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<b>(71) Applicant (for all designated States except US):</b>	<b>COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION</b> [AU/AU]; Limestone Avenue, Campbell, Australian Capital Territory 2612 (AU).	
<b>(72) Inventors; and</b>		
<b>(75) Inventors/Applicants (for US only):</b>	<b>GRAICHEN, Florian, Hans, Maximilian</b> [DE/AU]; 6/23 River Street, Richmond, Victoria 3121 (AU). <b>KYI, Stella</b> [AU/AU]; 20 Prospect Hill Crescent, Dandenong North, Victoria 3175	
<b>(54) Title:</b> CONJUGATED UNSATURATED COMPOUNDS		
<b>(57) Abstract:</b> The present invention relates to a class of conjugated unsaturated compounds, to a method of preparing such compounds, and to the polymerisation and bio-active uses of such compounds including their use as antimicrobial agents. The invention particularly relates to compounds containing three conjugated unsaturated moieties, at least two of which are yne moieties.		

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## CONJUGATED UNSATURATED COMPOUNDS

### FIELD OF THE INVENTION

- 5 The present invention relates to a class of conjugated unsaturated compounds, to a method of preparing such compounds, and to the polymerisation and bio-active uses of such compounds. The invention particularly relates to compounds containing three conjugated unsaturated moieties, at least two of which are yne moieties.

### 10 BACKGROUND OF THE INVENTION

Compounds containing three conjugated unsaturated moieties are known to exhibit an array of interesting properties. For example, a range of compounds comprising a conjugated yne-ene-yne moiety, so called enediyne compounds have been shown to exhibit 15 potent antibiotic and anti-cancer properties. The yne-ene-yne moiety in such compounds is often called a "warhead" due to its ability to cyclize, forming a benzene ring structure via a highly reactive 1,4 benzeniod diradical intermediate. This diradical intermediate is believed to promote the oxidative cleavage of DNA, which in turn is believed to give rise to the potent biological activity of such compounds.

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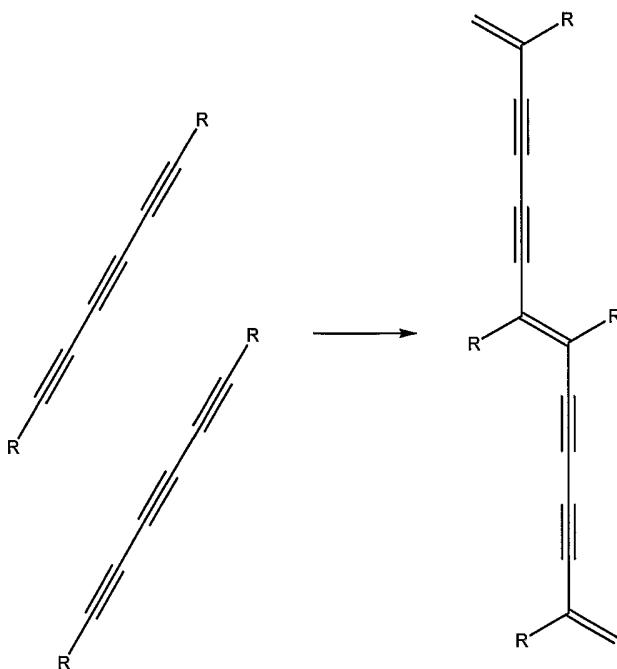
Other compounds containing three unsaturated conjugated moieties, such as ene-yne-yne, yne-yne-ene and yne-yne-yne moieties, are also known to exhibit a diverse range of biological activities including cytotoxicity, antimicrobial and herbicidal. However, unlike their yne-ene-yne counterparts, the mechanism by which compounds containing these 25 moieties act upon biological systems is largely unknown.

In addition to presenting biological activity, compounds containing conjugated yne moieties have been employed as monomers in preparing polymeric materials. For example, polymerisation of conjugated diyne compounds can provide polydiacetylenes 30 (PDA's) having highly aligned conjugated ene-yne-ene polymer backbones structured in the form of, for example, bulk single crystals, vesicles, and mono and multi layer films.

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PDA's have been found to exhibit a number of unique properties, the most notable and widely studied of which is their ability to undergo dramatic chromogenic transitions upon being subjected to various stimuli, such as the binding of chemical or biological entities to the polymer structure (affinochromism/biochromism), the exposure to electromagnetic radiation (photochromism), the exposure to heat (thermochromism), the application of stress (mechanochromism), and the exposure to a different chemical environment (chemochromism).

The polymerisation of triyne compounds (see Scheme 1 below) can also give rise to a  
10 unique class of polymeric materials known as polytriacetylenes (PTA's).



**Scheme 1:** A simplified schematic representation of the polymerisation of a conjugated  
15 triyne compound, where R represents an organic substituent.

Unlike the polymerisation of most unsaturated monomers, the polymerisation of conjugated yne moieties to form polyacetylenes occurs via topochemical polymerisation in the solid state. In other words, the polymerisation requires the ordered packing of the  
20 monomers so as to present the yne moieties in an appropriate spatial arrangement. Such

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monomers will typically require specific end groups (often referred to as the "head" and "tail" of the monomer) that facilitate the alignment of the monomers to achieve the required packing. For example, a monomer such as 4,6,8-dodecatriyne-1,12-dioic acid can self assemble to provide the requisite alignment of the yne moieties to be polymerised into  
 5 a PTA. In that case, the carboxyl head and tail of the monomer are believed to facilitate its alignment into a suitably ordered packing arrangement. As with PDA's, PTA's are conjugated unsaturated polymers with a delocalised  $\pi$  system along the polymer backbone. This structural feature imparts special properties to these compounds making them particularly attractive candidates for the development into advanced materials.

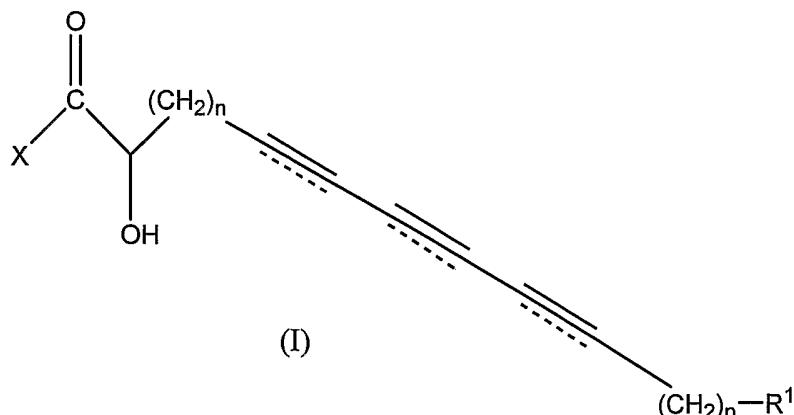
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From the foregoing, it can be seen that compounds comprising three conjugated unsaturated moieties may be utilised in numerous applications. It would therefore be desirable to provide new compounds comprising three conjugated unsaturated moieties that may add further versatility to this general class of compound.

