 108.3, 81.7, 77.4, 55.4, 37.1, 26.6, 16.5, 16.1.

EXAMPLE 2: SYNTHESIS OF FRAGMENTS 21 AND 22

Scheme 2 provides an example of the synthesis of fragments 21 and 22.



Scheme 2

Synthesis of intermediate 11

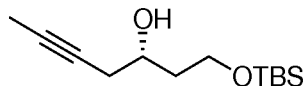
5

- 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)
- 15 to provide epoxide as a colourless oil (64.5 g, 82%). To a solution of racemic epoxide (30 g, 0.15 mol) in anhydrous THF (7.5 mL) (*R,R*)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) [(*R,R*)Co(II) complex] (448 mg, 0.74 mmol) was added, followed by AcOH (0.14 mL). The solution was cooled to 0 °C and water (1.2 mL) was
- 20 added dropwise. The reaction was allowed to warm to room temperature and stirred for 18 h. After that time the volatile materials were concentrated in vacuo and the crude was directly loaded on a silica gel column. Flash chromatography using Hexane/EtOAc (15:1 to 12:1) as eluent, provided chiral epoxide **(+)-11** (13.6 g, yield: 46%) as a
- 25 colourless oil.

$[\alpha]_D = +14.1$ (c 1, CHCl₃).

- ¹H NMR (CDCl₃, 300 MHz)δ: 3.74 (t, 2H, J = 6.3 Hz), 3.01 (m, 1H), 2.74 (t, 1H, J = 4.6 Hz), 2.48 (dd, 1H, J = 5.1, 3.1 Hz), 1.70 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).
- 30

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

Synthesis of intermediate 12

5

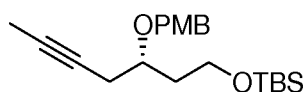
Propyne (10 mL, 0.176 mol) was condensed at -78°C and dissolved in anhydrous THF (165 mL). n-Butyllithium (75.1 mL, 0.188 mol) was added dropwise under N₂ over 30 min, and the resultant white suspension was stirred for an additional 30 min at -78°C. A solution of (+) (R)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxirane **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]⁺

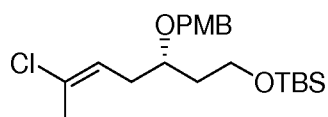
Synthesis of intermediate 13

30

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 EtOAc (3 x 500 mL). The combined organic layers were washed with saturated aqueous solution of NaCl, dried over anhydrous Na₂ SO₄, 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

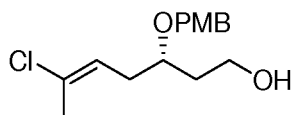
To a solution of **13** (61.3 g, 0.169 mol) in anhydrous toluene (2.1 L), under N₂ atmosphere and at 0 °C Schwartz's reagent (Bis(cyclopentadienyl)zirconium(IV) chloride hydride, Cp₂ZrHCl) (130.3 g, 0.507 mol) was added and the reaction was stirred 5 min at room temperature. The reaction temperature 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

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 %).

$[\alpha]_D = +20.5$ (c 1, CHCl_3).

- 5 ^1H NMR (CDCl_3 , 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).
- ^{13}C NMR (CDCl_3 , 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

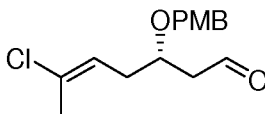


15

- To a solution of **14** (23 g, 0.058 mol) in anhydrous THF (288 mL) under N_2 and at 0 °C a solution of Tetrabutylammonium fluoride (TBAF) (115.3 mL, 0.115 mol) was added dropwise over a period of 20 min (the solution turned red). The reaction mixture was stirred at room
- 20 temperature for 2 h, and then was quenched with saturated aqueous solution of NH_4Cl (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 Na_2SO_4 , filtered, and concentrated. Flash chromatography (hexane /EtOAc 4:1 to 1:1)
- 25 provided **15** as a colourless oil (11.9 g, yield: 73%).

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

- 30 Synthesis of intermediate 16

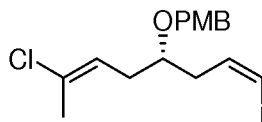


(Diacetoxyiodo)benzene (BAIB) (11.5 g, 35.7 mmol) was added to a
 5 solution of alcohol **15** (9.2 g, 32.4 mmol) and 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) (515 mg, 3.3 mmol) in anhydrous dichloromethane (92 mL). The reaction mixture was stirred at room temperature for 20 h until the alcohol was 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%)

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

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

20 Synthesis of intermediate 17

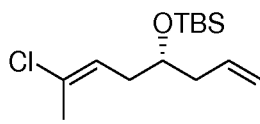


To a suspension of iodomethyltriphenylphosphonium iodide (16.6 g; 31
 25 mmol) in anhydrous THF (126 mL), at room temperature, a 1M solution of NaHMDS in anhydrous THF (31.27 mL, 31.27 mol) was slowly added. After stirring for 2 min, the yellow mixture was cooled to -78°C and a solution of **16** (6.3 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®. 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 yellow oil (5.6 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



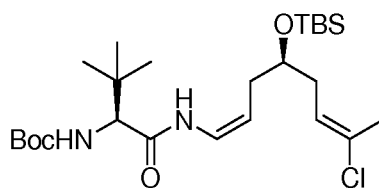
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (3.6g, 16 mmol) was added to a solution of **17** (5 g, 12 mmol) in DCM-H₂O (20:1, 98 mL) under N₂ atmosphere at room temperature. After 1.5 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into Et₂O (200 mL) and 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%).

To a solution of secondary alcohol (2.8 g; 10 mmol) in anhydrous DCM (38 mL), under N₂ atmosphere and at 0 °C, 2,6-lutidine (2.28 mL, 20 mmol) was added dropwise, followed by addition of *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (2.33 mL, 12 mmol). The reaction mixture was stirred for 2 h. At this point the crude was quenched with 0.5M HCl (25 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (Hexane /EtOAc 100:1 to 20:1) provided **18** as a colourless oil (3.14 g, yield: 80%).

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

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

Synthesis of intermediate 19a



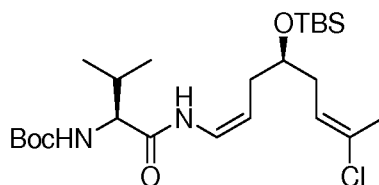
20

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

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/
5 EtOAc, 20:1 to 15:1). 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
10 (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 (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 μL, 0.426 mmol), vinyl iodide **18** (283 mg, 0.71 mmol) and anhydrous DMF
25 (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

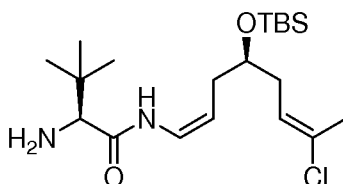
67

flash chromatography on silica gel (Hexane/EtOAc, 7:1 to 3:1). Intermediate **19b** (270 g, yield: 77%) was obtained as an oil.

¹H NMR (CDCl₃, 300 MHz)δ: 7.80 (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* = 8.4, 6.0 Hz), 3.80-3.73 (m, 1H), 2.12-2.22 (m, 5H), 2.02 (s, 3H), 1.45 (s, 9H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

Synthesis of intermediate 20a

10



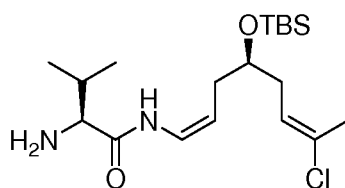
A solution of amino protected derivative **19a** (670 mg, 1.33 mmol) in ethylenglycol (30 mL) was heated at 200 °C for 15 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached 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).

25 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

68

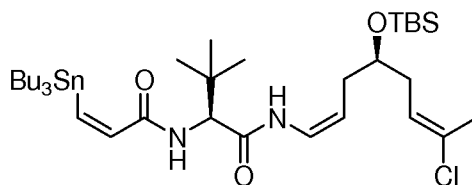


A solution of amino protected derivative **19b** (255 mg, 0.52 mmol) in ethylenglycol (15 mL) was heated at 200 °C for 15 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtrated 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, 1H), 2.20-2.16 (m, 4H), 2.03 (s, 3H), 1.59 (br s, 2H), 1.00 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.82 (d, 3H, *J* = 6.9 Hz), 0.05 (s, 6H).

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

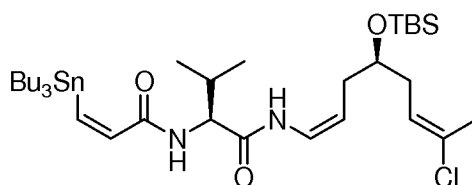


To a solution of amine **20a** (918 mg, 2.27 mmol) in anhydrous DCM/DMF (10:1, 39.6 mL), a solution of (Z)-3-tributylstannylpropenoic acid (1028 mg, 2.84 mmol) in anhydrous DCM was added, under N₂ atmosphere, and then was cooled at 0 °C. Diisopropylethylamine

(DIPEA) (0.6 mL, 3.4 mmol), 1-Hydroxy-7-azabenzotriazole (HOAt) (310 mg, 2.27 mmol), and N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) (860 mg, 2.27 mmol) were added to the solution and after 30 min the cold bath was removed. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated aqueous solution of 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: 7.63 (d, 1H, *J* = 10.5 Hz), 6.97 (d, 1H, *J* = 12.3 Hz), 6.75 (d, 1H, *J* = 12.3 Hz), 6.72 (t, 1H, *J* = 9.5 Hz), 6.50 (d, 1H, *J* = 9.0 Hz), 5.56 (t, 1H, *J* = 6.6 Hz), 4.83 (q, 1H, *J* = 9.0 Hz), 4.41 (d, 1H, *J* = 9.6 Hz) 3.76 (m, 1H), 2.17 (m, 4H), 2.01 (s, 3H), 1.45 (m, 6H), 1.25 (m, 8H), 1.0 (s, 9H), 0.88 (s, 9H), 0.84 (m, 13H), 0.06 (s, 6H).

Synthesis of intermediate 21b



20

To a solution of amine **20b** (170 mg, 0.437 mmol) in anhydrous DCM/DMF (10:1, 7.7 mL), a solution of (Z)-3-tributylstannylpropenoic acid (197.2 mg, 0.546 mmol) in anhydrous DCM was added, under N₂ atmosphere, and then was cooled at 0 °C. DIPEA (0.11 mL, 0.655 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

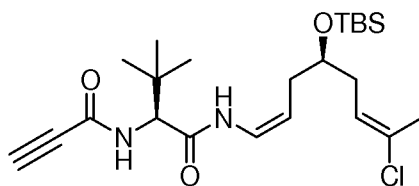
25

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

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

Synthesis of intermediate 22a

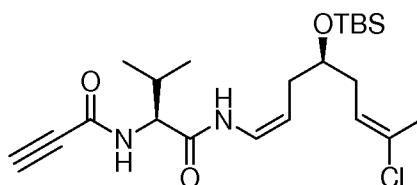


To a solution of **20a** (120 mg, 0.30 mmol) and propionic acid (23 μL, 0.37 mmol) in anhydrous DCM/DMF 10:1 (4.2 mL) at 0 °C, HATU (113 mg, 0.30 mmol), HOAt (40 mg, 0.30 mmol) and DIPEA (0.78 μL, 0.44 mmol) were added. The reaction was stirred at 0 °C for 30 min and 2 hours at room temperature. Then, the crude mixture was treated with a saturated aqueous solution of 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%).

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).

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

5 Synthesis of intermediate 22b



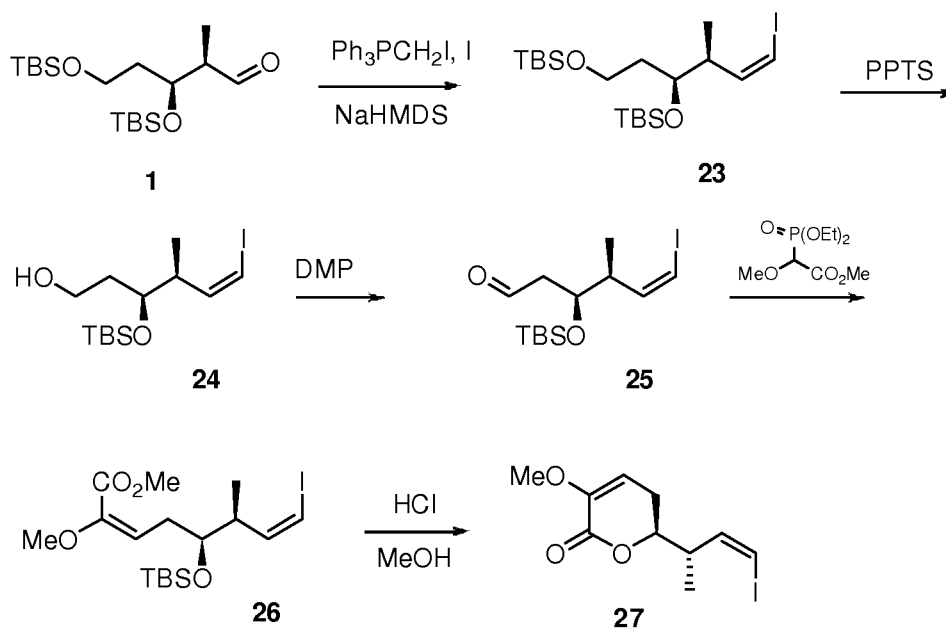
To a solution of **20b** (200 mg, 0.51 mmol) and propiolic acid (39 μL , 0.64 mmol) in anhydrous DCM/DMF 10:1 (8 mL) at 0 $^{\circ}\text{C}$, HATU (194 mg, 0.51 mmol), HOAt (69 mg, 0.51 mmol) and DIPEA (133 μL , 0.76 mmol) were added. The reaction was stirred at 0 $^{\circ}\text{C}$ for 30 min and 2 hours at room temperature. Then, the crude mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 . The combined filtrates were washed with H_2O . After drying and evaporating the solvent under reduced pressure the crude was purified by column chromatography (Ethyl acetate/hexanes mixture) to afford pure compound **22b** (150 mg, yield: 67%).

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

25 EXAMPLE 3: SYNTHESIS OF FRAGMENT 27

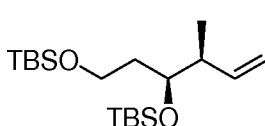
Scheme 3 provides an example of the synthesis of fragment 27.

72



Scheme 3

5 Synthesis of intermediate 23



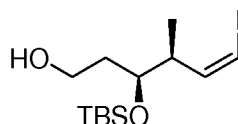
To a suspension of iodomethyl triphenylphosphonium iodide (Gilbert
 10 Stork, KZ. *Tetrahedron letters* 1989, 30(17), 2173) (6.6 g, 12.47 mmol)
 in anhydrous THF (50 mL) at 0°C, a 1M solution of sodium
 hexamethyldisilazane (NaHMDS) (12.5 mL, 12.47 mmol) was slowly
 added, via addition funnel, over a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

- 5 ¹H NMR (CDCl₃, 300 MHz) δ: 6.18-6.09 (m, 2H), 3.79 (m, 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), 0.04 (m, 12H).

Synthesis of intermediate 24

10

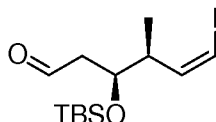


- To a solution of iodide **23** (520 mg, 1.07 mmol) in EtOH (5.3 mL) pyridinium p-toluenesulfonate (PPTS) (94.4 mg, 0.38 mmol) was added
15 and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 380 mg (yield: 87%) of alcohol **24**.

- ¹H NMR (CDCl₃, 300 MHz) δ: 6.20 (d, 1H, *J* = 7.5 Hz), 6.08 (m, 1H),
20 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

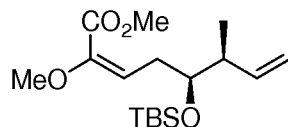


To a 0 °C solution of alcohol **24** (380 mg, 1.03 mmol) in anhydrous DCM (10.3 mL), Dess-Martin periodinane (870 mg, 2.05 mmol) was added.

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**.

- 5 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).

10 Synthesis of intermediate 26

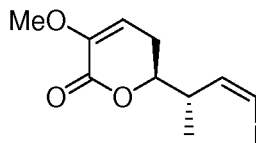


- To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (362 mg, 1.42 mmol) and 18-crown-6 (754 mg, 2.85 mmol) in anhydrous THF (27 mL) stirred under argon atmosphere at -78°C, a 0.5 M Potassium bis(trimethylsilyl)amide solution (KHMDs) (2.85 mL, 1.42 mmol) was added dropwise. After 15 min aldehyde **25** (350 mg, 0.95 mmol) in anhydrous THF (14 mL) was added dropwise over a period of 20 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) 25 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

75

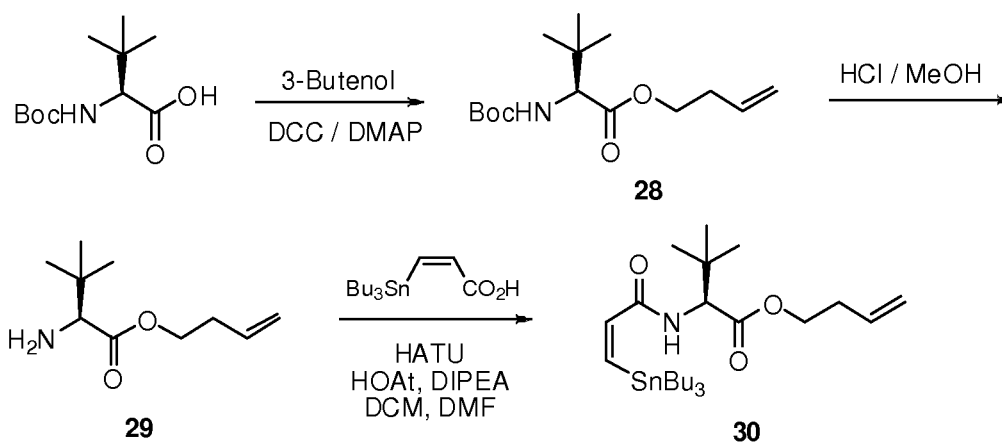


To a solution of ester **26** (95 mg, 0.21 mmol) in MeOH (3.15 mL) at
 5 room temperature, HCl 37% (26 μ L) was added and the reaction mixture
 was stirred for 6 hours. Then the mixture was neutralized with a
 saturated aqueous solution of NaHCO₃ (pH 7-8) and the organic solvent
 was evaporated under 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**.

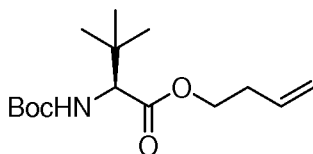
¹H NMR (CDCl₃, 300 MHz) δ : 6.32 (dd, 1H, J = 0.6, 7.5 Hz), 6.08 (dd,
 1H, J = 1.5, 9.3 Hz), 5.62 (dd, 1H, J = 3.0, 6.3 Hz), 4.28 (m, 1H), 3.63 (s,
 15 3H), 2.84 (m, 1H), 2.54 (m, 1H), 2.34 (m, 1H), 1.13 (d, 3H, J = 6.6Hz).

EXAMPLE 4: SYNTHESIS OF FRAGMENT 30

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



Scheme 4

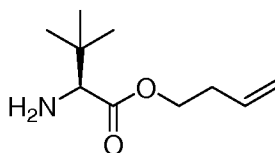
Synthesis of intermediate 28

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 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), 2.41 (q, 2H, *J* = 6.7 Hz), 1.43 (s, 9H), 0.96 (s, 9H).

20 Synthesis of intermediate 29

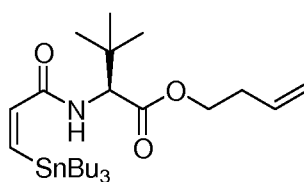
25

The solution of the ester **28** (180 mg, 0.63mmol) in HCl·MeOH 1M (3.6ml) was stirred at room temperature for 24 hours. The organic solvent was evaporated under reduced pressure and the resulting solid was diluted in DCM and washed with H₂O, the resulting organic phase

was dried over anhydrous Na_2SO_4 , filtered, and the solvent was evaporated affording 116mg (yield: 100%) of **29**.