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### SUMMARY OF THE INVENTION

The present invention provides a compound of general formula (I)



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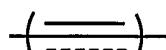
wherein X is OR<sup>2</sup> or NR<sup>2</sup>R<sup>3</sup>, where R<sup>2</sup> and R<sup>3</sup> are each independently selected from H and an organic substituent or form together with N a heterocyclyl substituent;

R<sup>1</sup> is selected from H and an organic substituent;

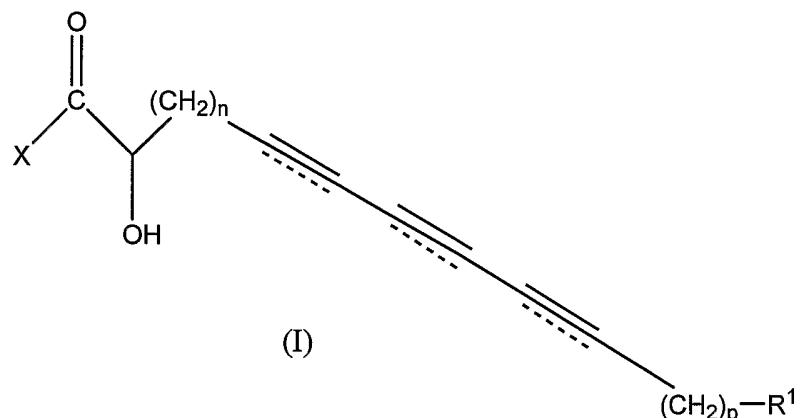
25 n is an integer from 2 to 15;

p is an integer from 0 to 15; and

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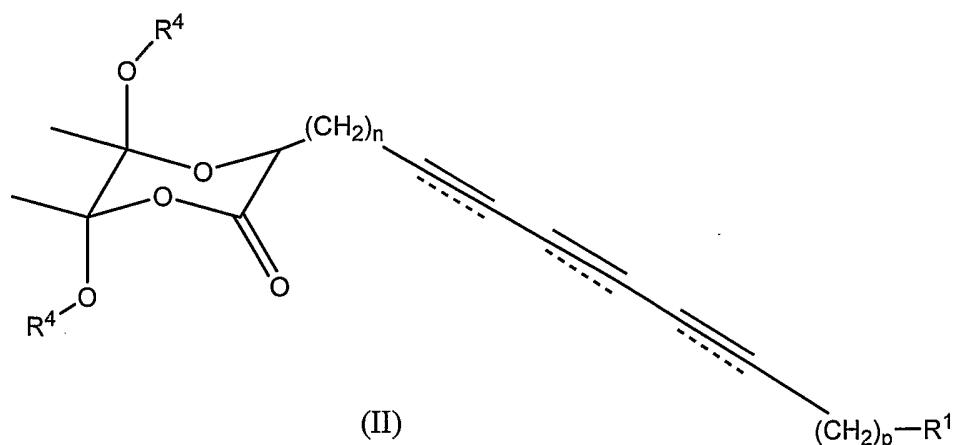
each  group represents a double or triple bond with at least two of such groups being triple bonds.

5 The present invention further provides a method of preparing a compound of general formula (I)



said method comprising the diacetal deprotection of a compound of general formula (II)

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wherein X is OR<sup>2</sup> or NR<sup>2</sup>R<sup>3</sup>, where R<sup>2</sup> and R<sup>3</sup> are each independently selected from H and an organic substituent or form together with N a heterocyclyl substituent;

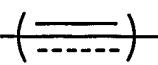
15 R<sup>1</sup> is selected from H and an organic substituent;

R<sup>4</sup> is selected from H and an organic substituent;

n is an integer from 2 to 15;

p is an integer from 0 to 15; and

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each  group represents a double or triple bond with at least two of such groups being triple bonds.

- 5 Compounds of general formula (II), where n is an integer from 1 to 15 or 2 to 15 and p, R<sup>1</sup> and R<sup>4</sup> are as herein defined, are believed to be novel in their own right and therefore represent a further aspect of the invention.

In some embodiments of the invention, n in the general formula of compounds in accordance with the invention is preferably an integer from 3 to 15, 4 to 15, or 5 to 15.

In some embodiments of the invention, p in the general formula of compounds in accordance with the invention is 0. Where p is 0, R<sup>1</sup> in such compounds may be an optionally substituted alkyl group, for example an optionally substituted C<sub>1</sub> to C<sub>18</sub> alkyl group, or a C<sub>1</sub> to C<sub>18</sub> alkyl group. In that case, it may be, and in some embodiments is, preferable that n in such compounds is an integer ranging from 3 to 15, 4 to 15, or 5 to 15.

In one embodiment of the invention, relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>- moiety, compounds in accordance with the invention have an yne-yne-yne structure (i.e. ...-(CH<sub>2</sub>)<sub>n</sub>-yne-yne-yne-...).

In a further embodiment of the invention, relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>- moiety, compounds in accordance with the invention have an yne-yne-ene structure (i.e. ...-(CH<sub>2</sub>)<sub>n</sub>-yne-yne-ene-...).

25 In another embodiment of the invention, relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>- moiety, compounds in accordance with the invention have an ene-yne-yne structure (i.e. ...-(CH<sub>2</sub>)<sub>n</sub>-ene-yne-yne-...).

30 In a further embodiment of the invention, relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>- moiety, compounds in accordance with the invention have an yne-ene-yne structure (i.e. ...-

(CH<sub>2</sub>)<sub>n</sub>-yne-ene-yne-...).

Without wishing to be limited by theory, it is believed that locating a hydroxyl substituent in the  $\alpha$  (i.e. -2-) position relative to the carbonyl moiety in the structure of general formula 5 (I) may provide the conjugated unsaturated compounds with further utility. In particular, it is believed that the  $\alpha$ -OH substituent may give rise to hydrogen bonding interactions that lead to new and/or improved applications for such compounds. For example, the hydrogen bonding function and the increased hydrophilicity provided by the  $\alpha$ -OH substituent is expected to provide new and/or enhanced interactions with biological systems. The unique 10 structure of compounds of general formula (II) is also expected to provide new and/or enhanced interactions with biological systems.

The present invention therefore also provides bio-active compositions and applications based on the compounds in accordance with the invention, further details of which are 15 described below.

The  $\alpha$ -OH substituent in compounds of general formula (I) may also provide a hydrogen bonding function that influences the manner in which compounds of formula (I) can self assemble and subsequently be polymerised. The influence of hydrogen bonding provided 20 by the  $\alpha$ -OH substituent is expected to vary with different compounds. Thus,  $\alpha$ -OH substituent may facilitate the formation of unique multi-dimensional packing arrangements relative to a conjugated compound absent the  $\alpha$ -OH substituent. The  $\alpha$ -OH substituent may also promote self assembly in conjugated compounds that would not otherwise be amenable to forming such a structure, or even enhance the integrity of an otherwise 25 unstable self assembled structure. The unique structure of compounds of general formula (II) may also facilitate self assembly of the compounds and their subsequent polymerisation. Triyne compounds of general formulae (I) and (II) are preferred for preparing such polymers.

30 The present invention therefore further provides polymers and a method of preparing the same based on compounds in accordance with the invention, details of which are described

below.

Other aspects of the invention are also described below.

## 5 DETAILED DESCRIPTION OF THE INVENTION

Substituents R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> of the general formulae described herein are each independently selected from H and any organic substituent. R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may each be independently selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl. R<sup>1</sup> may be further selected from optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted alkylthio, optionally substituted alkynylthio, optionally substituted alkynylthio, optionally substituted arylthio, optionally substituted acyl, sulfoxide, sulfonyl, sulfonamide, amino, amido, carboxy ester, amino acid, and a peptide.

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may also each be independently selected from H, optionally substituted C<sub>1</sub> to C<sub>18</sub> alkyl, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkenyl, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkynyl, optionally substituted C<sub>6</sub> to C<sub>18</sub> aryl, optionally substituted C<sub>3</sub> to C<sub>18</sub> carbocyclyl, optionally substituted C<sub>3</sub> to C<sub>18</sub> heterocyclyl, and optionally substituted C<sub>3</sub> to C<sub>18</sub> heteroaryl. R<sup>1</sup> may be further selected from optionally substituted C<sub>1</sub> to C<sub>18</sub> alkoxy, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkenoxy, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkynoxy, optionally substituted C<sub>6</sub> to C<sub>18</sub> aryloxy, optionally substituted C<sub>1</sub> to C<sub>18</sub> acyloxy, optionally substituted C<sub>1</sub> to C<sub>18</sub> alkylthio, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkynylthio, optionally substituted C<sub>2</sub> to C<sub>18</sub> alkynylthio, optionally substituted C<sub>6</sub> to C<sub>18</sub> arylthio, optionally substituted C<sub>1</sub> to C<sub>18</sub> acyl, sulfoxide, sulfonyl, sulfonamide, amino, amido, carboxy ester, amino acid, and a peptide.

30

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> may also each be independently selected from H, optionally substituted C<sub>1</sub> to

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C<sub>18</sub> alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted naphthyl, optionally substituted anthracenyl, optionally substituted pyridyl, optionally substituted pyrrolyl, optionally substituted thienyl, and optionally substituted furanyl.

5

Where X = NR<sup>2</sup>R<sup>3</sup>, R<sup>2</sup> and R<sup>3</sup> may form together with the N atom a heterocyclyl substituent. The heterocyclyl substituent may be optionally substituted. The heterocyclyl substituent may, for example, be an optionally substituted C<sub>3</sub> to C<sub>20</sub> heterocyclyl substituent.

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As used herein, the term "alkyl", used either alone or in compound words denotes straight chain, branched or cyclic alkyl, preferably C<sub>1-20</sub> alkyl, e.g. C<sub>1-10</sub> or C<sub>1-6</sub>. Examples of straight chain and branched alkyl include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethyl-pentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like. Where an alkyl group is referred to generally as "propyl", "butyl" etc, it will be understood that this can refer to any of straight, branched and cyclic isomers where appropriate. An

alkyl group may be optionally substituted by one or more optional substituents as herein defined.

The term "alkenyl" as used herein denotes groups formed from straight chain, branched or 5 cyclic hydrocarbon residues containing at least one carbon to carbon double bond including ethylenically mono-, di- or polyunsaturated alkyl or cycloalkyl groups as previously defined, preferably C<sub>2-20</sub> alkenyl (e.g. C<sub>2-10</sub> or C<sub>2-6</sub>). Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 10 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl. An alkenyl group may be optionally substituted by one or more optional substituents as herein defined.

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As used herein the term "alkynyl" denotes groups formed from straight chain, branched or cyclic hydrocarbon residues containing at least one carbon-carbon triple bond including ethylenically mono-, di- or polyunsaturated alkyl or cycloalkyl groups as previously defined. Unless the number of carbon atoms is specified the term preferably refers to C<sub>2-20</sub> 20 alkynyl (e.g. C<sub>2-10</sub> or C<sub>2-6</sub>). Examples include ethynyl, 1-propynyl, 2-propynyl, and butynyl isomers, and pentynyl isomers. An alkynyl group may be optionally substituted by one or more optional substituents as herein defined.

The term "halogen" ("halo") denotes fluorine, chlorine, bromine or iodine (fluoro, chloro, 25 bromo or iodo). Preferred halogens are chlorine, bromine or iodine.

The term "aryl" (or "carboaryl") denotes any of single, polynuclear, conjugated and fused residues of aromatic hydrocarbon ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, 30 dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl,

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pyrenyl, idenyl, azulenyl, chrysanyl. Preferred aryl include phenyl and naphthyl. An aryl group may be optionally substituted by one or more optional substituents as herein defined.

The term "carbocyclyl" includes any of non-aromatic monocyclic, polycyclic, fused or conjugated hydrocarbon residues, preferably C<sub>3-20</sub> (e.g. C<sub>3-10</sub> or C<sub>3-8</sub>). The rings may be saturated, e.g. cycloalkyl, or may possess one or more double bonds (cycloalkenyl) and/or one or more triple bonds (cycloalkynyl). Particularly preferred carbocyclyl moieties are 5-6-membered or 9-10 membered ring systems. Suitable examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopentenyl, cyclohexenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cyclooctatetraenyl, indanyl, decalinyl and indenyl.

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The term "heterocyclyl" when used alone or in compound words includes any of monocyclic, polycyclic, fused or conjugated hydrocarbon residues, preferably C<sub>3-20</sub> (e.g. C<sub>3-10</sub> or C<sub>3-8</sub>) wherein one or more carbon atoms are replaced by a heteroatom so as to provide a non-aromatic residue. Suitable heteroatoms include O, N, S, P and Se, particularly O, N and S. Where two or more carbon atoms are replaced, this may be by two or more of the same heteroatom or by different heteroatoms. The heterocyclyl group may be saturated or partially unsaturated, i.e. possess one or more double bonds. Particularly preferred heterocyclyl are 5-6 and 9-10 membered heterocyclyl. Suitable examples of heterocyclyl groups may include azridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 2H-pyrrolyl, pyrrolidinyl, pyrrolinyl, piperidyl, piperazinyl, morpholinyl, indolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, thiomorpholinyl, dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrrolyl, tetrahydrothiophenyl, pyrazolinyl, dioxalanyl, thiazolidinyl, isoxazolidinyl, dihydropyranyl, oxazinyl, thiazinyl, thiomorpholinyl, oxathianyl, dithianyl, trioxanyl, thiadiazinyl, dithiazinyl, trithianyl, azepinyl, oxepinyl, thiepinyl, indenyl, indanyl, 3H-indolyl, isoindolinyl, 4H-quinolazinyl, chromenyl, chromanyl, isochromanyl, pyranyl and dihydropyranyl.

30 The term "heteroaryl" includes any of monocyclic, polycyclic, fused or conjugated hydrocarbon residues, wherein one or more carbon atoms are replaced by a heteroatom so

as to provide an aromatic residue. Preferred heteroaryl have 3-20 ring atoms, e.g. 3-10. Particularly preferred heteroaryl are 5-6 and 9-10 membered bicyclic ring systems. Suitable heteroatoms include, O, N, S, P and Se, particularly O, N and S. Where two or more carbon atoms are replaced, this may be by two or more of the same heteroatom or by different heteroatoms. Suitable examples of heteroaryl groups may include pyridyl, pyrrolyl, thienyl, imidazolyl, furanyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, quinolyl, isoquinolyl, phthalazinyl, 1,5-naphthyridinyl, quinozalinyl, quinazolinyl, quinolinyl, oxazolyl, thiazolyl, isothiazolyl, isoxazolyl, triazolyl, 10 oxadiazolyl, oxatriazolyl, triazinyl, and furazanyl.

The term "acyl" either alone or in compound words denotes a group containing the moiety C=O (and not being a carboxylic acid, ester or amide) Preferred acyl includes C(O)-R<sup>x</sup>, wherein R<sup>x</sup> is hydrogen or an alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl residue. Examples of acyl include formyl, straight chain or branched alkanoyl (e.g. C<sub>1-20</sub>) such as, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as 15 cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl]; aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, 20 phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aryloxyalkanoyl such as phenoxyacetyl and phenoxypropionyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and naphtylsulfonyl; heterocycliccarbonyl; 25 heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl;

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heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolyglyoxyloyl and thienylglyoxyloyl. The R<sup>x</sup> residue may be optionally substituted as described herein.

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The term "sulfoxide", either alone or in a compound word, refers to a group  $-S(O)R^y$  wherein R<sup>y</sup> is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, carbocyclyl, and aralkyl. Examples of preferred R<sup>y</sup> include C<sub>1-20</sub>alkyl, phenyl and benzyl.

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The term "sulfonyl", either alone or in a compound word, refers to a group  $S(O)_2R^y$ , wherein R<sup>y</sup> is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, carbocyclyl and aralkyl. Examples of preferred R<sup>y</sup> include C<sub>1-20</sub>alkyl, phenyl and benzyl.