^1H NMR (CDCl_3 , 300 MHz) δ : 5.85-5.72 (m, 1H), 5.15-5.06 (m, 2H), 4.16
5 (t, 2H, $J = 6.7$ Hz), 3.15 (s, 1H), 4.44-4.37 (m, 2H), 0.96 (s, 9H)

Synthesis of intermediate 30



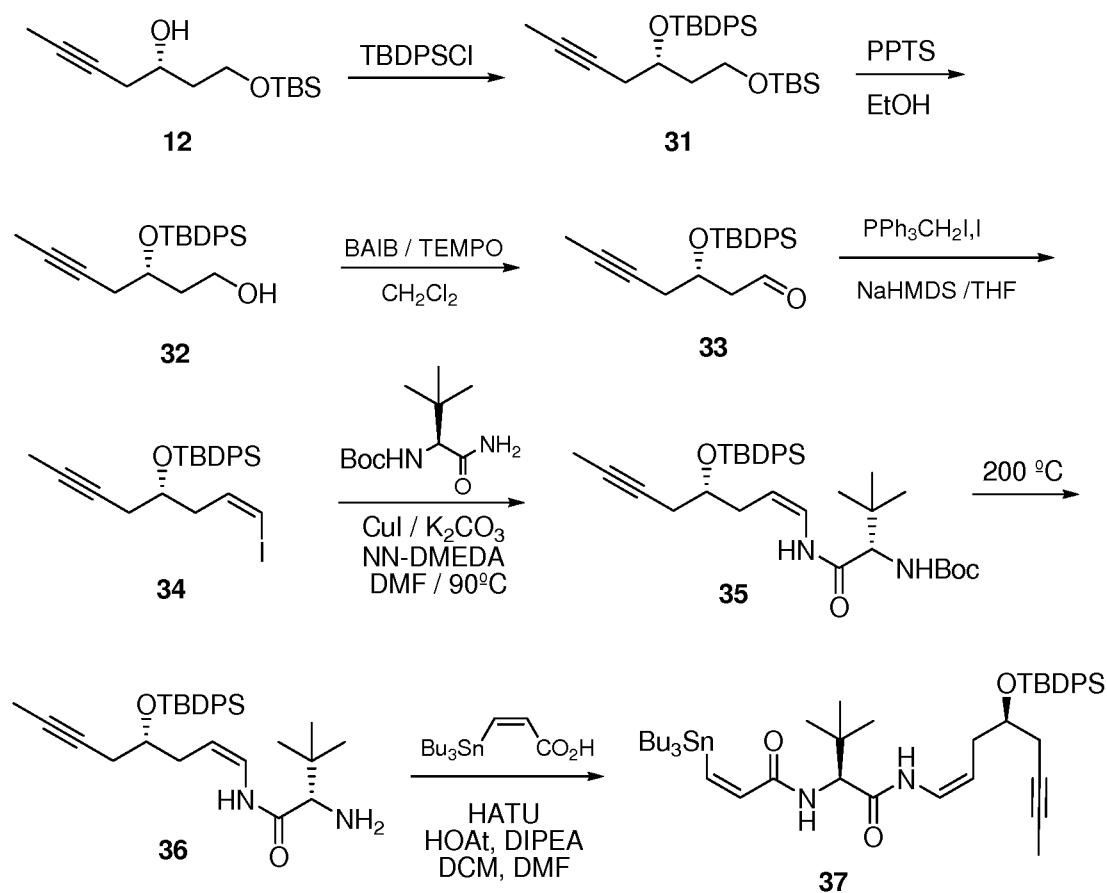
10

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 1hour, quenched with 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
20 (Hexane/EtOAc 15:1 to 10:1) to give **30** (340 mg; yield: 72%).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.01 (d, 1H, $J = 12.3$ Hz), 6.75 (d, 1H, $J = 12.3\text{Hz}$), 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, $J = 6.70$
25 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.

Scheme 5 provides the synthesis of the fragment 37.

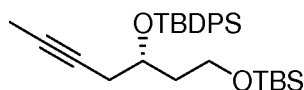


5

Scheme 5

Synthesis of intermediate 31

10



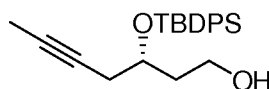
A solution of alcohol **12** (2.88 g, 11.9 mmol), tert-butyldiphenylsilyl chloride (4.39 mL, 16.89 mmol), and 4-(dimethylamino)pyridine (43.6 mg) in DMF (14 mL) was stirred overnight at room temperature. The mixture was diluted with water and extracted with Et₂O, and the organic phase was washed with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

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.

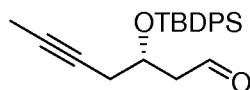
10 Synthesis of intermediate 32



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).

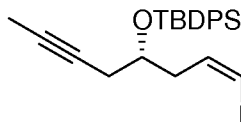
Synthesis of intermediate 33



(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 NH_4Cl and extracted with DCM (3 x 500 mL). 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 10:1) to afford **33** as colourless oil (1.64 g; yield: 82%).

^1H NMR (CDCl_3 , 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).

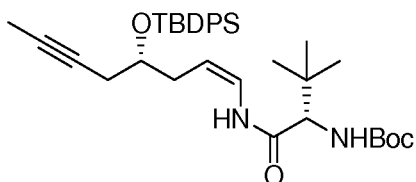
Synthesis of intermediate 34



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%).

^1H NMR (500 MHz, CDCl_3) 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).

5 Synthesis of intermediate 35

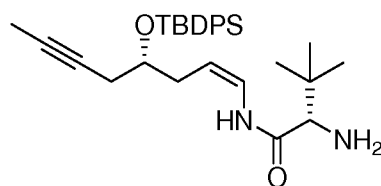


A resealable Schlenk tube was charged with copper (I) iodide (85.1 mg, 0.447 mmol), potassium carbonate (0.618 g, 4.47 mmol) and Boc-*tert*-LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (0.514 g, 2.23 mmol), evacuated and filled with 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, CDCl_3) 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

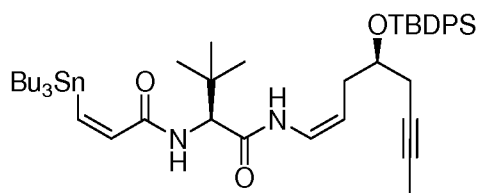
82



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 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

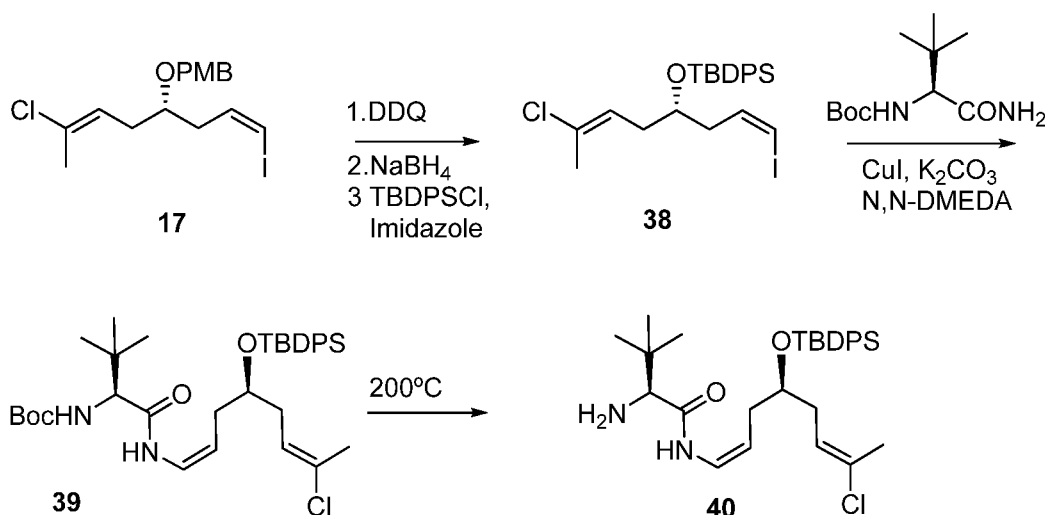
To a solution of amine **36** (221 mg, 0.450 mmol) in anhydrous DCM/DMF (4:1, 5 mL), a solution of (*Z*)-3-tributylstannylpropenoic acid (195 mg, 0.54 mmol) in anhydrous DCM was added, under argon atmosphere, and then was cooled at 0 °C. DIPEA (0.094 mL, 0.54 mmol), HOAt (73.5 mg, 0.54 mmol), and HATU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

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), 2.39-2.24 (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.

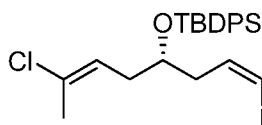
Scheme 6 provides the synthesis of the fragment 40.



Scheme 6

Synthesis of intermediate 38

84

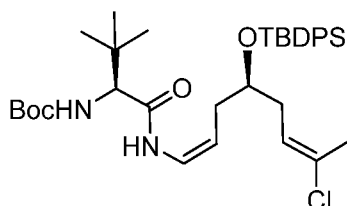


2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (8.70 g, 38 mmol) was added to a solution of **17** (12 g; 30 mmol) in dichloromethane-H₂O (20:1) (236 mL) under Ar atmosphere at room temperature. After 1:30 h (TLC Hexane/EtOAc 4:1 showed no starting material) the reaction was quenched by pouring into 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.

^1H NMR (CDCl_3 , 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), 2.14 (t, 2H, $J = 6.4$ Hz), 1.85 (s, 3H), 1.07 (s, 9H).

5 Synthesis of intermediate 39

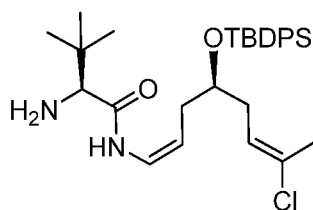


A resealable Schlenk tube was charged with copper (I) iodide (1.05 g, 5.54 mmol), potassium carbonate (7.65 g, 55.4 mmol) and Boc-*tert*-LeuCONH₂ (prepared following the procedure described in Pozdnev, V. F., *Tetrahedron Letters* 1995, 36, 7115-7118) (6.8 g, 29.6 mmol), evacuated and filled with argon. *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 (CDCl_3 , 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

86



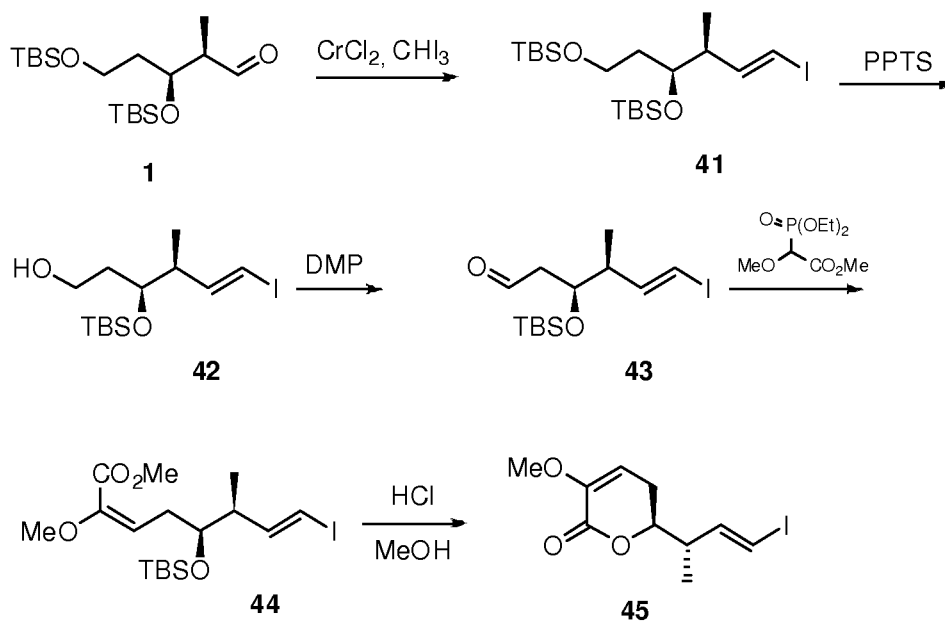
A solution of amino protected derivative **39** (4.75 g, 7.6 mmol) in ethylene-glycol (140 mL) was heated at 200 °C for 15 min. The reaction mixture was then cooled at room temperature, diluted with dichlorometane, quenched with brine and poured into water. A few drops of 3M NaOH were added until the 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 resduced pressure to afford the primary amine **40** (3.8 g, 95% yield) as a yellow oil which was used without further purification.

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

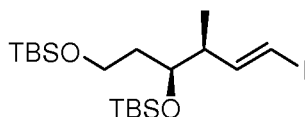
Scheme 7 provides an example of the synthesis of fragment 45.

87



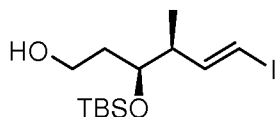
Scheme 7

5 Synthesis of intermediate 41



To a solution of anhydrous CrCl_2 (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, 2.76 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 Et_2O and filtered through Celite®. 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** (0.79 g, 57% yield) as a slightly yellow oil.

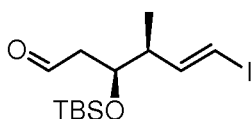
^1H NMR (CDCl_3 , 300 MHz) δ : 6.58 (dd, 1H, $J = 14.5, 6.7$ Hz), 5.98 (dd, 1H, $J = 14.5, 1.3$ Hz), 3.76-3.70 (m, 1H), 3.67-3.59 (m, 2H), 2.37-2.32 (m, 1H), 1.62-1.53 (m, 2H), 0.96 (d, 3H, $J = 7.2$ Hz), 0.89 (m, 18H), 0.04 (m, 12H).

Synthesis of intermediate 42

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 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).

10
15Synthesis of intermediate 43

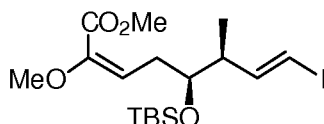
20

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.

25

^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

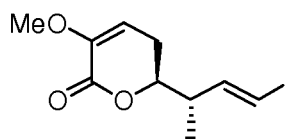


To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate
10 (348.4 mg, 1.37 mmol) and 18-crown-6 (722.3 mg, 2.73 mmol) in anhydrous THF (13 mL) stirred under argon atmosphere at -78°C , a 0.5 M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (2.74 mL, 1.37 mmol) was added dropwise. 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 (2*E*,7*E*)-**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

90



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).

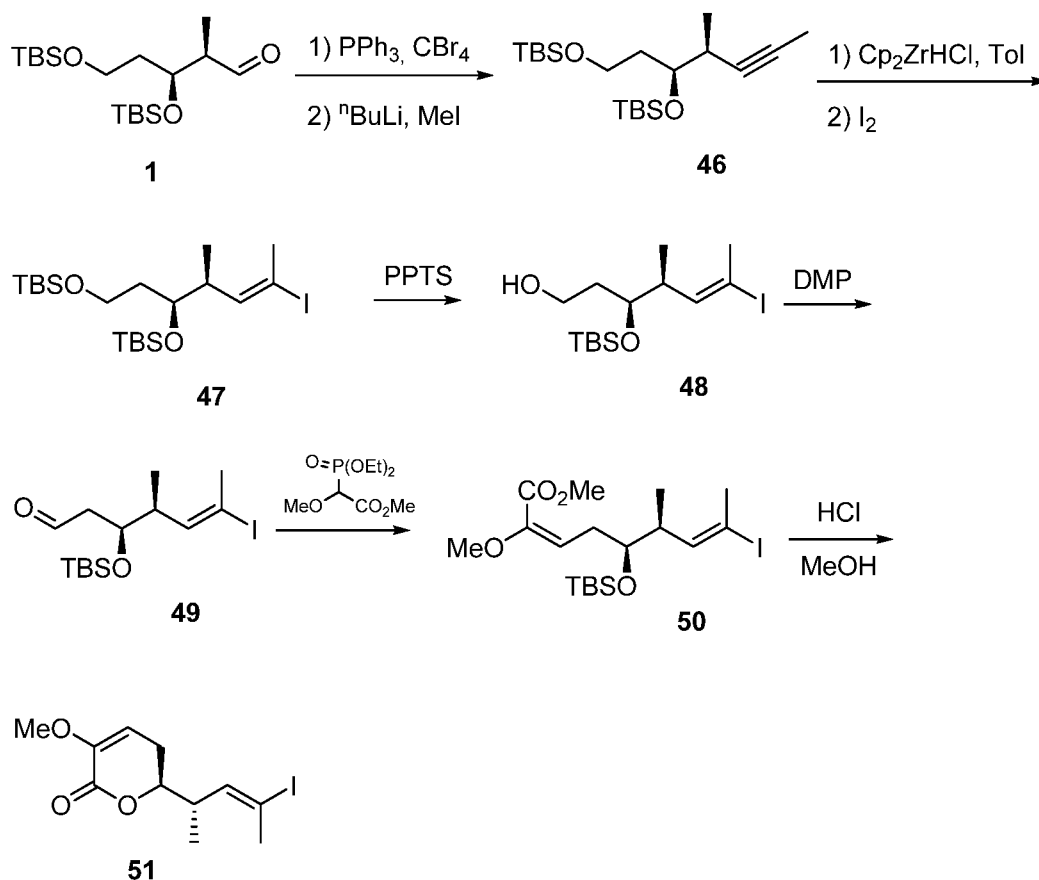
MS (ES) $[m/z]$ = 331.1 $[M+Na]^+$.

EXAMPLE 8: SYNTHESIS OF FRAGMENT 51

20

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

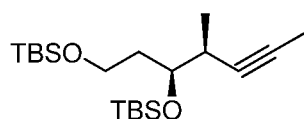
91



Scheme 8

Synthesis of intermediate 46

5

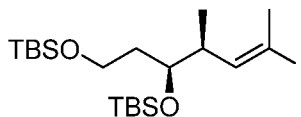


To a solution of carbon tetrabromide (8.74 g, 26.35 mmol) in dry dichloromethane (26 mL) was added dropwise a solution of triphenylphosphine (1.38 g, 52.69 mmol) in anhydrous DCM (50 mL) at 0 °C. The dark yellow solution was cooled to -78 °C and aldehyde **1** (4.75 g, 13.2 mmol) in anhydrous DCM (13 mL) was added quickly. The resulting mixture was stirred at -78°C (30 min) and at 0 °C (10 min). The reaction was diluted with Et_2O and then washed with brine. The aqueous layer was extracted with Et_2O and the organic layers were combined, dried, filtered and evaporated under reduced pressure.

Purification by flash chromatography (hexane/ dichloromethane 10:1) afforded 4.37 g (66% yield) of vinyl dibromide as colourless oil. To a solution of the dibromoolefin in anhydrous THF (80 mL) was added dropwise a 2.5 M 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 (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 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) 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



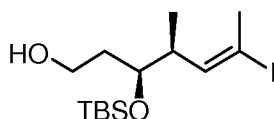
To a solution of **46** (200 mg, 0.56 mmol) in anhydrous toluene (7 mL), under Ar and at 23 °C bis(cyclopentadienyl)zirconium(IV) chloride hydride (432.3 mg, 1.68 mmol) was added and the reaction was stirred at 50°C for 1 hour. During this time the reaction solution turned of orange colour. The reaction 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 residue which was purified by flash chromatography eluting with

hexane/ dichloromethane (from 10:1 to 1:2) to furnish vinyl iodine **47** (140.4 mg, 49% yield) as pale yellow oil.

¹H NMR (CDCl₃, 300 MHz) δ : 6.07 (dd, 1H, J = 9.9, 1.5 Hz), 3.72-3.67 (m, 1H), 3.65-3.61 (t, 2H, J = 6.6 Hz), 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 (m, 18H), 0.05 (m, 12H).

Synthesis of intermediate 48

10

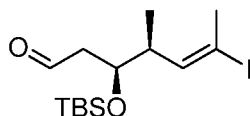


To a solution of iodide **47** (140.4 mg, 0.27 mmol) in EtOH (2 mL) pyridinium p-toluenesulfonate (PPTS) (24 mg, 0.09 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (hexane/EtOAc 4:1) affording 90.3 mg (83% yield) of alcohol **48** as colourless oil.