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The term "sulfonamide", either alone or in a compound word, refers to a group  $S(O)NR^yR^y$  wherein each R<sup>y</sup> is independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, carbocyclyl, and aralkyl. Examples of preferred R<sup>y</sup> include C<sub>1-20</sub>alkyl, phenyl and benzyl. In a preferred embodiment at least one R<sup>y</sup> is hydrogen. In 20 another form, both R<sup>y</sup> are hydrogen.

The term, "amino" is used here in its broadest sense as understood in the art and includes groups of the formula NR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> may be any independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, aralkyl, and 25 acyl. R<sup>A</sup> and R<sup>B</sup>, together with the nitrogen to which they are attached, may also form a monocyclic, or polycyclic ring system e.g. a 3-10 membered ring, particularly, 5-6 and 9-10 membered systems. Examples of "amino" include NH<sub>2</sub>, NHalkyl (e.g. C<sub>1-20</sub>alkyl), NHaryl (e.g. NHphenyl), NHaralkyl (e.g. NHbenzyl), NHacyl (e.g. NHC(O)C<sub>1-20</sub>alkyl, NHC(O)phenyl), Nalkylalkyl (wherein each alkyl, for example C<sub>1-20</sub>, may be the same or 30 different) and 5 or 6 membered rings, optionally containing one or more same or different heteroatoms (e.g. O, N and S).

- The term "amido" is used here in its broadest sense as understood in the art and includes groups having the formula  $C(O)NR^A R^B$ , wherein  $R^A$  and  $R^B$  are as defined as above. Examples of amido include  $C(O)NH_2$ ,  $C(O)NHalkyl$  (e.g.  $C_{1-20}alkyl$ ),  $C(O)NHaryl$  (e.g. 5  $C(O)NHphenyl$ ),  $C(O)NHaralkyl$  (e.g.  $C(O)NHbenzyl$ ),  $C(O)NHacyl$  (e.g.  $C(O)NHC(O)C_{1-20}alkyl$ ,  $C(O)NHC(O)phenyl$ ),  $C(O)Nalkylalkyl$  (wherein each alkyl, for example  $C_{1-20}$ , may be the same or different) and 5 or 6 membered rings, optionally containing one or more same or different heteroatoms (e.g. O, N and S).
- 10 The term "carboxy ester" is used here in its broadest sense as understood in the art and includes groups having the formula  $CO_2R^Z$ , wherein  $R^Z$  may be selected from groups including alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heteroaryl, heterocyclyl, aralkyl, and acyl. Examples of carboxy ester include  $CO_2C_{1-20}alkyl$ ,  $CO_2aryl$  (e.g..  $CO_2phenyl$ ),  $CO_2aralkyl$  (e.g.  $CO_2benzyl$ ). 15
- In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one, two, three or more of organic and inorganic groups, including those selected from: alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, heteroaryl, acyl, aralkyl, alkaryl, 20 alkheterocyclyl, alk heteroaryl, alk carbocyclyl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, halocarbocyclyl, halo heterocyclyl, halo heteroaryl, halo acyl, halo aryalkyl, hydroxy, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycarbocyclyl, hydroxyaryl, hydroxyheterocyclyl, hydroxyheteroaryl, hydroxy acyl, hydroxy aralkyl, alkoxyalkyl, alkoxyalkenyl, alkoxyalkynyl, alkoxy carbocyclyl, alkoxyaryl, 25 alkoxyheterocyclyl, alkoxyheteroaryl, alkoxy acyl, alkoxy aralkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, carbocyclyoxy, aralkyloxy, heteroaryloxy, heterocyclyoxy, acyloxy, haloalkoxy, haloalkenyloxy, haloalkynyloxy, haloaryloxy, halocarbocyclyoxy, haloaralkyloxy, halo heteroaryloxy, halo heterocyclyoxy, halo acyloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitro heterocyclyl, nitro heteroaryl, nitro carbocyclyl, 30 nitro acyl, nitro aralkyl, amino ( $NH_2$ ), alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, aralkylamino, diaralkylamino, acylamino,

diacylamino, heterocyclamino, heteroarylarnino, carboxy, carboxyester, amido, alkylsulphonyloxy, arylsulphenyloxy, alkylsulphenyl, arylsulphenyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, aralkylthio, carbocyclylthio, heterocyclylthio, heteroarylthio, acylthio, sulfoxide, sulfonyl, sulfonamide, aminoalkyl, aminoalkenyl, 5 aminoalkynyl, aminocarbocyclyl, aminoaryl, aminoheterocyclyl, aminoheteroaryl, aminoacyl, aminoaralkyl, thioalkyl, thioalkenyl, thioalkynyl, thiocarbocyclyl, thioaryl, thioheterocyclyl, thioheteroaryl, thioacyl, thioaralkyl, carboxyalkyl, carboxyalkenyl, carboxyalkynyl, carboxycarbocyclyl, carboxyaryl, carboxyheterocyclyl, carboxyheteroaryl, carboxyacetyl, carboxyaralkyl, carboxyesteralkyl, carboxyesteralkenyl, carboxyesteralkynyl, 10 carboxyestercarbocyclyl, carboxyesteraryl, carboxyesterheterocyclyl, carboxyesterheteroaryl, carboxyesteracyl, carboxyesteraralkyl, amidoalkyl, amidoalkenyl, amidoalkynyl, amidocarbocyclyl, amidoaryl, amidoheterocyclyl, amidoheteroaryl, amidoacyl, amidoaralkyl, formylalkyl, formylalkenyl, formylalkynyl, formylcarbocyclyl, formylaryl, formylheterocyclyl, formylheteroaryl, formylacyl, formylaralkyl, acylalkyl, 15 acylalkenyl, acylalkynyl, acylcarbocyclyl, acylaryl, acylheterocyclyl, acylheteroaryl, acylacyl, acylaralkyl, sulfoxidealkyl, sulfoxidealkenyl, sulfoxidealkynyl, sulfoxidecarbocyclyl, sulfoxidearyl, sulfoxideheterocyclyl, sulfoxideheteroaryl, sulfoxideacyl, sulfoxidearalkyl, sulfonylalkyl, sulfonylalkenyl, sulfonylalkynyl, sulfonylcarbocyclyl, sulfonylaryl, sulfonylheterocyclyl, sulfonylheteroaryl, sulfonylacyl, 20 sulfonylaralkyl, sulfonamidoalkyl, sulfonamidoalkenyl, sulfonamidoalkynyl, sulfonamidocarbocyclyl, sulfonamidoaryl, sulfonamidoheterocyclyl, sulfonamidoheteroaryl, sulfonamidoacyl, sulfonamidoaralkyl, nitroalkyl, nitroalkenyl, nitroalkynyl, nitrocarbocyclyl, nitroaryl, nitroheterocyclyl, nitroheteroaryl, nitroacyl, nitroaralkyl, cyano, sulfate and phosphate groups. Optional substitution may also be taken 25 to refer to where a CH<sub>2</sub> group in a chain or ring is replaced by a group selected from -O-, -S-, -NR<sup>A</sup>-, -C(O)- (i.e. carbonyl), -C(O)O- (i.e. ester), and -C(O)NR<sup>A</sup>- (i.e. amide), where R<sup>A</sup> is as defined herein.

Preferred optional substituents include alkyl, (e.g. C<sub>1-6</sub> alkyl such as methyl, ethyl, propyl, 30 butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), hydroxyalkyl (e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl), alkoxyalkyl (e.g. methoxymethyl,

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methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl etc) alkoxy (e.g.. C<sub>1-6</sub> alkoxy such as methoxy, ethoxy, propoxy, buotoxy, cyclopropoxy, cyclobutoxy), halo, trifluoromethyl, trichloromethyl, tribromomethyl, hydroxy, phenyl (which itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy,  
5 haloC<sub>1-6</sub>alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), benzyl (wherein benzyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub> alkoxy, haloC<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), phenoxy (wherein phenyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, haloC<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), benzyloxy (wherein benzyl itself  
10 may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, haloC<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), amino, alkylamino (e.g. C<sub>1-6</sub> alkyl, such as methylamino, ethylamino, propylamino etc), dialkylamino (e.g. C<sub>1-6</sub> alkyl, such as dimethylamino, diethylamino, dipropylamino), acylamino (e.g. NHC(O)CH<sub>3</sub>), phenylamino (wherein phenyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo,  
15 hydroxy hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, haloC<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), nitro, formyl, -C(O)-alkyl (e.g. C<sub>1-6</sub> alkyl, such as acetyl), O-C(O)-alkyl (e.g. C<sub>1-6</sub> alkyl, such as acyloxy), benzoyl (wherein the phenyl group itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, haloC<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub>alkyl, and amino), replacement of CH<sub>2</sub> with C=O, CO<sub>2</sub>H, CO<sub>2</sub>alkyl  
20 (e.g. C<sub>1-6</sub> alkyl such as methyl ester, ethyl ester, propyl ester, butyl ester), CO<sub>2</sub>phenyl (wherein phenyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyl C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo C<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), CONH<sub>2</sub>, CONHphenyl (wherein phenyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy, hydroxyl C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo C<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub>  
25 alkyl, and amino), CONHbenzyl (wherein benzyl itself may be further substituted e.g., by C<sub>1-6</sub> alkyl, halo, hydroxy hydroxyl C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo C<sub>1-6</sub> alkyl, cyano, nitro OC(O)C<sub>1-6</sub> alkyl, and amino), CONHalkyl (e.g. C<sub>1-6</sub> alkyl such as methyl ester, ethyl ester, propyl ester, butyl amide) CONHdialkyl (e.g. C<sub>1-6</sub> alkyl) aminoalkyl (e.g., HN C<sub>1-6</sub> alkyl-, C<sub>1-6</sub>alkylHN-C<sub>1-6</sub> alkyl- and (C<sub>1-6</sub> alkyl)<sub>2</sub>N-C<sub>1-6</sub> alkyl-), thioalkyl (e.g., HS C<sub>1-6</sub> alkyl-),  
30 carboxyalkyl (e.g., HO<sub>2</sub>CC<sub>1-6</sub> alkyl-), carboxyesteralkyl (e.g., C<sub>1-6</sub> alkylO<sub>2</sub>CC<sub>1-6</sub> alkyl-), amidoalkyl (e.g., H<sub>2</sub>N(O)CC<sub>1-6</sub> alkyl-, H(C<sub>1-6</sub> alkyl)N(O)CC<sub>1-6</sub> alkyl-), formylalkyl (e.g.,

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OHCC<sub>1-6</sub>alkyl-), acylalkyl (e.g., C<sub>1-6</sub> alkyl(O)CC<sub>1-6</sub> alkyl-), nitroalkyl (e.g., O<sub>2</sub>NC<sub>1-6</sub> alkyl-), sulfoxidealkyl (e.g., R(O)SC<sub>1-6</sub> alkyl, such as C<sub>1-6</sub> alkyl(O)SC<sub>1-6</sub> alkyl-), sulfonylalkyl (e.g., R(O)<sub>2</sub>SC<sub>1-6</sub> alkyl- such as C<sub>1-6</sub> alkyl(O)<sub>2</sub>SC<sub>1-6</sub> alkyl-), sulfonamidoalkyl (e.g., <sub>2</sub>HRN(O)SC<sub>1-6</sub> alkyl, H(C<sub>1-6</sub> alkyl)N(O)SC<sub>1-6</sub> alkyl-).

5

The term "heteroatom" or "hetero" as used herein in its broadest sense refers to any atom other than a carbon atom which may be a member of a cyclic organic group. Particular examples of heteroatoms include nitrogen, oxygen, sulfur, phosphorous, boron, silicon, selenium and tellurium, more particularly nitrogen, oxygen and sulfur.

10

As used herein, the term "amino acid" refers to compounds having an amino group and a carboxylic acid group. The amino acid may be a naturally or non-naturally occurring and may be proteogenic or non-proteogenic. The amino acid may also be an L-amino acid, D-amino acid,  $\alpha$ -amino acid, or a  $\beta$ -amino acid.

15

Suitable naturally occurring proteogenic amino acids are shown in Table 1 together with their one letter and three letter codes.

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**Table 1:** List of naturally occurring proteogenic amino acids

Amino Acid	one letter code	three letter code
L-alanine	A	Ala
L-arginine	R	Arg
L-asparagine	N	Asn
L-aspartic acid	D	Asp
L-cysteine	C	Cys
L-glutamine	Q	Gln
L-glutamic acid	E	Glu
glycine	G	Gly
L-histidine	H	His
L-isoleucine.	I	Ile
L-leucine	L	Leu
L-lysine	K	Lys
L-methionine	M	Met
L-phenylalanine	F	Phe
L-proline	P	Pro
L-serine	S	Ser
L-threonine	T	Thr
L-tryptophan	W	Trp
L-tyrosine	Y	Tyr
L-valine	V	Val

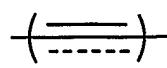
Suitable non-proteogenic or non-naturally occurring amino acids may be prepared by  
 5 techniques known in the art such as side chain modification or by total synthesis.

As used herein, the term "peptide" refers to any of various natural or synthetic compounds containing two or more amino acids linked by the carboxyl group of one amino acid to the amino group of another.

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Terms written as "[group]oxy" refer to a particular group when linked by oxygen, for example, the terms "alkoxy" or "alkyloxy", "alkenoxy" or "alkenyloxy", "alkynoxy" or alkynyloxy", "aryloxy" and "acyloxy", respectively, denote alkyl, alkenyl, alkynyl, aryl and acyl groups as hereinbefore defined when linked by oxygen. Terms written as 5 "[group]thio" refer to a particular group when linked by sulfur, for example, the terms "alkylthio", "alkenylthio", alkynylthio" and "arylthio", respectively, denote alkyl, alkenyl, alkynyl, aryl groups as hereinbefore defined when linked by sulfur. Similarly, terms written as "[groupA][group B]" refer to group A when linked by a divalent form of group B. For example, "[group A][alkyl]" refers to a particular group A (such as hydroxy, 10 amino, etc.) when linked by divalent alkyl, i.e. alkylene (e.g. hydroxyethyl is intended to denote HO-CH<sub>2</sub>-CH-).

Those skilled in the art will appreciate that compounds of general formulae (I) and (II) contain one chiral centre. Accordingly, general formulae (I) and (II) may give rise to 15 stereoisomers. Enantiomerically pure forms and racemic mixtures of compounds of general formulae (I) and (II) are contemplated by the present invention.

As indicated above, each  group in general formulae (I) and (II) represents a double or triple bond, with at least two of such groups being triple bonds. Those skilled in 20 the art will appreciate that the conjugated structure of the three  groups in these formulae can provide for a yne-yne-yne, yne-yne-ene, ene-yne-yne, and yne-ene-yne type structure. Those skilled in the art will also appreciate that cis and trans isomers can present in those conjugated structures that include an -ene- moiety. Such cis and trans isomers are intended to be embraced by compounds in accordance with the invention.