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



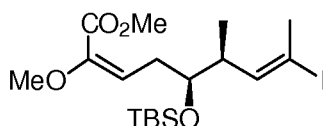
To a 0 °C solution of alcohol **48** (87 mg, 0.22 mmol) in anhydrous DCM (2 mL), Dess-Martin periodinane (140 mg, 0.33 mmol) was added. After 1 hour stirring at 0 °C and 30 min at 23 °C the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The organic layer was decanted, dried 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, 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



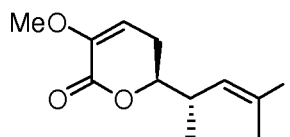
To a solution of Diethyl(methoxy[methoxycarbonyl]methyl)phosphonate (73.7 mg, 0.29 mmol) and 18-crown-6 (153.4 mg, 0.58 mmol) in anhydrous THF (3 mL) stirred under argon atmosphere at -78 °C, a 0.5 M Potassium bis(trimethylsilyl)amide (KHMDs) solution in toluene (0.58 mL, 0.29 mmol) was added dropwise. 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. Purification by column chromatography (hexane/EtOAc 30:1 to 5:1)

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 (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



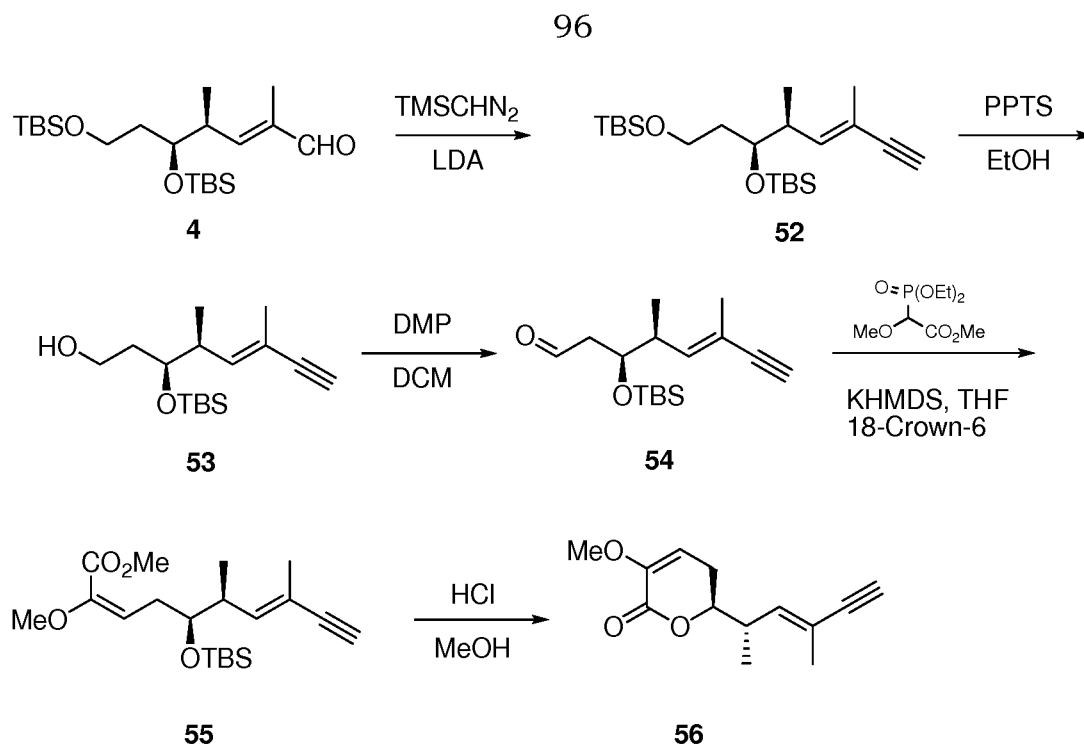
To a solution of ester **50** (90.8 mg, 0.19 mmol) in MeOH (3 mL) at room
15 temperature, aqueous HCl 37% (34 μL) was added and the reaction
mixture was stirred for 6 hours. Then the mixture was neutralized with
a saturated aqueous solution of NaHCO_3 (pH 7-8) and the organic
solvent was evaporated under 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 (CDCl_3 , 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).

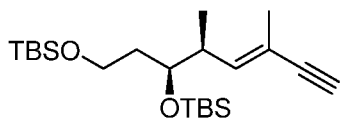
25

EXAMPLE 9: SYNTHESIS OF FRAGMENT 56

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



5

Synthesis of intermediate 52

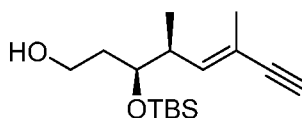
- 10 A solution of 1.8 M of Lithium diisopropylamide in heptane/THF/ethylbenzene (8.96 mL, 16.13 mmol) was diluted in 88 mL of anhydrous THF. After cooling down to -78°C , trimethylsilyldiazomethane (8.06 mL, 2M in THF, 16.13 mmol) was added and the resulting mixture was stirred for 30 min. A solution 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 Et_2O . The combined organic layers were dried (anhydrous Na_2SO_4) 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.

^1H NMR (CDCl_3 , 300 MHz) δ : 5.86 (d, 1H, $J = 9.9$ Hz), 3.73-3.63 (m, 3H), 2.74 (s, 1H), 2.58-2.50 (m, 1H), 1.80 (s, 3H), 1.70-1.63 (m, 2H), 0.93 (d, 3H, $J = 6.6$ Hz), 0.88 (m, 18H), 0.04 (m, 12H).

5 ^{13}C NMR (CDCl_3 , 75 MHz) δ : 143.3, 116.3, 87.1, 73.7, 72.8, 60.0, 38.6, 38.0, 26.1, 26.1, 18.5, 18.3, 17.4, 15.3, -4.2, -5.1.

Synthesis of intermediate 53

10

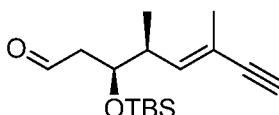


To a solution of **52** (2.05 g, 5.17 mmol) in EtOH (50 mL) pyridinium p-toluenesulfonate (PPTS) (511.7 mg, 2.04 mmol) was added and the reaction mixture was stirred at room temperature for 25 hours. Then
 15 the solvent was removed under reduced pressure and the resulting oil was purified by column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

^1H NMR (CDCl_3 , 300 MHz) δ : 5.76 (d, 1H, $J = 9.9$ Hz), 3.73-3.63 (m, 3H),
 20 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



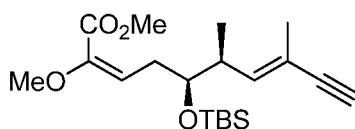
To a 0°C solution of alcohol **53** (140 mg, 0.48 mmol) in anhydrous DCM (5 mL), Dess-Martin periodinane (308.5 mg, 0.73 mmol) was added.

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 (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, 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.

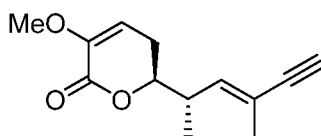
Synthesis of intermediate 55



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 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 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 (regioselectivity > 4:1 determined by ¹H NMR).

¹H NMR (CDCl₃, 300 MHz) for (2*E*,7*E*)-**55** δ: 5.73 (d, 1H, *J* = 9.9 Hz), 5.33 (dd, 1H, *J* = 7.8, 6.9 Hz), 3.80 (s, 3H), 3.61-3.57 (m, 1H), 3.59 (s, 3H), 2.77-2.68 (m, 1H), 2.73 (bs, 1H), 2.58-2.44 (m, 2H), 1.72 (bs, 3H),
5 0.95 (d, 3H, *J* = 6.6 Hz), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

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 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
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).

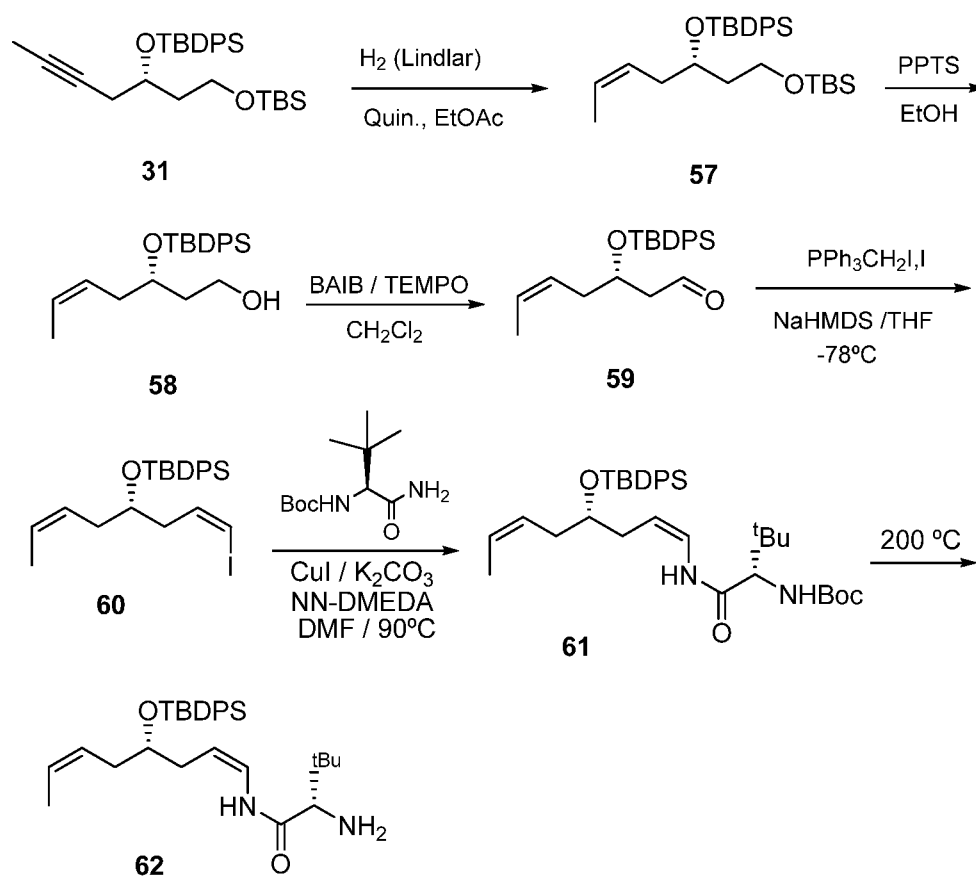
25 ¹³C NMR (CDCl₃, 125 MHz) δ: 161.3, 145.1, 138.6, 118.9, 108.0, 85.9, 81.3, 74.8, 55.4, 37.2, 26.2, 17.5, 16.2.

MS (ES) [*m/z*] = 243.2 [*M*+Na]⁺.

EXAMPLE 10: SYNTHESIS OF FRAGMENT 62

30

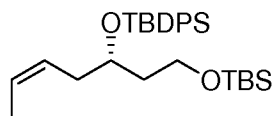
Scheme 10 provides an example of the synthesis of fragment 62.



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

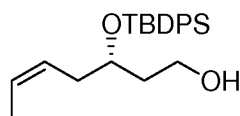
anhydrous Na₂SO₄, filtered and concentrated to afford intermediate **57** (4.27 g, yield: 90%) as a colourless oil that was used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.48 (m, 1H), 5.36-5.27 (m, 1H), 3.95-3.87 (m, 1H), 3.71-3.55 (m, 2H), 2.16 (dd, 2H, *J* = 6.9, 6.3 Hz), 1.73-1.66 (m, 2H), 1.41 (dd, 3H, *J* = 6.6, 1.2 Hz), 1.05 (s, 9H), 0.84 (s, 9H), -0.02 (s, 6H).

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.

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 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.

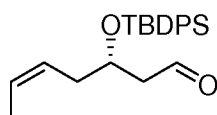
20 ¹H NMR (CDCl₃, 300 MHz) δ: 7.73-7.69 (m, 4H), 7.44-7.36 (m, 6H), 5.44-5.38 (m, 1H), 5.21-5.17 (m, 1H), 4.01-3.94 (m, 1H), 3.84-3.76 (m, 1H), 3.69-3.64 (m, 1H), 2.32-2.14 (m, 2H), 1.89-1.78 (m, 1H), 1.70-1.60 (m, 1H), 1.37 (d, 3H, *J* = 6.9 Hz), 1.07 (s, 9H).

25

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, 27.2, 19.5, 13.0.

Synthesis of intermediate 59

102



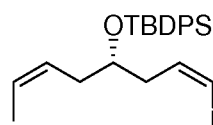
BAIB (1.97 g, 6.11 mmol) was added to a solution of alcohol **58** (2.05 g, 5.56 mmol) and TEMPO (86.87 mg, 0.56 mmol) in 25 mL of DCM. The reaction mixture was stirred at room temperature for 16-18 h until the alcohol was no longer detectable (TLC), and then it was quenched with a saturated aqueous solution of NH_4Cl , and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 , 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 (CDCl_3 , 300 MHz) δ : 9.72 (t, 1H, $J = 2.7$ Hz), 7.74-7.67 (m, 4H), 7.48-7.37 (m, 6H), 5.56-5.45 (m, 1H), 5.32-5.23 (m, 1H), 4.29-4.20 (m, 1H), 2.51-2.48 (m, 2H), 2.31-2.27 (m, 2H), 1.43 (dd, 3H, $J = 6.9, 1.5$ Hz), 1.06 (s, 9H).

^{13}C NMR (CDCl_3 , 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

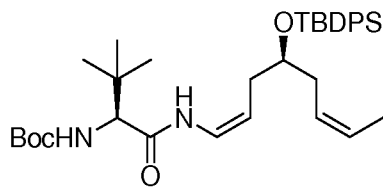
plug celite/SiO₂. The plug was rinsed with Hexane/EtOAc (10:1 to 5:1) to afford compound **60** (2 g, yield: 89%) as a colourless oil that was used without further purification.

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

¹³C 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.

10

Synthesis of intermediate 61



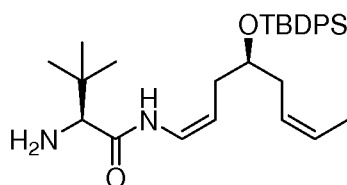
15 A resealable Schlenk tube was charged with copper (I) iodide (232.4 mg, 1.22 mmol), potassium carbonate (1.688 g, 12.23 mmol) and Boc-*tert*-LeuCONH₂ (2.474 g, 6.12 mmol), evacuated and filled with argon. *N,N*-Dimethylethylenediamine (0.26 mL, 2.45 mmol), vinyl iodide **60** (2 g, 4.08 mmol) and 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),

5.36-5.28 (m, 2H), 4.86-4.78 (m, 2H), 3.88-3.77 (m, 1H), 2.26-2.04 (m, 4H), 1.44 (d, 3H, $J = 6.9$ Hz), 1.43 (s, 9H), 1.06 (s, 9H), 0.96 (s, 9H).

Synthesis of intermediate 62

5



A solution of amino protected derivative **61** (847 mg, 1.43 mmol) in ethylenglycol (50 mL) was heated at 200 °C for 10-20 min. The reaction mixture was then cooled at room temperature, diluted with DCM, quenched with brine and poured into water. A few drops of 3M NaOH were added until the solution reached pH 14 and then was extracted thoroughly with DCM. The combined organic phases were dried over anhydrous Na₂SO₄, filtrated and concentrated in vacuo to afford the primary amine **62** (435 mg, 62%) as a white foam after purification by flash chromatography (Hexane/EtOAc 10:1 to 1:2).

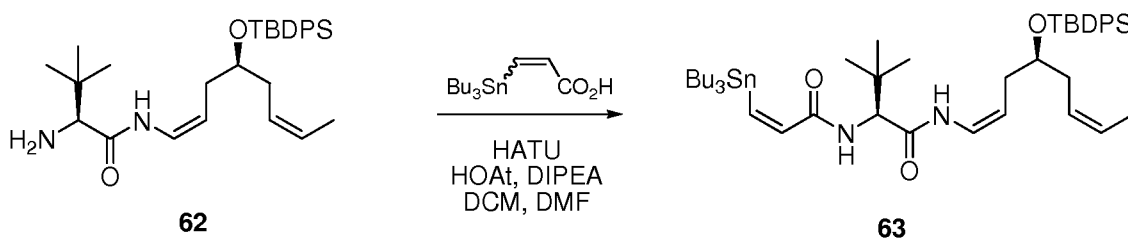
¹H NMR (CDCl₃, 300 MHz) δ : 8.50 (d, 1H, $J = 10.8$ Hz), 7.70-7.66 (m, 4H), 7.45-7.33 (m, 6H), 6.67 (dd, 1H, $J = 11.1, 9.3$ Hz), 5.48-5.40 (m, 1H), 5.36-5.28 (m, 1H), 4.79 (dd, 1H, $J = 16.2, 7.5$ Hz), 3.87-3.79 (m, 1H), 3.08 (s, 1H), 2.22-2.14 (m, 4H), 1.43 (d, 3H, $J = 6.9$ Hz), 1.05 (s, 9H), 0.97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

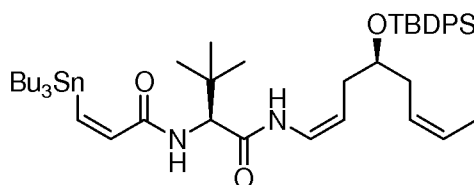
105



Scheme 11

Synthesis of intermediate 63

5



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, 1.76mmol), 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.

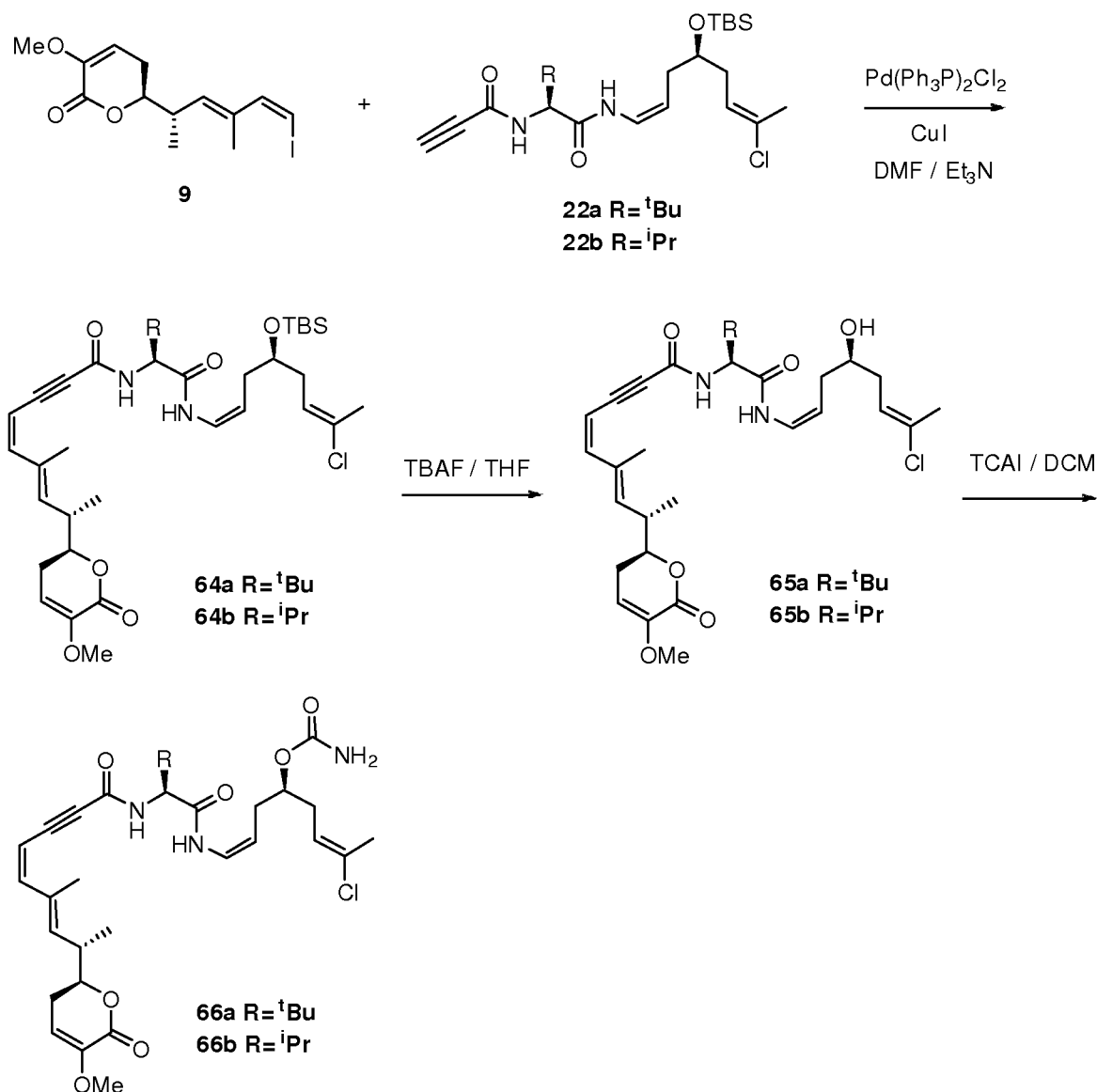
¹H NMR (CDCl₃, 300 MHz) δ: 7.70-7.68 (m, 4H), 7.43-7.36 (m, 6H), 7.02 (d, 1H, *J* = 12.3 Hz), 7.00 (d, 1H, *J* = 10.8 Hz), 6.75 (d, 1H, *J* = 12.3 Hz), 6.66 (t, 1H, *J* = 9.3 Hz), 6.26 (d, 1H, *J* = 9.6 Hz), 5.57-5.34 (m, 1H), 5.38-5.28 (m, 1H), 4.83 (dd, 1H, *J* = 16.5, 7.8 Hz), 4.31 (d, 1H, *J* = 9.6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

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).

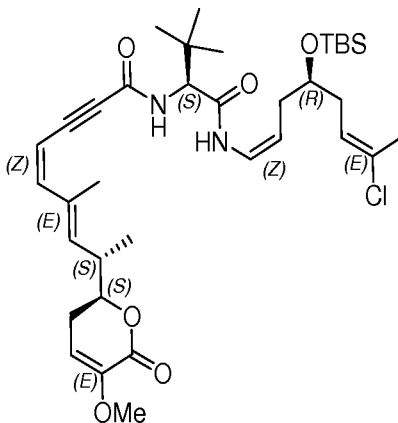
^{13}C -RMN (CDCl_3 , 75 MHz) δ : 168.0, 166.2, 153.8, 136.3, 136.1, 134.3, 130.0, 127.8, 126.7, 126.0, 121.6, 109.0, 72.6, 60.7, 35.7, 34.0, 32.7, 29.5, 27.7, 27.2, 26.7, 19.5, 14.0, 13.2, 11.8.

EXAMPLE 12

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



Scheme 12

Synthesis of intermediate 64a

5

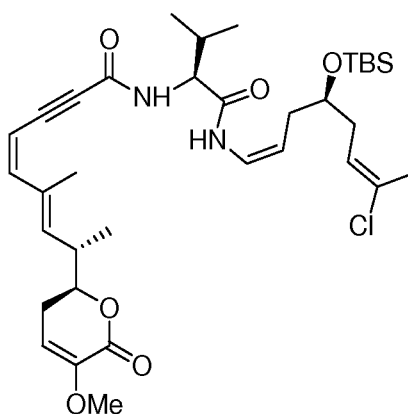
To a solution of iodo compound **9** (11 mg, 0.033 mmol) in DMF/Et₃N (0.25 ml and 0.05 ml) under N₂ at -20°C, Pd(Ph₃P)₂Cl₂ (2.3 mg, 0.0033 mmol) and CuI (1.9 mg, 0.01 mmol) were added. Then, compound **22a** (15 mg, 0.03 mmol in 0.1 ml DMF) was added and the reaction mixture was stirred at -20 °C to 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 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, 2H), 2.20 (m, 4H), 2.09 (s, 3H), 2.01 (s, 3H), 1.15 (d, 3H, *J* = 6.6 Hz), 1.02 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

20

Synthesis of intermediate 64b

108

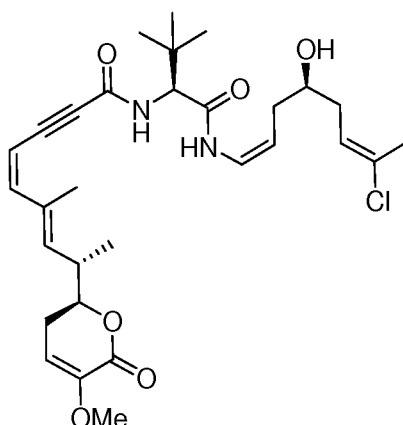


To a solution of **9** (40 mg, 0.113 mmol) in DMF/Et₃N (1 ml and 0.19 ml) at -20°C, Pd(Ph₃P)₂Cl₂ (7.9 mg, 0.113 mmol) and CuI (6.5 mg, 0.034 mmol) were added. Then, **22b** (50 mg, 0.113 mmol in 0.4 ml DMF) was added and the reaction was stirred at -20 °C to room temperature for 3 hours. The crude mixture 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

109

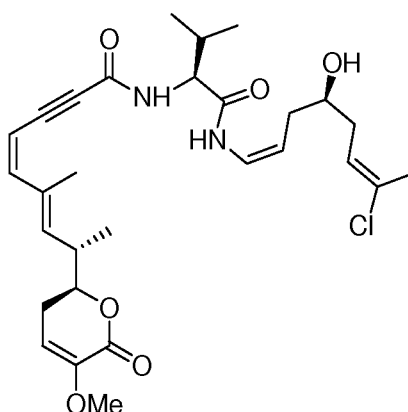


To a solution of **64a** (15 mg, 0.022 mmol) in anhydrous THF (0.5 mL) under N₂ and at room temperature, TBAF 1M in THF (0.044 mL, 0.044 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The 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 **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), 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).

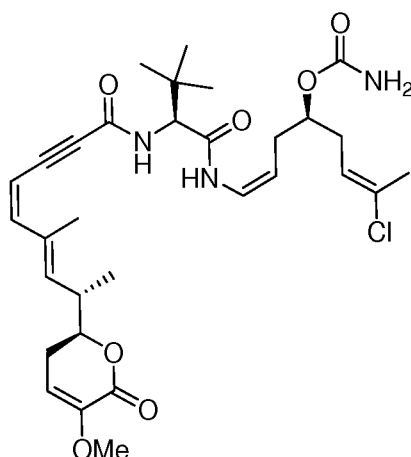
Synthesis of compound 65b

110



- 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



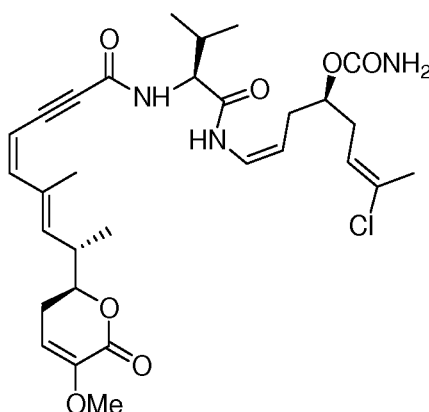
To a solution of **65a** (3.5 mg, 0.0062 mmol) in anhydrous DCM (0.45 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (1 μ L, 0.0075 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (100 mg). The mixture was stirred for 30 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 product which was purified by column chromatography (Hexane/EtOAc 2:1 to 1:2) affording compound **66a** (2.5 mg, yield: 70%).

^1H NMR (CDCl_3 , 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 $[\text{M}+1]^+$, 626.2 ($\text{M}+\text{Na}^+$).

Synthesis of compound 66b

112

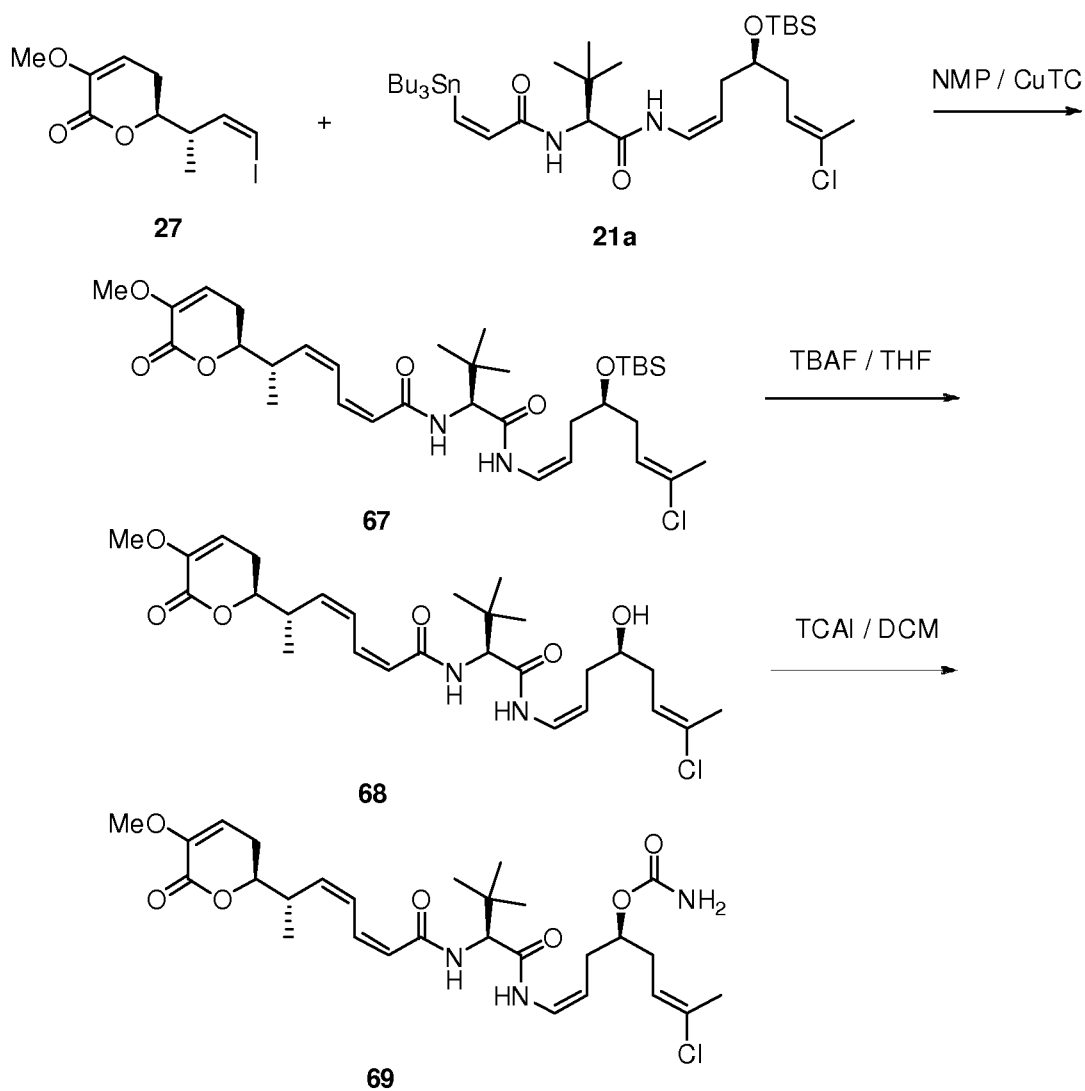


- To a solution of **65b** (32 mg, 0.06 mmol) in CH₂Cl₂ (4.2 ml) at r.t., trichloroacetyl isocyanate (TCAI) (8.5 μ l, 0.072 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral
- 5 Alumina was added (450 mg) while stirring for additional 30 min. The reaction mixture was filtered over alumina using a mixture of CH₂Cl₂ /MeOH 1:1 and after evaporation of the filtrate at reduced pressure the product was purified by column chromatography (Hexane/EOAct mixtures) to afford pure **66b** (12 mg, yield: 35%).
- 10 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
- 15 Hz), 1.00-0.96 (m, 6H).

EXAMPLE 13

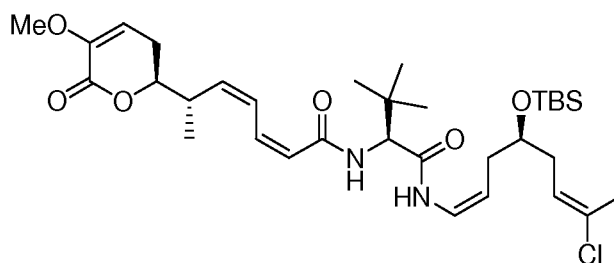
- Scheme 13 provides the synthesis of several compounds of the
- 20 invention.

113



Scheme 13

5 Synthesis of compound 67



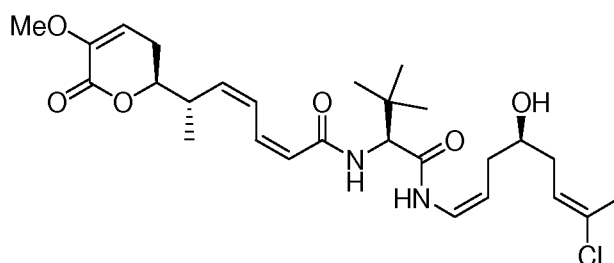
To a solution of alkenylstannane **21a** (50 mg, 0.07 mmol) and iodide **27**
 10 (24.8 mg, 0.08 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1 mL) at 0°C,

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 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), 3.79-3.72 (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).

15

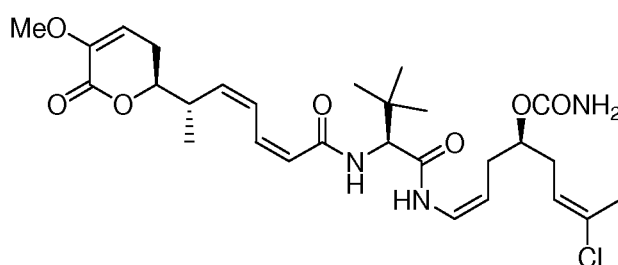
Synthesis of compound 68



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
25 over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (Hexane/EtOAc 3:1 to 1:2) to give alcohol **68** (16 mg, yield: 80 %) as an oil.

¹H NMR (CDCl₃, 300 MHz) δ : 8.90 (d, 1H, J = 10.5 Hz), 7.42 (dd, 1H, J = 11.7, 11.1 Hz), 6.78-6.69 (m, 2H), 6.59 (d, 1H, J = 9.3 Hz), 5.75 (d, 1H, J = 11.4 Hz), 5.64-5.53 (m, 3H), 4.88-4.80 (m, 1H), 4.37 (d, 1H, J = 9.3 Hz), 4.22-4.15 (m, 1H), 3.77-3.69 (m, 1H), 3.64 (s, 3H), 3.11-3.01 (m, 1H), 2.39-2.35 (m, 2H), 2.24-2.14 (m, 4H), 2.03 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H).

Synthesis of compound 69



10

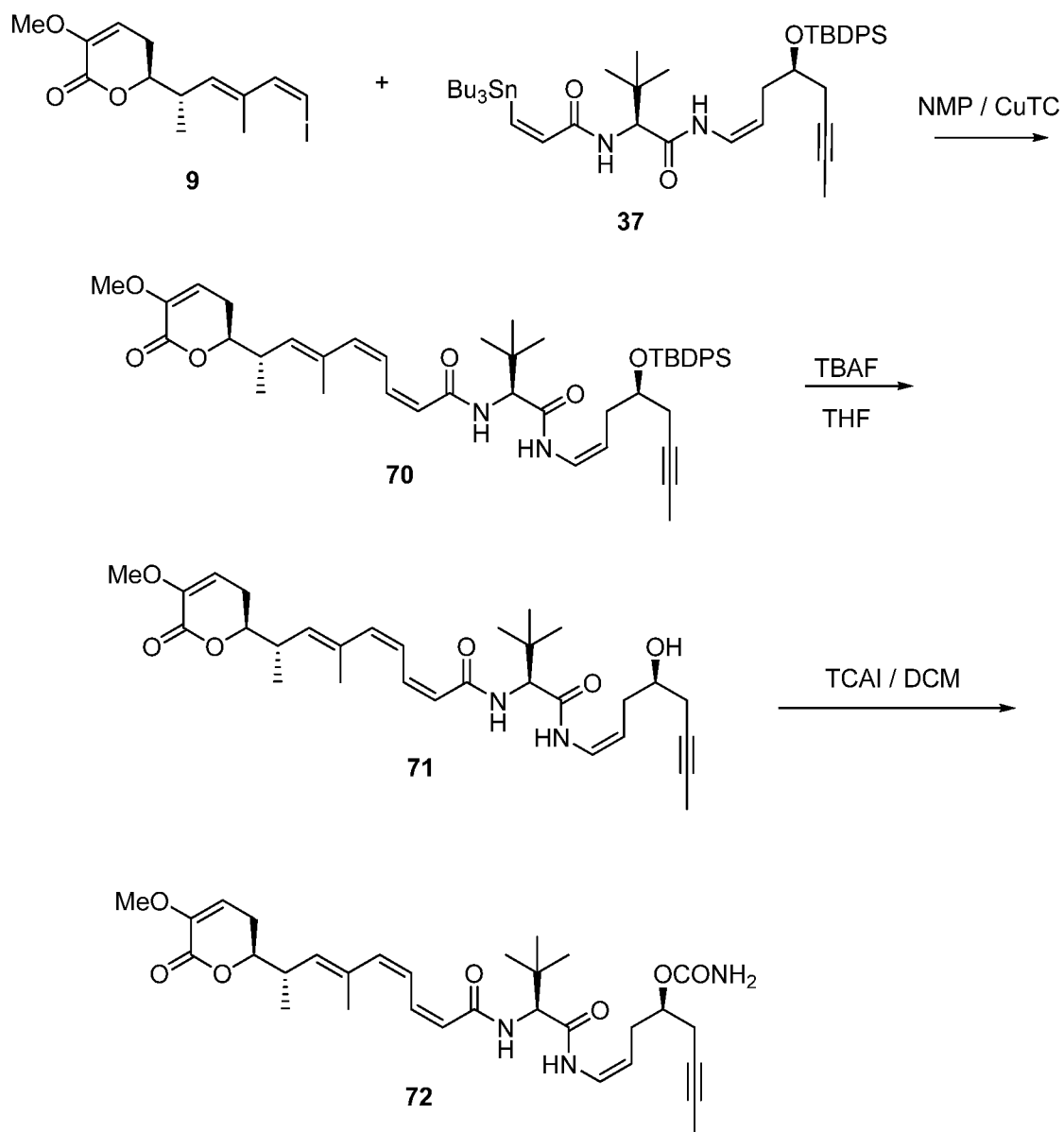
To a solution of **68** (15 mg, 0.02 mmol) in anhydrous DCM (0.3 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (4.1 μ L, 0.64 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (450 mg). The mixture was stirred for 30 min and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

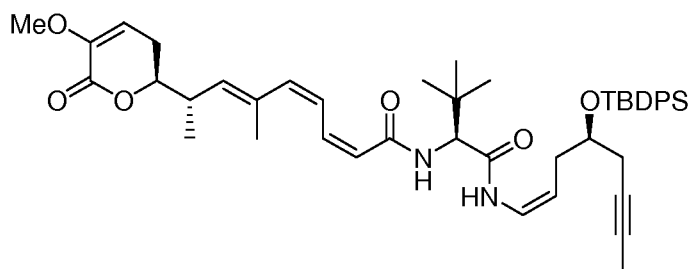
¹³C NMR (CDCl₃, 75.5 MHz) δ : 168.1, 165.9, 161.4, 157.7, 145.2, 138.3, 135.2, 132.0, 125.9, 124.5, 122.3, 121.8, 108.1, 105.2, 81.4, 75.1, 60.7, 55.4, 36.1, 35.0, 32.9, 30.8, 26.7, 26.3, 21.0, 17.0

EXAMPLE 14

Scheme 14 provides the synthesis of several compounds of the
5 invention



Scheme 14

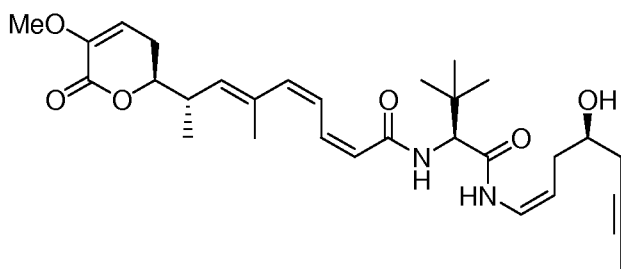
Synthesis of compound 70

- 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 0°C, Copper thiophenecarboxylate (CuTC) (32.2 mg, 0.168 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,
- 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* = 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).
- 20

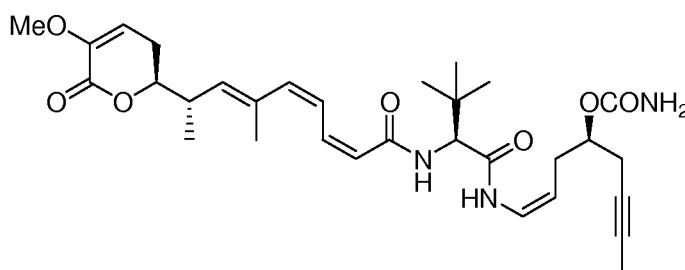
- 25 Synthesis of compound 71



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, 0.2 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 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), 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

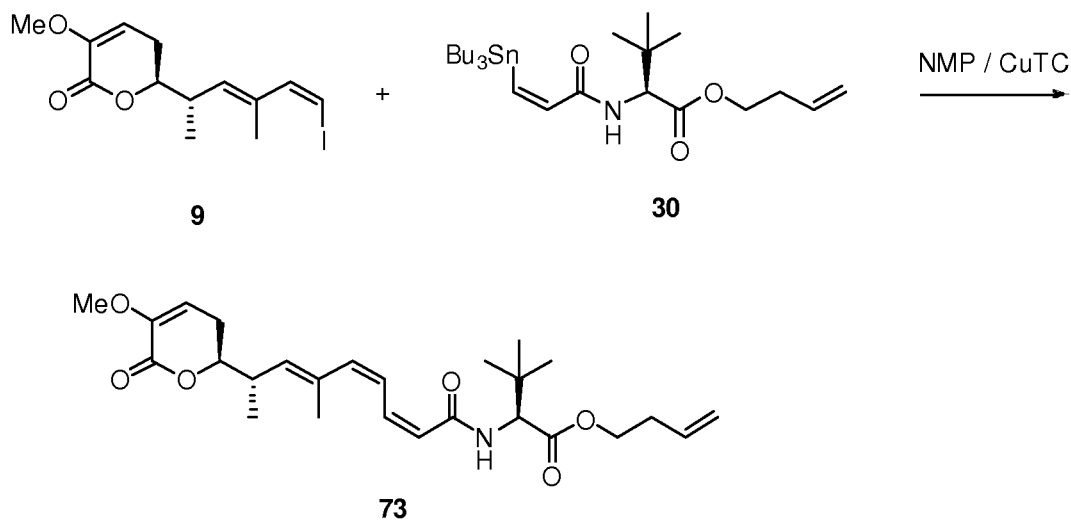
To a solution of **71** (21.6 mg, 0.0443 mmol) in anhydrous DCM (3.1 mL) at 0°C, trichloroacetyl isocyanate (TCAI) (6.4 μ l, 0.053 mmol) was added. The reaction was stirred at 0°C for 30 min and then neutral aluminium

oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 1:2). Compound **72** (19.1 mg, yield: 76%) was obtained as a white solid.