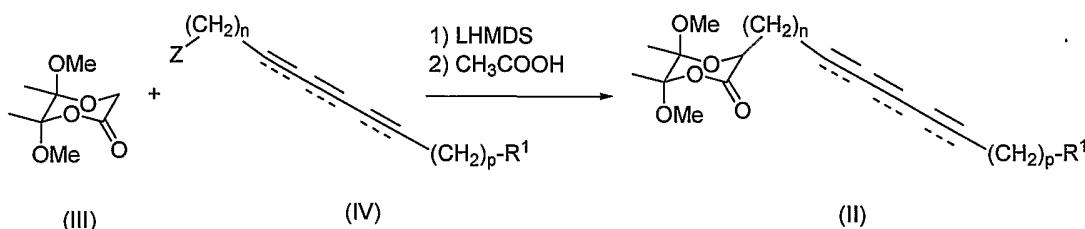
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In accordance with one embodiment of the invention, compounds of general formula (I) are prepared by the diacetal deprotection of a compound of general formula (II). By the expression "diacetal deprotection" is meant that the diacetal moiety of general formula (II) is involved in a reaction with a reagent that gives rise to the X-C(O)-CH(OH)- moiety of 30 general formula (I).

- Those skilled in the art will appreciate that the conditions employed to promote the diacetal deprotection will dictate the functionality of substituent X in general formula (I). Thus, acid mediated diacetal deprotection can provide for the acid form of general formula 5 (I) (i.e. where X = OH). For example, a compound of general formula (II) may be reacted with trifluoroacetic acid (TFA) in water. Diacetal deprotection using an appropriate alcohol R<sup>2</sup>-OH (where R<sup>2</sup> is as hereinbefore defined) can provide the ester form of general formula (I) (i.e. where X = OR<sup>2</sup>). In that case, it may be necessary to perform the reaction in the presence of a halo-silane such as trimethylsilylchloride. Diacetal deprotection using 10 an appropriate amine R<sup>2</sup>R<sup>3</sup>NH (where R<sup>2</sup> and R<sup>3</sup> are as hereinbefore defined) can provide for an amide form of general formula (I) (i.e. where X = NR<sup>2</sup>R<sup>3</sup>). In that case, it may be necessary to perform the reaction by activating the amine with a Grignard reagent such as i-PrMgCl. Preparing compounds of general formula (I) using this methodology therefore provides a relatively efficient pathway to produce a broad range of compounds falling 15 within the scope of general formula (I). As will be discussed in more detail below, this methodology also provides a convenient route for preparing enantiomerically pure compounds of general formula (I) through use of an enantiomerically pure butane-2,3-diacetal protected glycolic acid moiety.
- 20 Compounds of general formula (II) comprise a R<sup>4</sup> group attached to the pendant oxygen atoms of the diacetal moiety. In preparing compounds of general formula (II), those skilled in the art will appreciate that the R<sup>4</sup> groups function as protecting groups. Various protecting groups known to those skilled in the art may be employed. The protection groups may also be removed, for example to yield -OH groups.
- 25 Each R<sup>4</sup> group may, for example, be independently selected from H, optionally substituted alkyl, optionally substituted alkene, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted trialkylsilyl. In some embodiments each R<sup>4</sup> group is methyl.
- 30 Compounds of general formula (II) may be prepared using any suitable technique. One

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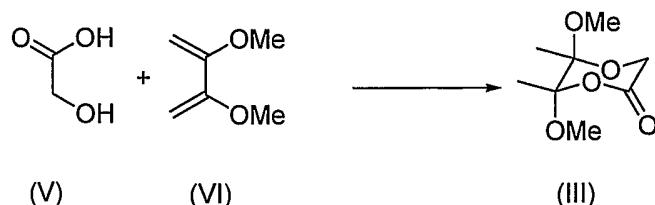
approach might involve the reaction sequences outlined below in Scheme 2 in which a compound of general formula (III) is alkylated with a halo unsaturated compound (preferably an iodo compound) of general formula (IV) using lithium bis(trimethylsilyl)amide (LHMDS) and excess electrophile according to a general procedure outlined in Org Biomol. Chem., 2004, 2, 3608 – 3617.



**Scheme 2:** Preparation of a compound of general formula (II) with PG = Me, where Z is a halogen,  $R^1$ , n and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

A compound of formula (III) may be prepared using any suitable technique. One approach might involve the reaction sequence outlined below in Scheme 3 in which glycolic acid (V) is protected with 2,3-dimethoxybutadiene (VI) in the presence of catalytic amounts of triphenylphosphine hydrobromide according to a general procedure outlined in Org. Biomol. Chem., 2004, 2, 3608 – 3617. 2,3-dimethoxybutadiene (V) may be obtained commercially or prepared using techniques known in the art such as that described in J. C. S. Perkin 1, 1979, 1893.

20



**Scheme 3:** Preparation of a compound of formula (III).

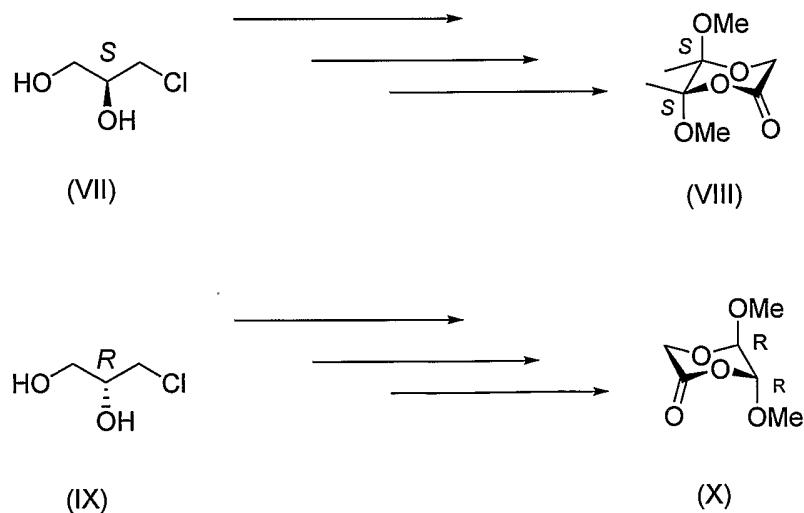
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One approach to preparing enantiomerically pure compounds of general formula (I) might involve a reaction sequence similar to that outlined in Scheme 2 above in which an enantiomerically pure form of butane-2,3-diacetal protected glycolic acid is alkylated with a halo unsaturated compound of general formula (IV). Diacetal deprotection of the 5 resulting alkylated product can then yield enantiomerically pure compounds of general formula (I).

Enantiomerically pure butane-2,3-diacetal protected glycolic acid may be prepared using any suitable technique. One approach might involve the reaction sequences outlined below 10 in Scheme 4 in which (S)-3-chloropropane-1,2-diol (VII) is converted in a three step synthesis to yield (S,S)butane-2,3-diacetal protected glycolic acid (VIII) according to a general procedure outlined in Org. Biomol. Chem., 2004, 2, 3608 – 3617. An analogous three step synthesis may be performed using (R)-3-chloropropane-1,2-diol (IX) to yield (R,R)butane-2,3-diacetal protected glycolic acid (X).

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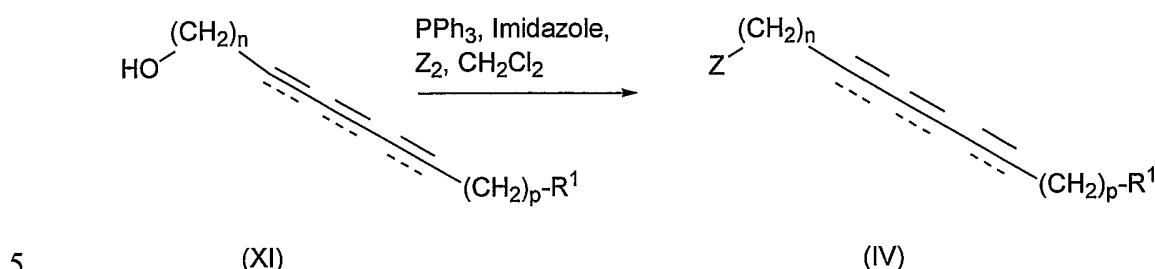
**Scheme 4:** Preparation of enantiomerically pure butane-2, 3-diacetal protected glycolic acids (VIII) and (X).