¹H NMR (CDCl₃, 500 MHz) δ : 8.61 (d, 1H, J = 11.1 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), 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).

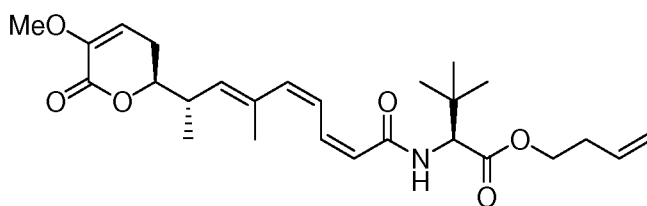
EXAMPLE 15

Scheme 15 provides the synthesis of compound 73.



Scheme 15

Synthesis of compound 73



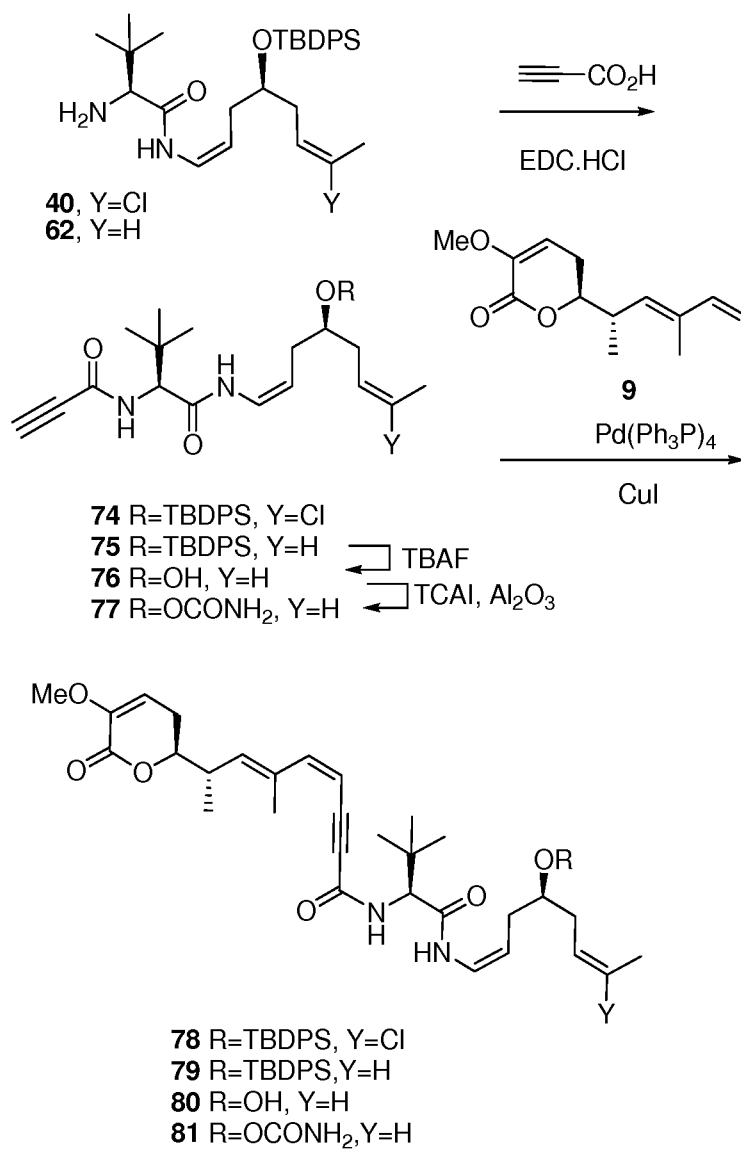
To a solution of **30** (40mg, 0.076 mmol) and **9** (31 mg, 0.09 mmol) in NMP (0.8 ml) at 0°C, Copper thiophenecarboxylate (CuTC, 22 mg, 0.11 mmol) was added. The reaction was stirred at 0 °C for 45 min and an hour at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, 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, $J = 11.52$ Hz), 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, $J = 6.65$ Hz), 0.99 (s, 9H).

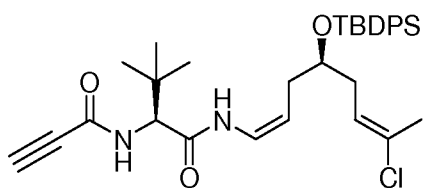
20 EXAMPLE 16

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

121



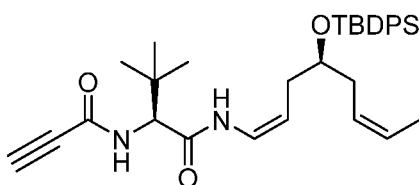
Scheme 16

5 Synthesis of compound 74

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

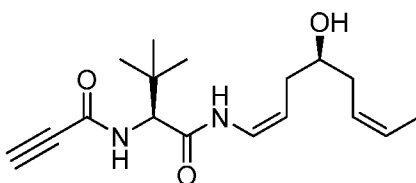


20

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.

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



10

To a solution of **75** (244.3 mg, 0.45 mmol) in anhydrous THF (5 mL) 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 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

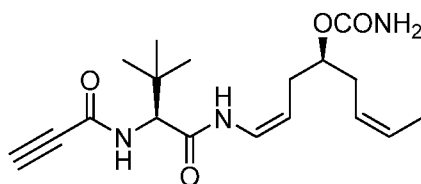
¹H NMR (CDCl₃, 300 MHz) δ: 9.02 (d, 1H, *J* = 9.9 Hz), 7.09 (d, 1H, *J* = 9.3 Hz), 6.74 (t, 1H, *J* = 9.9 Hz), 5.65-5.57 (m, 1H), 5.43-5.35 (m, 1H), 4.93-4.85 (m, 1H), 4.44 (d, 1H, *J* = 9.3 Hz), 3.78-3.70 (m, 1H), 2.87 (s, 1H), 2.32-2.12 (m, 4H), 1.61 (d, 3H, *J* = 6.6 Hz), 1.02 (s, 9H).

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.

25

Synthesis of intermediate 77

124



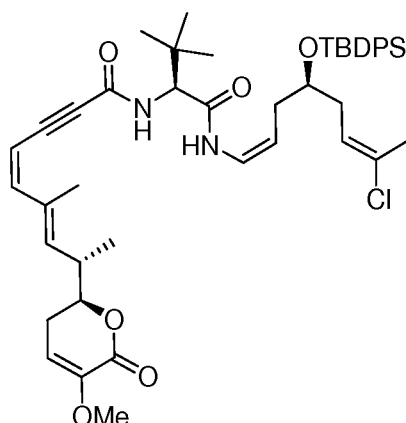
To a solution of **76** (48.6 mg, 0.159 mmol) in anhydrous DCM (1.6 mL)
5 at room temperature, trichloroacetyl isocyanate (TCAI) (23.0 μ l, 0.19 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (250 mg). The mixture was stirred for 60 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 (CDCl_3 , 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

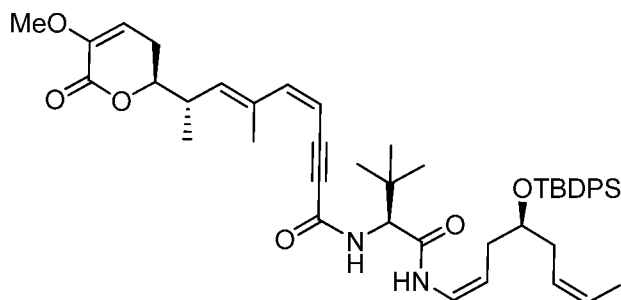
125



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.

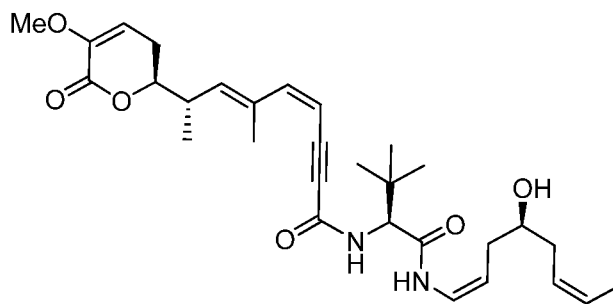
¹H NMR (CDCl₃, 300 MHz) δ : 7.67 (m, 4H), 7.48-7.37 (m, 6H), 7.75 (d, 1H, J = 10.5 Hz), 6.65 (t, 1H, J = 10.1 Hz), 6.46 (d, 1H J = 9.2 Hz), 6.38 (d, 1H, J = 12.0 Hz), 5.64-5.48 (m, 3H), 5.43 (d, 1H, J = 12.1 Hz), 4.78 (q, 1H, J = 7.7 Hz), 4.28 (d, 1H, J = 9.3 Hz), 4.20 (m, 1H), 3.82 (m, 1H), 3.65 (s, 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



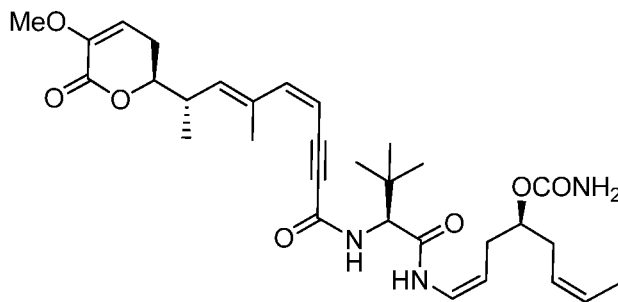
- To a solution of **9** (113 mg, 0.325 mmol) in DIPA (1.6 ml) at 23 °C, Pd(Ph₃P)₄ (7 mg, 0.006 mmol) and CuI (2.5 mg, 0.013 mmol) were added. Then **75** (195 mg, 0.358 mmol) was added and the reaction was stirred at 23 °C for 3 hours. The crude mixture was quenched with H₂O and extracted with EtOAc. 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 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), 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, 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



- 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 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.
- 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).
- 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.
- MS (ES) [*m/z*] = 549.2 [M+Na]⁺.

Synthesis of compound 81

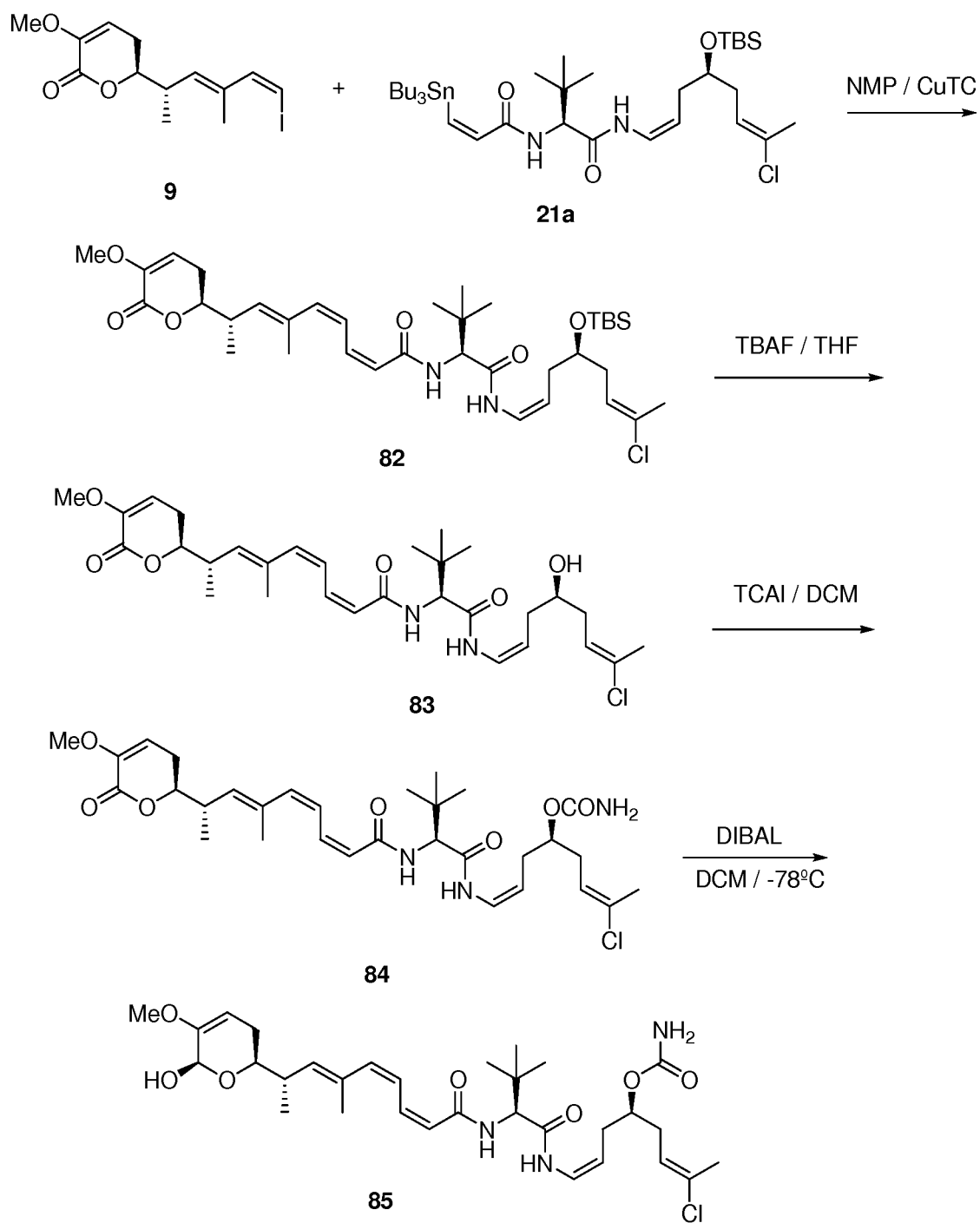


- To a solution of **9** (43 mg, 0.123 mmol) in DIPA (0.6 ml) at 23 °C, Pd(Ph₃P)₄ (2.8 mg, 0.0025 mmol) and CuI (1.0 mg, 0.005 mmol) were added. Then, **77** (43 mg, 0.123 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 120 min. The crude mixture was
- 5 quenched with H₂O and extracted with EtOAc. The organic phase was dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The residue was purified by 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).

EXAMPLE 17

- Scheme 17 provides the synthesis of several compounds of this
- 20 invention

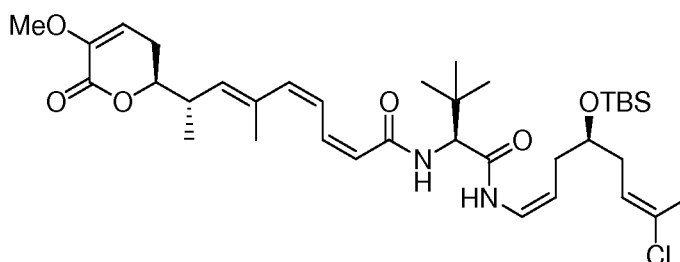
129



Scheme 17

5 Synthesis of compound 82

130



To a solution of alkenylstannane **21a** (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. The reaction was stirred at 0 °C for 45 min and 20 min at room temperature. Then, the crude mixture was filtered through a plug of neutral alumina, washed with EtOAc/Ether 50:50 and the combined filtrates were washed with HCl 0.5N (3x15 mL). The organic solution was dried and evaporated to give the crude product which was purified by column chromatography (Hexane/EtOAc 5:1 to 1:1) to give triene **82** (0.66 g, yield: 66%) as an oil.

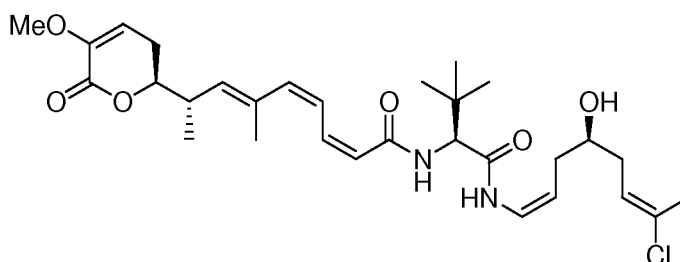
¹H NMR (CDCl₃, 300 MHz) δ: 7.89 (d, 1H, *J* = 10.8 Hz), 7.22 (dd, 1H, *J* = 12.3, 11.4 Hz), 6.86 (dd, 1H, *J* = 11.7, 11.4 Hz), 6.70 (dd, 1H, *J* = 9.9, 9.3 Hz), 6.35 (d, 1H, *J* = 9.3 Hz), 6.13 (d, 1H, *J* = 11.4 Hz), 5.66 (d, 1H, *J* = 11.4 Hz), 5.60 (dd, 1H, *J* = 5.4, 3.9 Hz), 5.55 (br t, 1H, *J* = 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

131

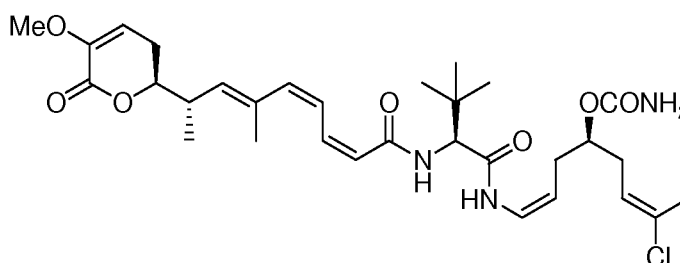


To a solution of **82** (275 mg, 0.41 mmol) in anhydrous THF (6 mL) under N₂ and at room temperature, TBAF 1M in THF (0.82 mL, 0.82 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined 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 **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



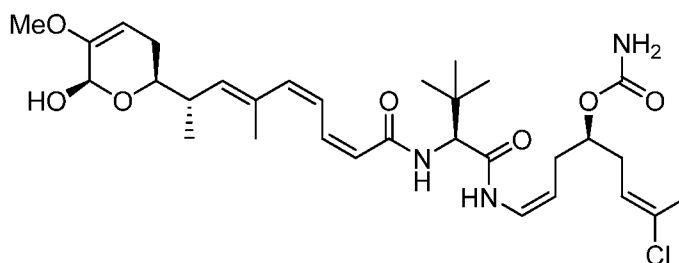
To a solution of **83** (300 mg, 0.53 mmol) in anhydrous DCM (7.5 mL) at 0°C, trichloroacetyl isocyanate (TCAI) (76 μ L, 0.64 mmol) was added. The reaction was stirred at 0 °C for 30 min and then neutral aluminium

oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in 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, 1H, J = 11.6 Hz), 5.63 (dd, 1H, J = 6.5, 2.6 Hz), 5.61 (br t, 1H, J = 6.8 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)

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. 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 (CDCl₃, 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), 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).

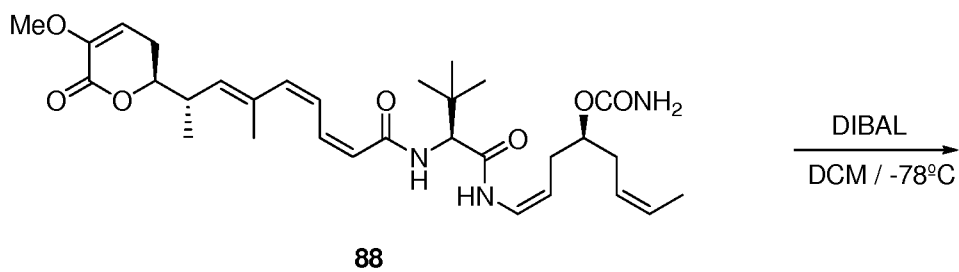
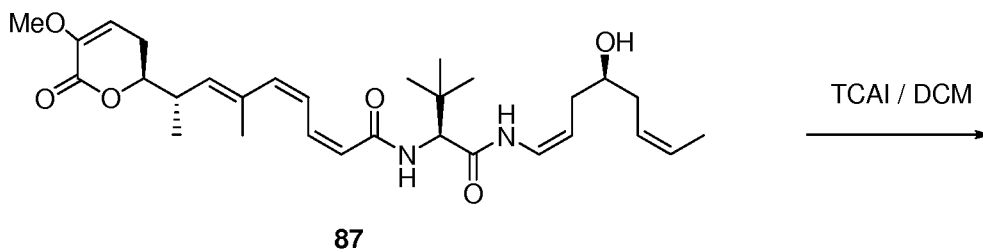
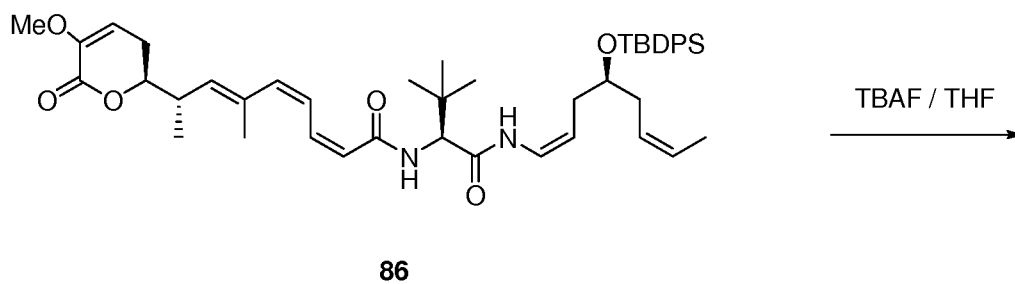
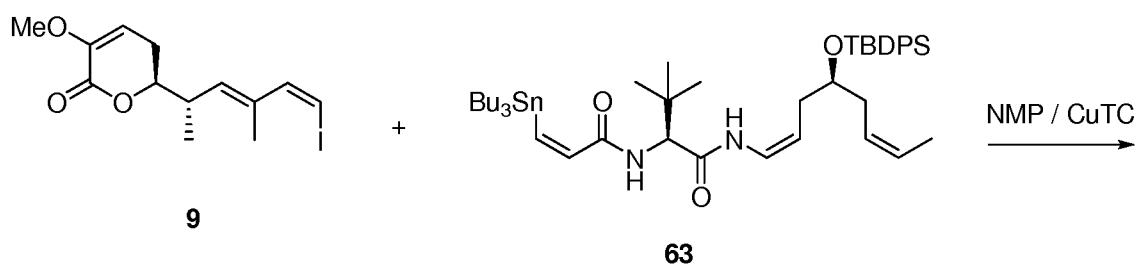
15

EXAMPLE 18

20

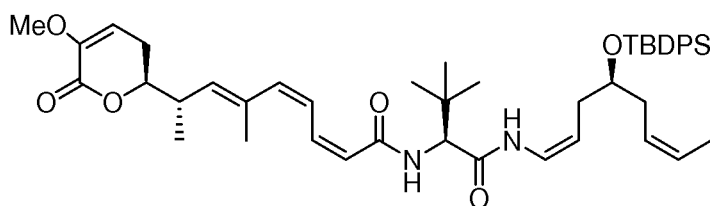
Scheme 18 provides the synthesis of several compounds of this invention

134



Scheme 18

5 Synthesis of compound 86



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** (459.7 mg,
yield: 66%) as an oil.

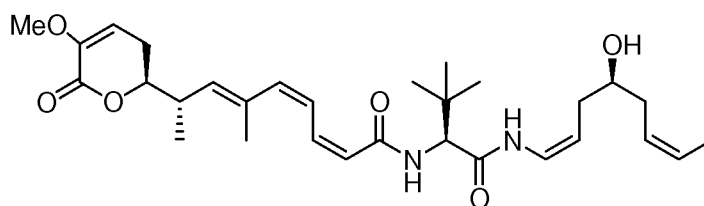
¹H NMR (CDCl₃, 300 MHz) δ: 7.66-7.64 (m, 4H), 7.43-7.32 (m, 7H), 7.23
(t, 1H, *J* = 11.7 Hz), 6.85 (t, 1H, *J* = 11.7 Hz), 6.62 (dd, 1H, *J* = 10.5, 9.3
15 Hz), 6.41 (d, 1H, *J* = 9.3 Hz), 6.11 (d, 1H, *J* = 11.7 Hz), 5.66 (d, 1H, *J* =
11.4 Hz), 5.60 (dd, 1H, *J* = 5.7, 5.1 Hz), 5.49-5.41 (m, 1H), 5.32-5.27
(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) δ: 168.3, 166.3, 161.8, 145.4, 140.2, 137.3,
136.1, 134.8, 134.4, 134.3, 129.9, 127.8, 126.4, 126.1, 124.4, 121.7,
121.2, 108.4, 109.1, 82.0, 72.6, 60.6, 55.6, 37.5, 35.2, 32.7, 31.1, 27.2,
26.8, 26.5, 19.5, 17.4, 16.9, 13.1.

25

Synthesis of compound 87

136

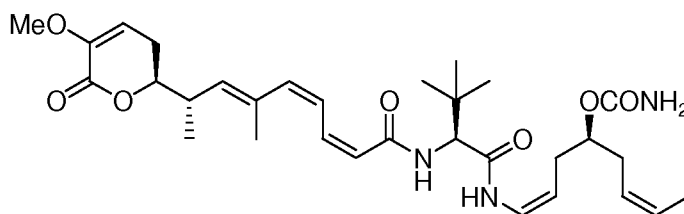


To a solution of **86** (586 mg, 0.76 mmol) in anhydrous THF (7.5 mL) under N₂ and at room temperature, TBAF 1M in THF (1.53 mL, 2 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined 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

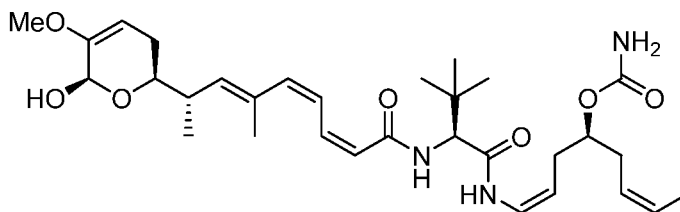


To a solution of **87** (56 mg, 0.105 mmol) in anhydrous DCM (1 mL) at 0°C, trichloroacetyl isocyanate (15 μ L, 0.126 mmol) was added. The reaction was stirred at 0 °C for 30 min and then neutral aluminium oxide was added. The mixture was stirred for 5-30 min and then was soaked into a pad of aluminium oxide. The product was washed out using a mixture of DCM/MeOH 50:1. The filtrate was evaporated in vacuo to give the crude product which was purified by column chromatography (Hexane/EtOAc 3:1 to 1:2) to give a compound **88** (57.6 mg, yield: 96%) as a white foam.

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, 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), 2.39 (m, 1H), 2.35 (m, 2H), 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), 1.04 (s, 9H).

¹³C NMR (CDCl₃, 75 MHz) δ : 168.2, 166.3, 161.6, 157.6, 145.2, 140.2, 137.5, 134.1, 133.8, 127.1, 124.9, 124.4, 124.2, 120.8, 108.2, 105.8, 81.9, 75.6, 60.7, 55.4, 37.1, 34.8, 31.4, 30.9, 26.7, 26.1, 17.1, 16.4, 13.0.

Synthesis of compound 89



Over a -78 °C cooled solution of compound **88** (15 mg, 0.0262 mmol) in anhydrous dichloromethane (0.5 mL) under argon atmosphere,

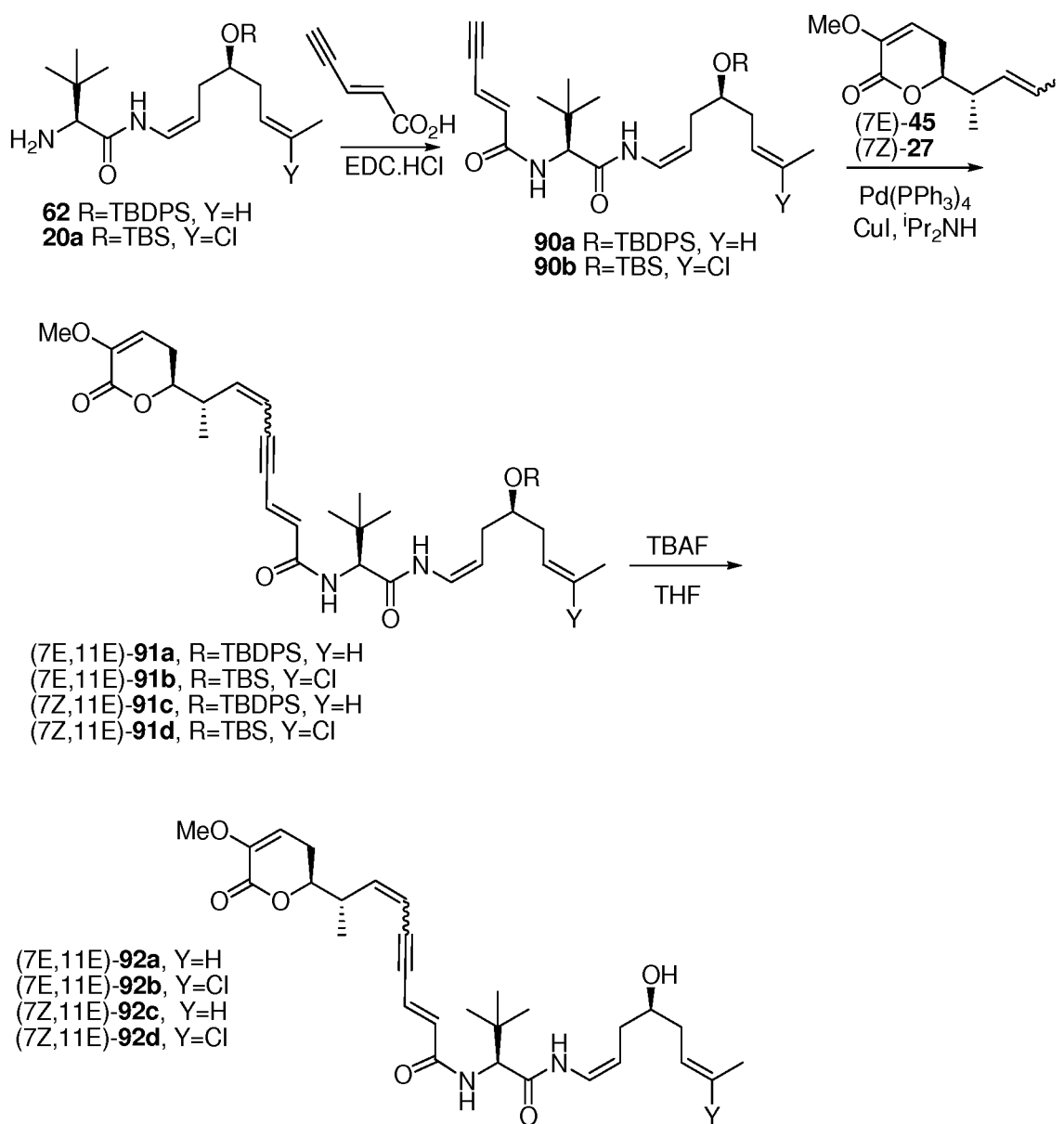
Diisobutylaluminum hydride (DIBAL) 1M in toluene (0.03 mL, 0.034 mol) was added and the mixture was stirred at -78 °C. After 2 hours the reaction was quenched with a saturated aqueous solution of NH₄Cl and diluted with dichloromethane (2 mL). This mixture was stirred for 0.5 h
5 at room temperature and 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).

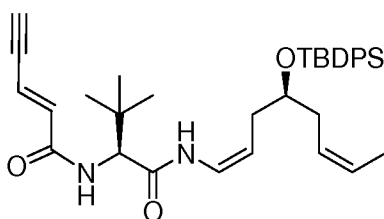
EXAMPLE 19

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

139



Scheme 19

Synthesis of intermediate 90a

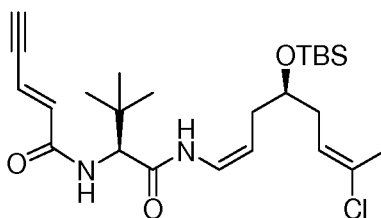
A solution of (*E*)-pent-2-en-4-ynoic acid (52 mg, 0.54 mmol), amine **62** (232 mg, 0.47 mmol) in anhydrous DCM (5 mL) was cooled to 0°C under argon and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC (100 mg, 0.52 mmol) was added. The reaction mixture was stirred at 0°C for 10 min 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 (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).

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

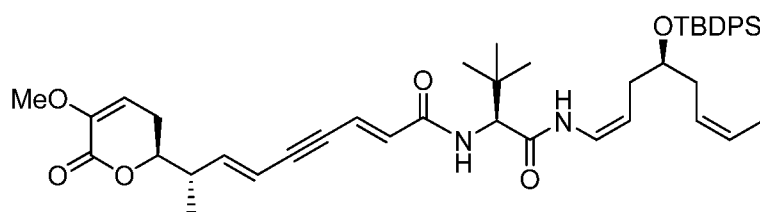
To a solution of amine **20a** (96.04 mg, 0.24 mmol) and (*E*)-pent-2-en-4-ynoic acid (27.4 mg, 0.28 mmol) in dry dichloromethane /DMF (10:1, 3.3 mL), under argon atmosphere and at 0 °C, DIPEA (0.049 mL, 0.28

mmol), HOAt (38.11 mg, 0.28 mmol), and HATU (106.4 mg, 0.28mmol) 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
5 water and extracted with dichloromethane. 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 10:1) to give amide **90b** (81.9 mg, 71% yield) as a white foam.

- 10 ^1H NMR (CDCl_3 , 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 ^{13}C NMR (CDCl_3 , 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



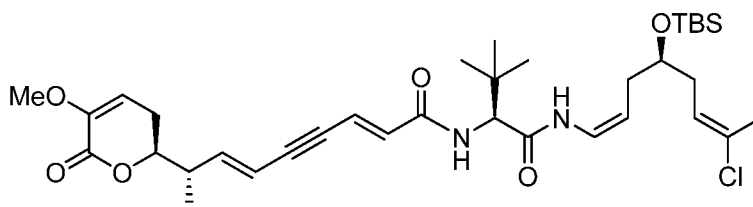
To a solution of **45** (56.2 mg, 0.182 mmol) in DIPA (1.6 ml) at 23°C, $\text{Pd}(\text{Ph}_3\text{P})_4$ (15.7 mg, 0.014 mmol) and CuI (5.2 mg, 0.028 mmol) were
25 added. Then, **90a** (114.6 mg, 0.200 mmol) in 0.4 ml of DIPA was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched with H_2O and extracted with EtOAc. The organic phase was dried (anhydrous Na_2SO_4) 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.

¹H NMR (CDCl₃, 300 MHz) δ : 7.68-7.66 (m, 4H), 7.46-7.35 (m, 6H), 7.11 (d, 1H, J = 10.8 Hz), 6.81 (dd, 1H, J = 15.3, 2.1 Hz), 6.30 (dd, 1H, J = 10.2, 9.3 Hz), 6.32 (d, 1H, J = 9.3 Hz), 6.25 (d, 1H, J = 15.3 Hz), 6.15 (dd, 1H, J = 15.9, 8.4 Hz), 5.74 (d, 1H, J = 15.9 Hz), 5.62 (dd, 1H, J = 6.3, 3.0 Hz), 5.54-5.46 (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, 3H), 2.68-2.62 (m, 1H), 2.43-2.36 (m, 2H), 2.22-2.04 (m, 4H), 1.43 (d, 3H, J = 6.6 Hz), 1.18 (d, 3H, J = 6.9 Hz), 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, 127.6, 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



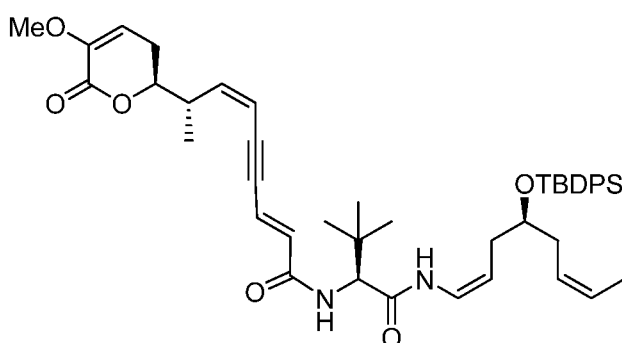
20

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.

¹H NMR (CDCl₃, 300 MHz) δ: 7.70 (d, 1H, *J* = 10.2 Hz), 6.82 (dd, 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), 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, 75 MHz) δ: 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, 26.1, 21.3, 18.3, 15.7, -4.3, -4.4.

Synthesis of compound 91c



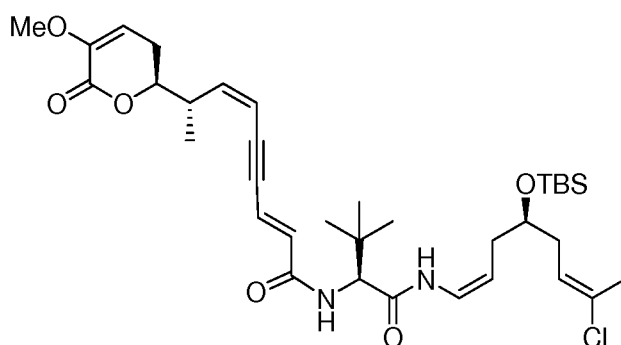
15

To a solution of **27** (58 mg, 0.188 mmol) in DIPA (1.6 mL) at 23°C, Pd(Ph₃P)₄ (16.3 mg, 0.014 mmol) and CuI (5.3 mg, 0.028 mmol) were added. Then, **90a** (118.2 mg, 0.207 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 **91c** (92 mg, 65 % yield) as a colourless oil.

25 ¹H NMR (CDCl₃, 300 MHz) δ: 7.68-7.66 (m, 4H), 7.46-7.35(m, 6H), 7.15 (d, 1H, *J* = 10.5 Hz), 6.85 (dd, 1H, *J* = 15.3, 2.1 Hz), 6.64 (dd, 1H, *J* =

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).
 ^{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, 32.7, 29.8, 27.2, 26.8, 23.5, 19.5, 15.8, 13.2.