20

Compounds of general formula (IV) may be prepared using any suitable technique. One approach might involve the reaction sequence outlined below in Scheme 5 in which a compound of general formula (XI) is converted into its corresponding halo derivative by

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reacting it with triphenylphosphine, imidazole and halogen (Z) according to a general procedure outlined in J. Org. Chem. 2005, 70, 3898 – 3902. In that case, the halogen is preferably iodine.



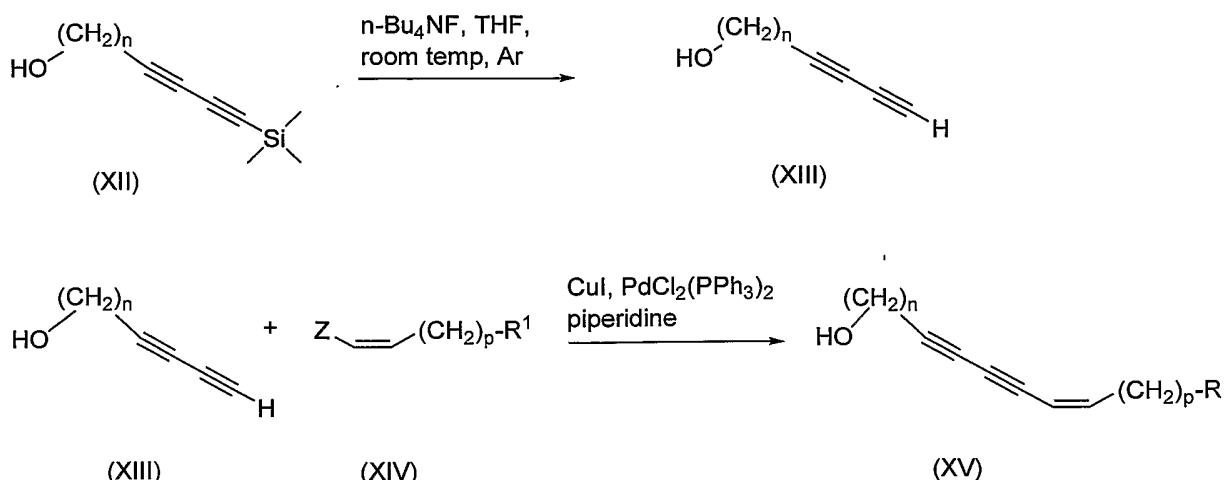
**Scheme 5:** Preparation of a compound of general formula (IV), where Z,  $R^1$ , n and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds of general formula (XI) may be prepared using any suitable technique. One approach to preparing the yne-yne-ene form of compounds of general formula (XI) with a cis configuration at the –ene moiety might involve the reaction sequence outlined below in Scheme 6 in which a compound of general formula (XII) is desilylated through reaction with tetrabutylammoniumfluoride in THF according to a general procedure outlined in J. Org. Chem., Vol. 53, No. 8, 1988, 1617. Reaction of the resulting compound (XIII) with a cis vinyl-halide (XIV) under Sonogashira cross coupling conditions [ $PdCl_2(PPh_3)_2$ , CuI, and piperidine] according to a general procedure outlined in Org. Lett., Vol. 5, No., 3725 – 20 3728, 2003 leads to compounds of general formula (XV) (i.e. the yne-yne-ene form of general formula (XI) with a cis configuration at the –ene moiety). The Z group in general formula (XIV) is preferably iodo.

One approach to preparing the yne-yne-ene form of compounds of general formula (XI) with a trans configuration at the –ene moiety might involve coupling a compound of general formula (XIII) with a trans vinyl halide (preferably a trans vinyl iodide) under conditions mentioned directly above or by using techniques known in the art such as

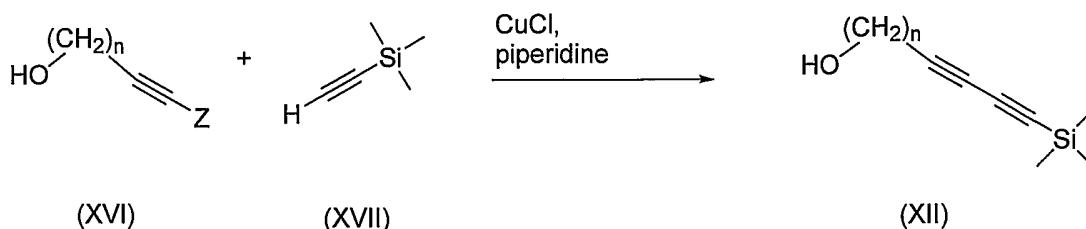
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described in Org. Lett., Vol. 3, No. 22, 3487 - 3490, 2001.



5 **Scheme 6:** Preparation of a compound of general formula (XV), where Z, R<sup>1</sup>, n and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds of general formula (XII) may be prepared using any suitable technique. One  
10 approach might involve the reaction sequence outlined below in Scheme 7 in which a compound of general formula (XVI) is coupled using an appropriate coupling reaction with a compound of general formula (XVII). The Z group in general formula (XVI) is preferably iodo. The coupling reaction may be performed according to a general procedure outlined in Org. Lett., Vol. 5, No. 20, 3725 – 3728, 2003 in which the  
15 compounds to be coupled are combined in degassed piperidine comprising copper chloride.

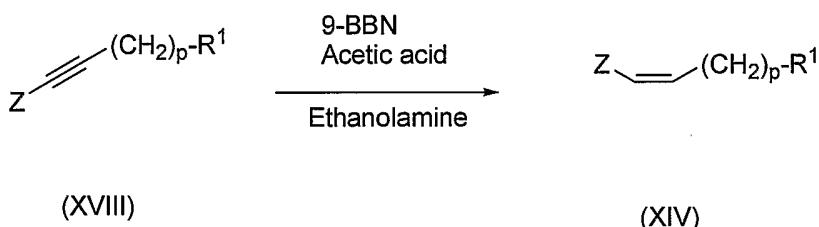


20 **Scheme 7:** Preparation of a compound of general formula (XII), where Z and n are as

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hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds of general formula (XIV) may be prepared using any suitable technique. One approach might involve the reaction sequence outlined below in Scheme 8 in which a compound of general formula (XVIII) is reduced with 9-BBN (9-borabicyclo [3.3.1] nonane) in THF according to a general procedure outlined in J. Org. Chem. 1989, 54, 6064 – 6067. The Z group in general formulas (XIV) and (XVIII) is preferably iodo. One approach to preparing compounds of general formula (XIV) with trans configuration at the –ene moiety might involve using techniques known in the art such as described in Org. Lett., Vol. 3, No. 19, 3029 – 3032, 2001.



**Scheme 8:** Preparation of a compound of general formula (XIV), where Z, R<sup>1</sup> and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds of general formula (XVI) and (XVIII) may be prepared using techniques well known in the art.