Synthesis of compound 91d

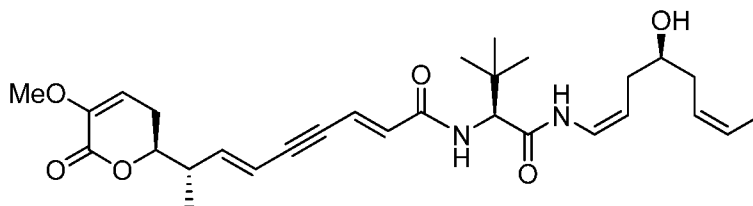


15 To a solution of **27** (26.2 mg, 0.085 mmol) in DIPEA (4 ml) at -20 °C, $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (6 mg, 0.0085 mmol) and CuI (5mg, 0.025 mmol) were added. Then, **90b** (45 mg, 0.094 mmol) was added and the reaction was stirred at 23 °C for 90 min. The crude mixture was quenched 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, 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),

4.28-4.18 (m, 1H), 3.81-3.72 (m, 1H), 3.64 (s, 3H), 3.16-3.06 (m, 1H), 2.56-2.46 (m, 1H), 2.40-2.32 (m, 1H), 2.26-2.13 (m, 4H), 2.04 (s, 3H), 1.17 (d, 3H, $J = 6.6$ Hz), 1.03 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

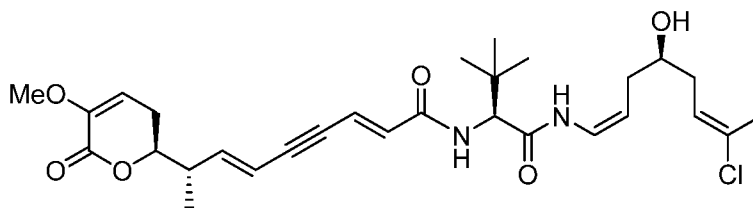
5 Synthesis of compound 92a



To a solution of **91a** (78.2 mg, 0.104 mmol) in anhydrous THF (2 mL) 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), 5.68-65 (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).

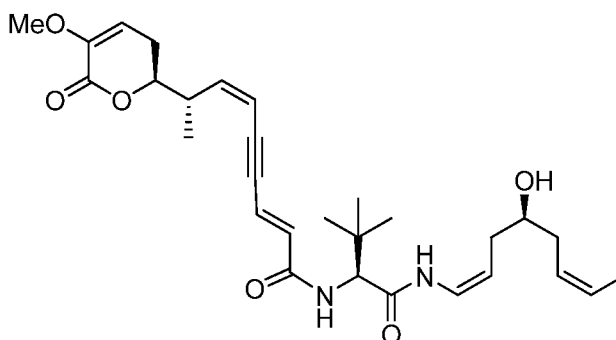
25 Synthesis of compound 92b



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



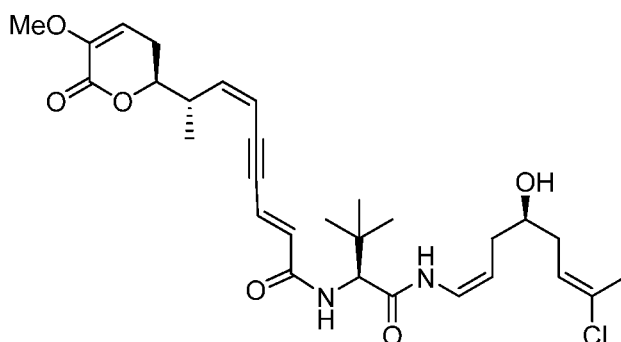
20

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 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 (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



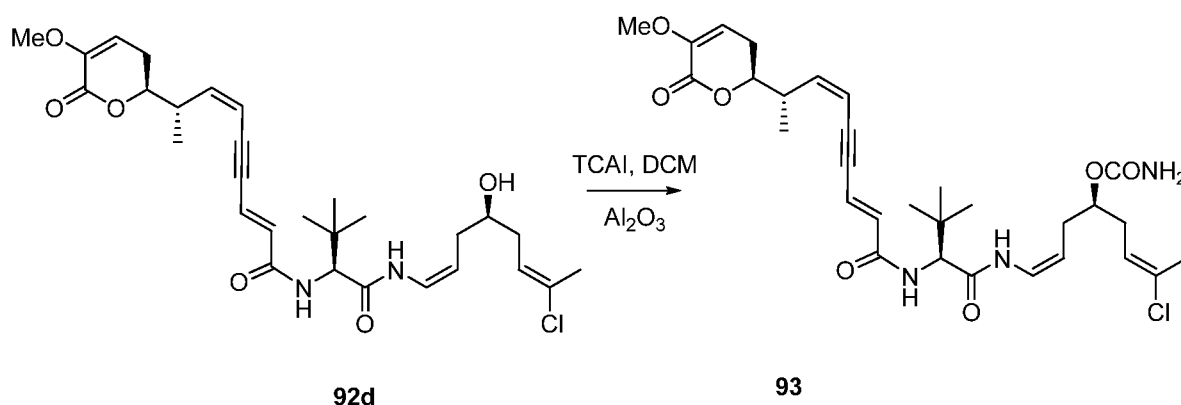
To a solution of **91d** (40 mg, 0.06 mmol) in anhydrous THF (0.6 mL) under N_2 and at room temperature, TBAF 1M in THF (0.12 mL, 0.12 mmol) was added. The reaction was stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The 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 alcohol **92d** (20 mg, 61 % yield) as a colourless oil.

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), 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

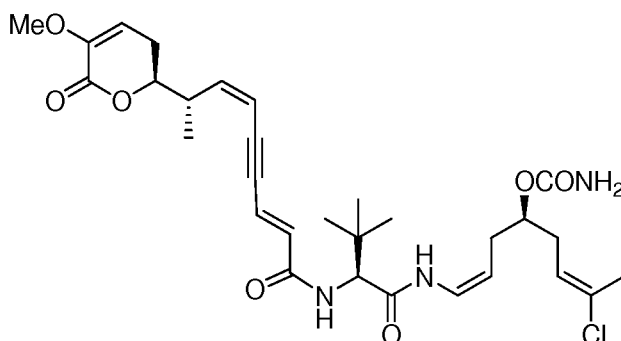
Scheme 20 provides the synthesis of the following compound of the invention.



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.

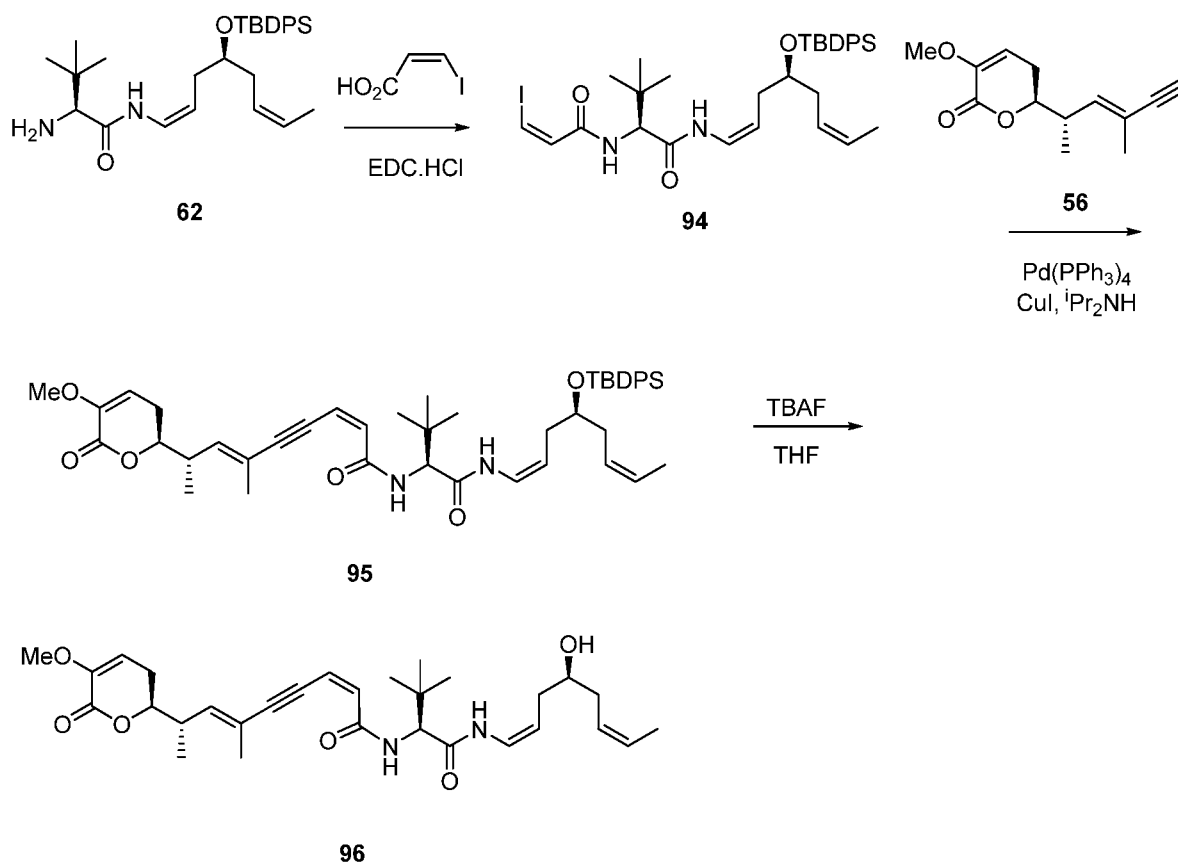
¹H NMR (CDCl₃, 300 MHz) δ : 8.83 (d, 1H, J = 10.5 Hz), 6.89-6.81 (m, 2H), 6.62 (d, 1H, J = 9.9 Hz), 6.32 (d, 1H, J = 15.3 Hz), 5.87 (t, 1H, J = 9.0 Hz), 5.73 (dd, 1H, J = 10.5, 2.4 Hz), 5.65-5.57 (m, 2H), 5.38 (bs, 2H), 4.84-4.76 (m, 1H), 4.48 (d, 1H, J = 9.3 Hz), 4.40-4.33 (m, 1H), 4.28-4.21 (m, 1H), 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).

¹³C NMR (CDCl₃, 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.

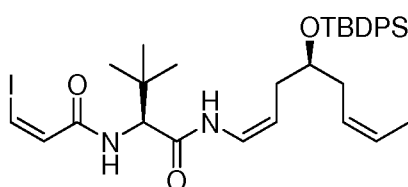


5

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,

65, 1558-1561), amine **62** (700 mg, 1.42 mmol) in anhydrous DCM (12 mL) was cooled to 0°C under argon and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC (340.8 mg, 1.78 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 a saturated aqueous solution of NaCl 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 1:1) to afford **94** (675 mg, 71 % yield) as a colourless foam solid.

10

¹H NMR (CDCl₃, 300 MHz) δ: 7.69-7.66 (m, 4H), 7.44-7.36 (m, 6H), 7.24 (d, 1H, *J* = 9.6 Hz), 7.06 (d, 1H, *J* = 9.3 Hz), 6.90 (d, 1H *J* = 9.0 Hz), 6.68-6.61 (m, 2H), 5.55-5.43 (m, 1H), 5.35-5.26 (m, 1H), 4.89-4.81 (m, 1H), 4.38 (d, 1H, *J* = 9.3 Hz), 3.88-3.80 (m, 1H), 2.23-2.06 (m, 4H), 1.43 (d, 3H, *J* = 6.9 Hz), 1.05 (s, 9H), 1.01 (s, 9H).

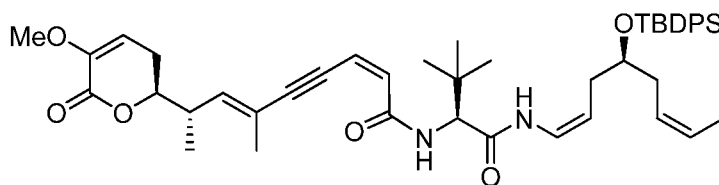
15

¹³C NMR (CDCl₃, 125 MHz) δ: 167.4, 164.3, 135.8, 134.1, 133.0, 129.7, 129.6, 127.6, 127.5, 126.4, 125.8, 121.4, 109.1, 88.3, 72.3, 60.4, 35.1, 33.8, 32.5, 27.0, 26.7, 19.3, 12.9.

MS (ES) [*m/z*] = 695.2 [*M*+Na]⁺.

20

Synthesis of compound 95



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

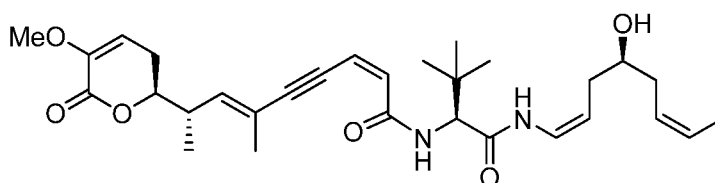
Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:4 to 3:1) to afford pure **95** (300 mg, 87 % yield) as a colourless foam solid.

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

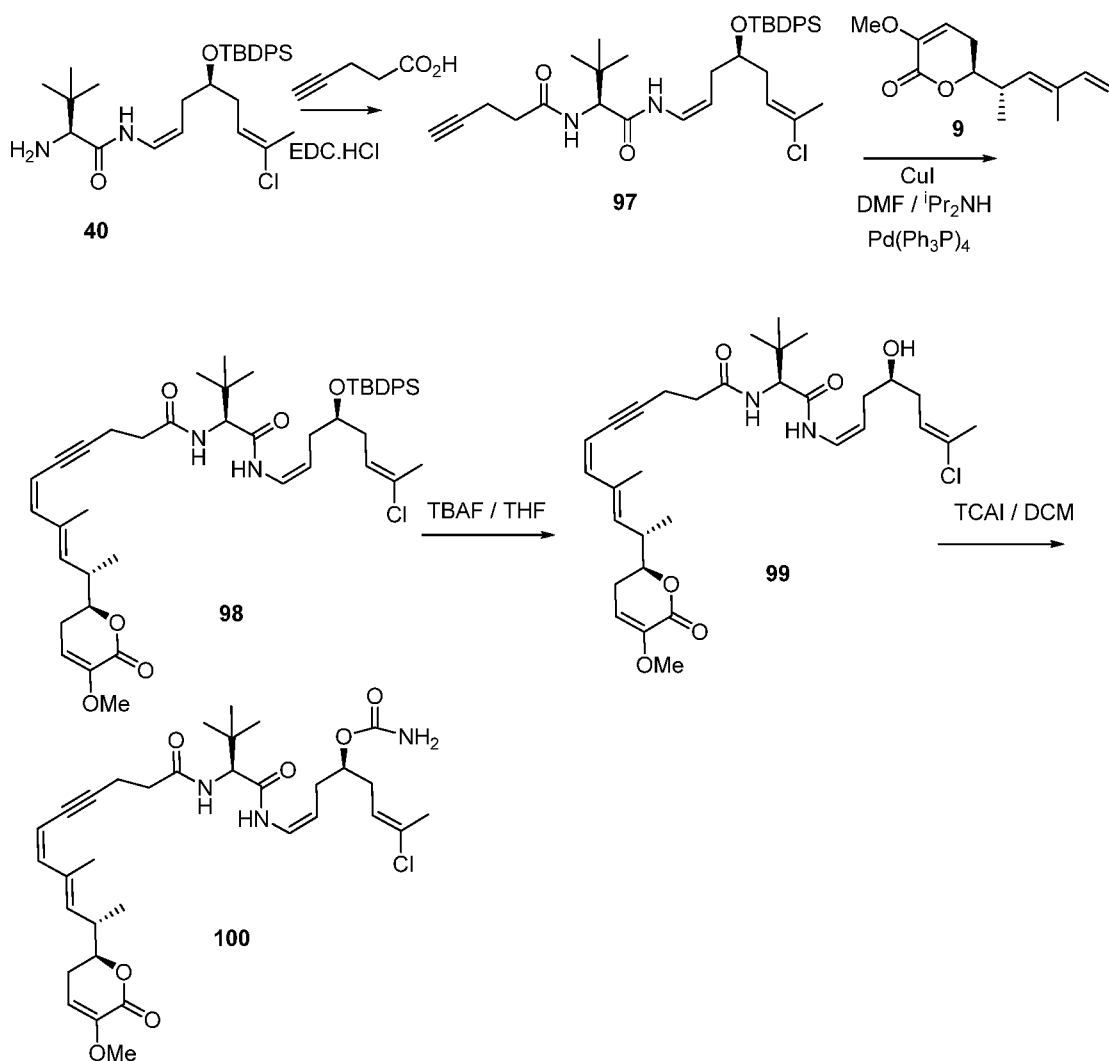
(hexane/EtOAc 4:1 to 1:3) to give alcohol **96** (150 mg, 87 % yield) as a colourless oil.

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

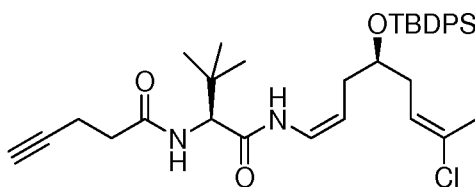
Scheme 22 provides the synthesis of several compounds of the invention.

154



Scheme 22

5 Synthesis of intermediate 97



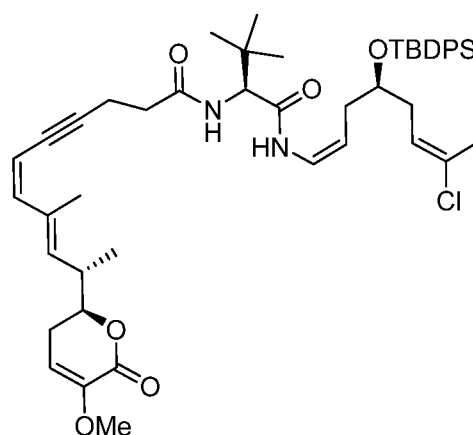
To a solution of **40** (200 mg, 0.38 mmol) and 4-pentynoic acid (48 mg, 0.49 mmol) in anhydrous DCM (3.8 ml) at 0 °C, EDC (91 mg, 0.47 mmol) was added. The reaction was stirred at 0°C for 30 min and 2 hours at room temperature. Then, the crude mixture was hydrolized

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 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 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.

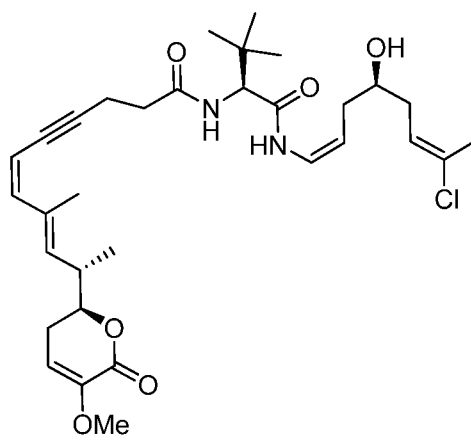
- ¹H NMR (CDCl₃, 300 MHz) δ: 7.66 (m, 4H), 7.41 (m, 6H), 7.26 (d, 1H, *J* = 10.6 Hz), 6.64 (t, 1H, *J* = 10.1 Hz), 6.42 (d, 1H, *J* = 9.3 Hz), 6.06 (d, 1H, *J* = 12.0 Hz), 5.61 (m, 1H), 5.48 (m, 2H), 5.35 (d, 1H, *J* = 11.8 Hz),

25

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 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
15 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.

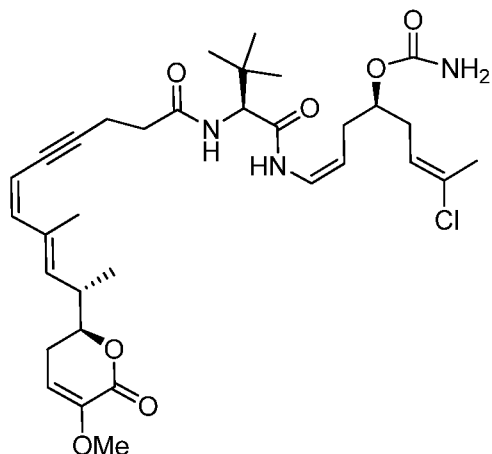
¹H NMR (CDCl₃, 300 MHz) δ : 8.92 (d, 1H, $J = 10.1$ Hz), 6.74 (t, 1H, $J = 9.5$ Hz), 6.67 (d, 1H, $J = 9.1$ Hz), 6.06 (d, 1H, $J = 12.0$ Hz), 5.62 (m, 2H),
20 5.47 (d, 1H, $J = 9.8$ Hz), 5.34 (d, 1H, $J = 11.9$ Hz), 4.84 (q, 1H, $J = 8.5$ Hz), 4.32 (d, 1H, $J = 9.1$ Hz), 4.18 (m, 1H), 3.73 (m, 1H), 3.64 (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 ¹³C NMR(CDCl₃, 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



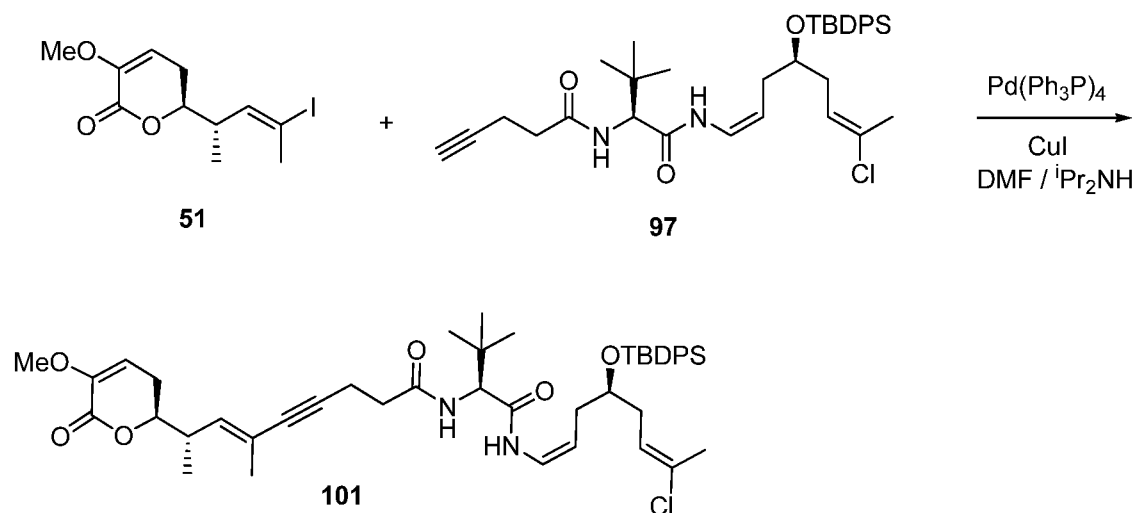
To a solution of **99** (30 mg, 0.05 mmol) in anhydrous DCM (3.15 mL) at room temperature, trichloroacetyl isocyanate (TCAI) (6 μ l, 0.06 mmol) was added. The reaction was stirred at room temperature for 30 min and then neutral aluminium oxide was added (375 mg). The mixture was stirred for 1 h and then 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(PPh₃)₄ (5 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 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

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

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

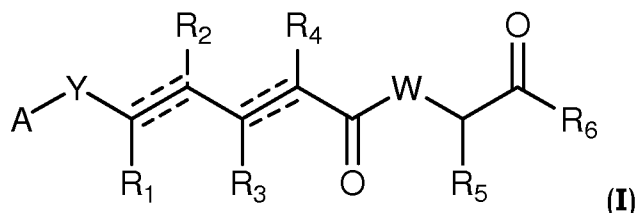
5

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

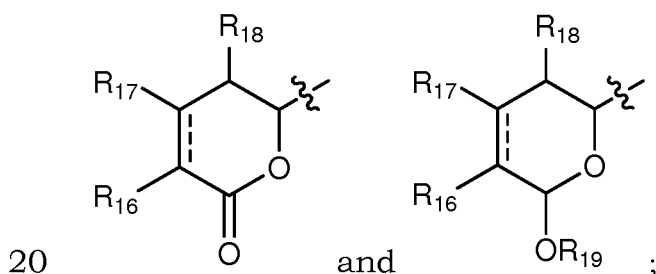
each R_{ay} , R_{by} , and R_{cy} is independently selected from hydrogen,
 10 substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl;

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

15

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

A is selected from



W is selected from O and NR_7 ;

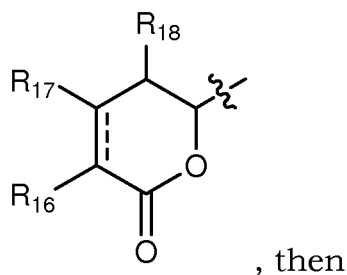
R₇ is selected from hydrogen, COR_a, COOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, or R₇ and R₅ together with the corresponding N atom and C atom to which they are
5 attached may form a substituted or unsubstituted 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
10 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;
15

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
20

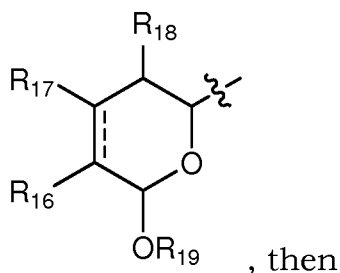
when A is



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 –
25

$\text{CHR}_{\text{ay}}\text{-CHR}_{\text{by}}\text{-CHR}_{\text{cy}}\text{-}$ or $\text{-CHR}_{\text{ay}}\text{-CR}_{\text{by}}\text{=CR}_{\text{cy}}\text{-}$ and a single or a double bond exists between the C atoms to which R_3 and R_4 are attached then R_9 is substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl; and

5 when A is



R_9 is selected from hydrogen, COR_a , COOR_a , substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, and substituted or unsubstituted $\text{C}_4\text{-C}_{12}$ alkenynyl;

each R_{16} , R_{17} and R_{18} are independently selected from hydrogen, OR_a , OCOR_a , OCOOR_a , NR_aR_b , NR_aCOR_b , and $\text{NR}_a\text{C(=NR}_a\text{)NR}_a\text{R}_b$, 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;

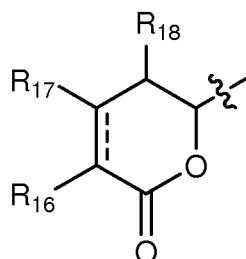
R_{19} is selected from hydrogen, COR_a , COOR_a , CONR_aR_b , S(O)R_a , SO_2R_a , $\text{P(O)(R}_a\text{)OR}_b$, $\text{SiR}_a\text{R}_b\text{R}_c$, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl; and

each R_a , R_b , and R_c are independently selected from hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclic group; or

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

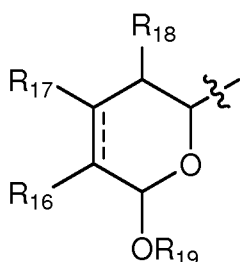
2. A compound according to claim 1, wherein A is

5



and R₁₆, R₁₇ and R₁₈ are as defined in claim 1.

10 3. A compound according to claim 1, wherein A is



and R₁₆, R₁₇, R₁₈ and R₁₉ are as defined in claim 1.

15

4. A compound according to claim 3, wherein R₁₉ is selected from hydrogen, substituted or unsubstituted C₁-C₆ alkyl and COR_a, and wherein R_a is a substituted or unsubstituted C₁-C₆ alkyl.

20 5. A compound according to claim 4, wherein R₁₉ is hydrogen.

6. A compound according to any preceding claim, wherein R₁₆ is selected from hydrogen, OR_a and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl.

7. A compound according to claim 6, wherein R_{16} is selected from hydrogen, OH and methoxy.
- 5 8. A compound according to any preceding claim, wherein one additional bond is present between the C atoms to which R_{16} and R_{17} are attached.
9. A compound according to any preceding claim, wherein R_{17} and R_{18}
10 are hydrogen.
10. A compound according to any preceding claim, 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.
- 15 11. A compound according to claim 10 wherein R_1 , R_2 , R_3 and R_4 are hydrogen.
12. A compound according to any preceding claim, wherein Y is selected
20 from $-CHR_{ay}-$, $-CR_{ay}=CR_{by}-$ and $-CHR_{ay}-CR_{by}=CR_{cy}-$, and wherein R_{ay} , R_{by} and R_{cy} are independently selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.
13. A compound according to claim 12, wherein R_{ay} , R_{by} and R_{cy} are
25 independently selected from hydrogen and methyl.
14. A compound according to any preceding claim, wherein R_5 is selected from hydrogen and a substituted or unsubstituted C_1 - C_6 alkyl.
- 30 15. A compound according to claim 14, wherein R_5 is selected from methyl, isopropyl and tert-butyl.

16. A compound according to any preceding claim, wherein W is NR₇ and wherein R₇ is as defined in claim 1.

17. A compound according to claim 16, wherein R₇ is hydrogen.

5

18. A compound according to any of claims 1 to 13, wherein W is NR₇ and wherein R₇ and R₅ together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted pyrrolidine group.

10

19. A compound according to any preceding claim, wherein R₆ is NR₈R₉ and wherein R₈ is hydrogen and R₉ is 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 C₄-C₁₂ alkenynyl.

15

20. A compound according to claim 19, wherein R₉ is selected from a 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 C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl and substituted or unsubstituted aryl.

20

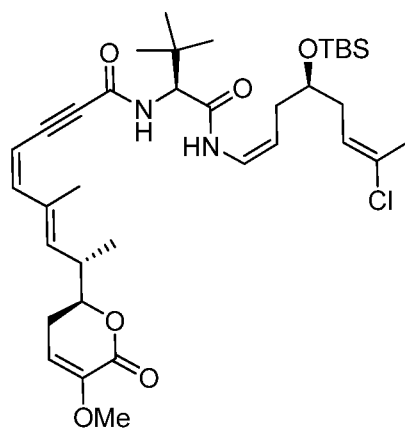
25

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

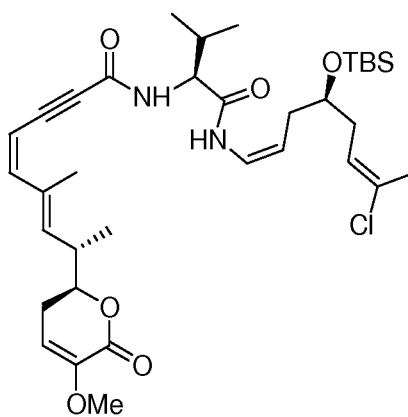
30

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

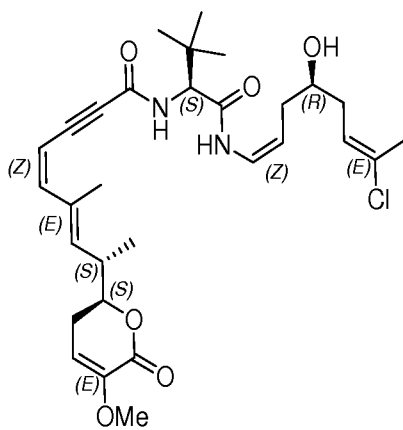
170



,

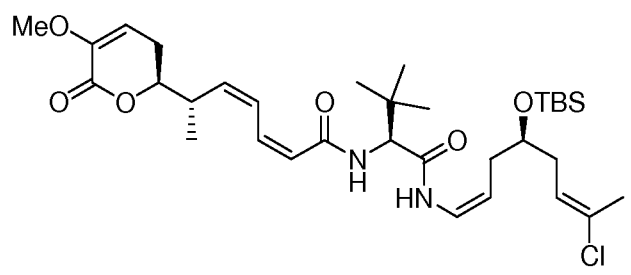
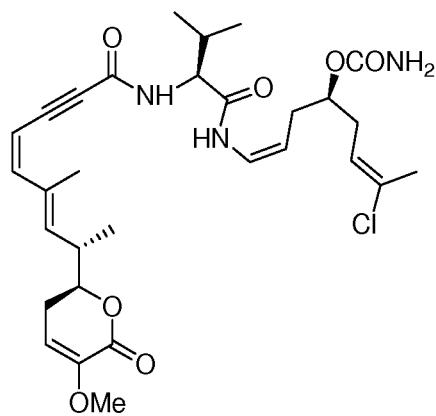
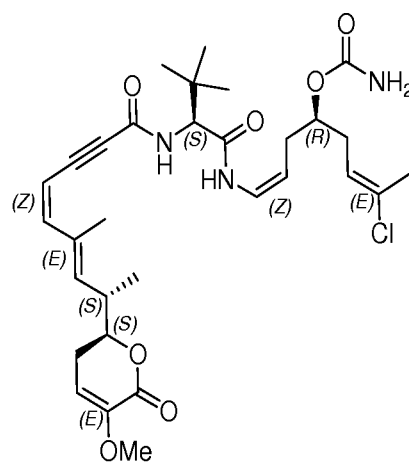
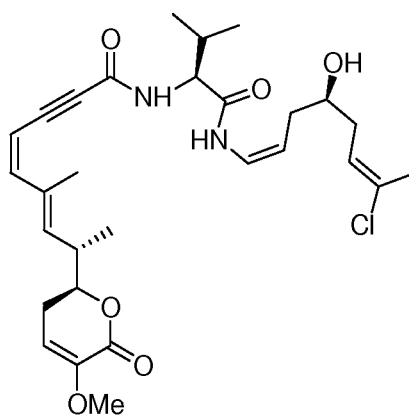


,

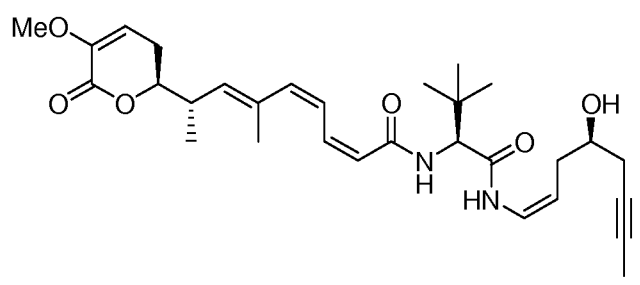
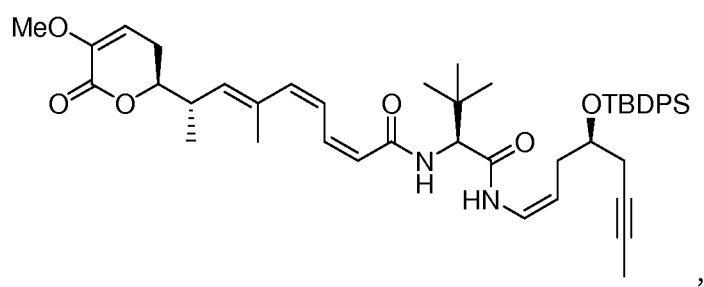
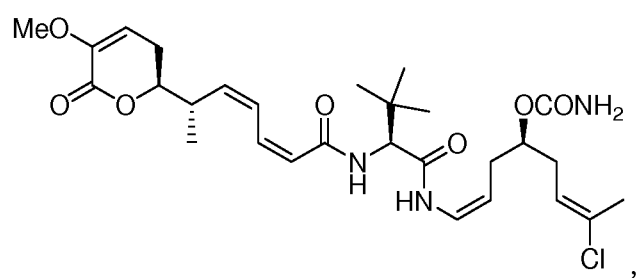
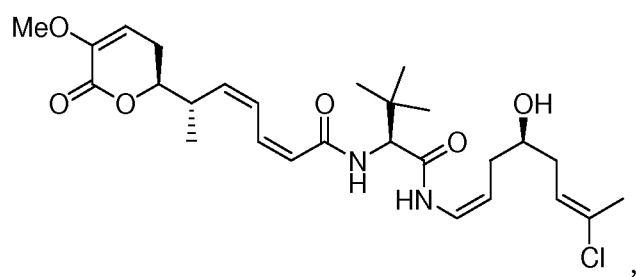


,

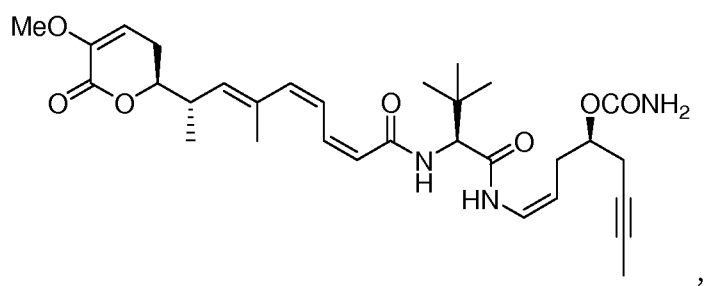
171



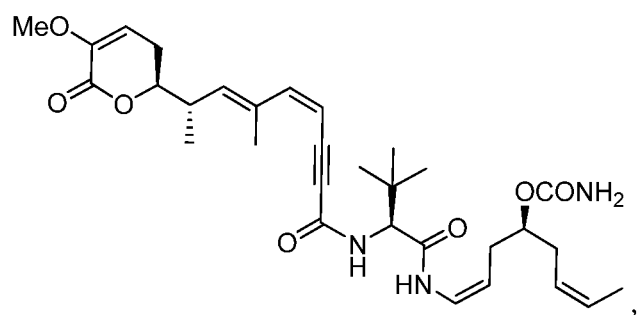
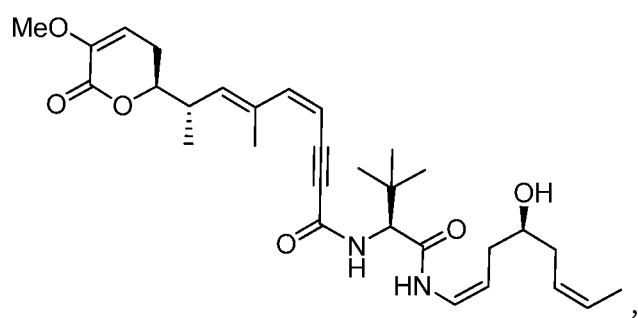
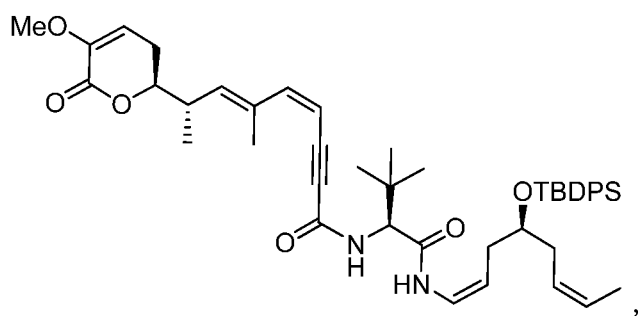
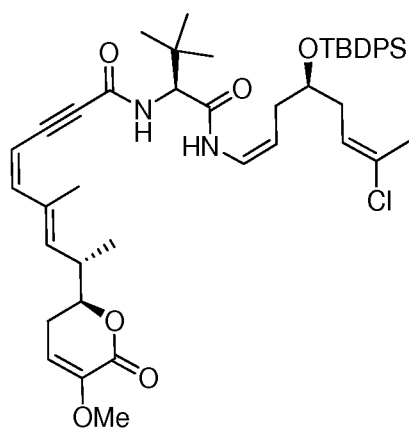
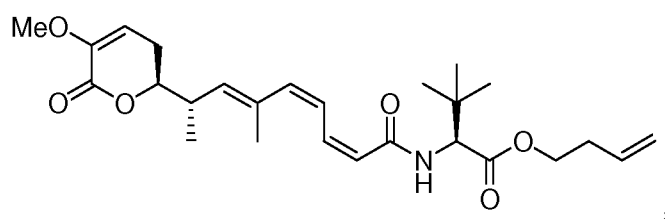
172

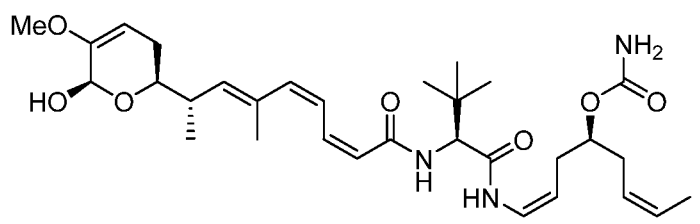
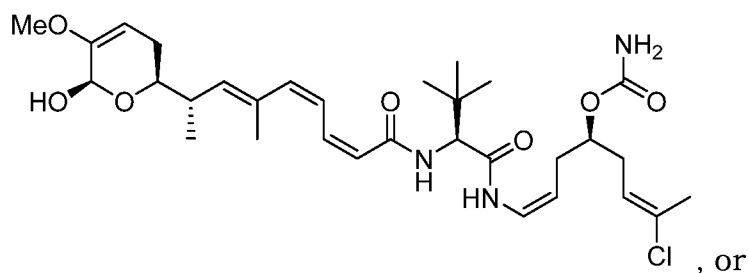


5



173





5

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

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

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

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

26. Use of a compound according to any of claims 1 to 22, or pharmaceutically acceptable salts, tautomers, prodrugs or

stereoisomers thereof, in the preparation of a medicament for the treatment of cancer.

27. A method of treating any mammal, notably a human, affected by
5 cancer which comprises administering to the affected individual a therapeutically effective amount of a compound according to any of claims 1 to 22, or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof.-