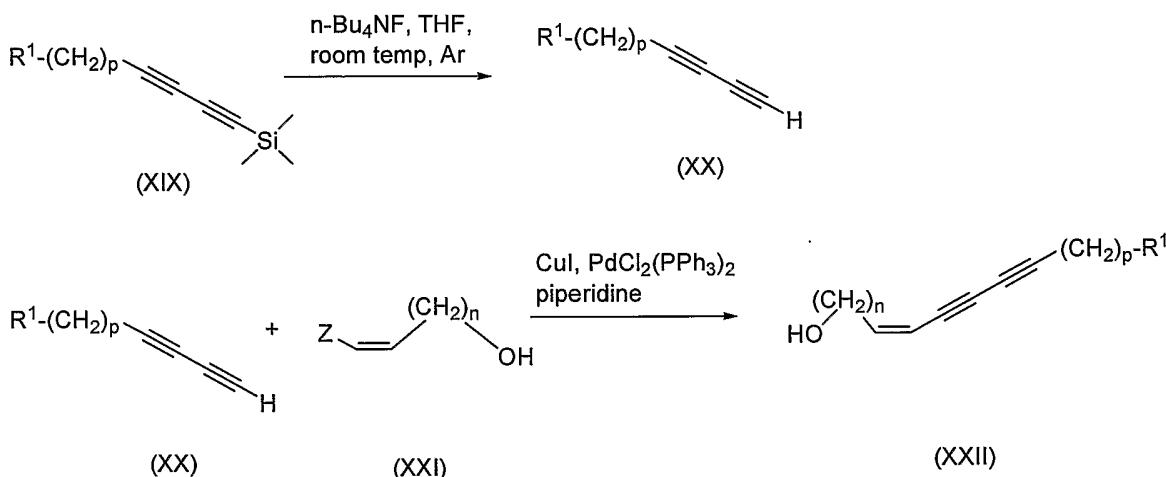
One approach to preparing the ene-yne-yne form of compounds of general formula (XI) with a cis-configuration at the –ene moiety might involve the reaction sequence outlined below in Scheme 9 in which a compound of general formula (XIX) is desilylated through reaction with tetrabutylammoniumfluoride in THF according to a general procedure outlined in J. Org. Chem., Vol. 53, No. 8, 1988, 1617. Reaction of the resulting compound (XX) with a cis halogen-compound (XXI) under Sonogashira cross coupling conditions [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI and piperidine] according to a general procedure outlined in Org. Lett.,

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Vol. 5, No. 20, 3725 – 3728, 2003, leads to compounds of general formula (XXII) (i.e. the ene-yne-yne form of general formula (XI) with a cis configuration at the –ene moiety). The Z group in general formula (XXI) is preferably iodo.

- 5 One approach to preparing the ene-yne-yne form of compounds of general formula (XI) with a trans configuration at the –ene moiety might involve coupling a compound of general formula (XX) with trans vinyl halide (preferably a trans vinyl iodide) under conditions mentioned directly above or by using techniques known in the art such as described in Org. Lett., Vol. 3, No. 19, 3029 – 3032, 2001.

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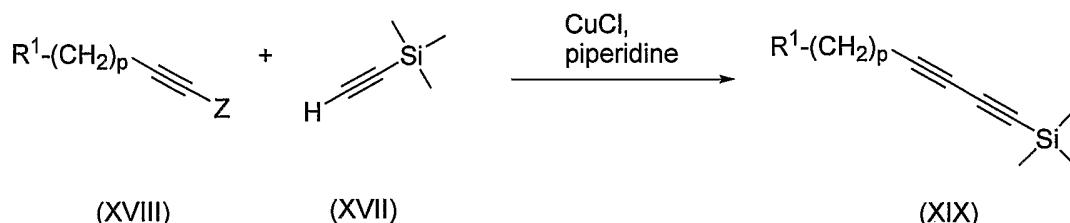


- Scheme 9:** Preparation of a compound of general formula (XXII), where  $Z$ ,  $R^1$ ,  $n$  and  $p$  are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds of general formula (XIX) may be prepared using any suitable technique. One approach might involve the reaction sequence outlined below in Scheme 10 in which a compound of general formula (XVIII) is coupled using an appropriate coupling reaction 15 with a compound of general formula (XVII). The  $Z$  group in general formula (XVIII) is preferably iodo. The coupling reaction may be performed according to a general procedure outlined in Org. Lett., Vol. 5, No. 20, 3725 – 3728, 2003 in which the compounds to be coupled are combined in degassed piperidine comprising copper chloride. Compounds of general formula (XVII), (XVIII) and (XXI) may be obtained

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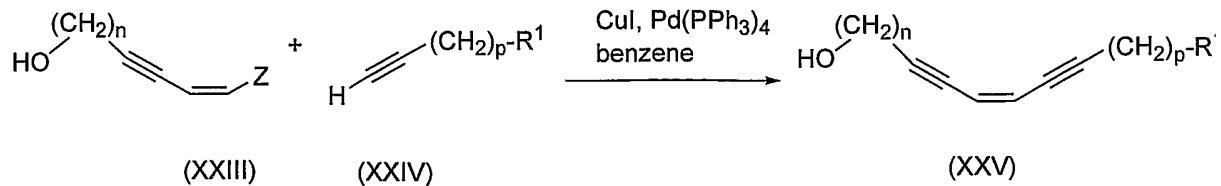
commercially or prepared using techniques well known in the art.



**Scheme 10:** Preparation of a compound of general formula (XIX), where Z,  $R^1$  and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

One approach to preparing the yne-ene-yne form of compounds of general formula (XI) with a cis configuration at the –ene moiety might involve the reaction sequence outlined below in Scheme 11 in which a compound of general formula (XXIII) with a cis configuration at the –ene moiety is treated with a terminal acetylene (XXIV) in the presence of  $Pd(PPh_3)_4$  and  $CuI$  in benzene according to a general procedure outlined in Tetrahedron Lett. 1984, 25, 6001-6004, to afford a compound of general formula (XXV) (i.e. the yne-ene-yne form of general formula (XI) with a cis configuration at the –ene moiety). The Z group in general formula (XXIII) is preferably chloro. Those skilled in the art will appreciate that the reaction Scheme 11 may be employed to prepare the trans form of general formula (XXV) simply by employing the trans form of a compound of general formula (XXIII). Compounds of general formula (XXIV) may be obtained commercially or can be prepared using techniques well known in the art.

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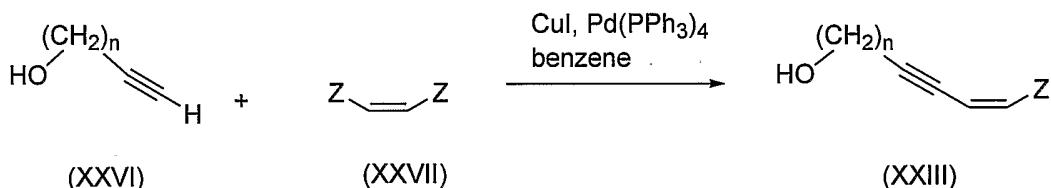


**Scheme 11:** Preparation of a compound of general formula (XXV), where Z,  $R^1$ , n and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

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Compounds of general formula (XXIII) in a cis or trans form may be prepared using any suitable technique. One approach to preparing the cis form of general formula (XXIII) might involve the reaction sequence outlined below in Scheme 12 in which a compound of general formula (XXVI) is treated with cis 1,2 dihaloethylene (XXVII) in the presence of 5 Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI in benzene according to a general procedure outlined in J. Org. Chem., Vol. 53, No. 11, 1988. The Z group in general formula (XXVII) is preferably chloro.

One approach to preparing the trans form of general formula (XXIII) might involve the reaction of trans 1, 2-dichloroethylene and a compound of general formula (XXVI) 10 according to a general procedure outlined in J. Org. Chem. 1988, 53, 2655 – 2657. Compounds of general formula (XXVI) and (XXVII) may be obtained commercially or can be prepared using techniques well known in the art.

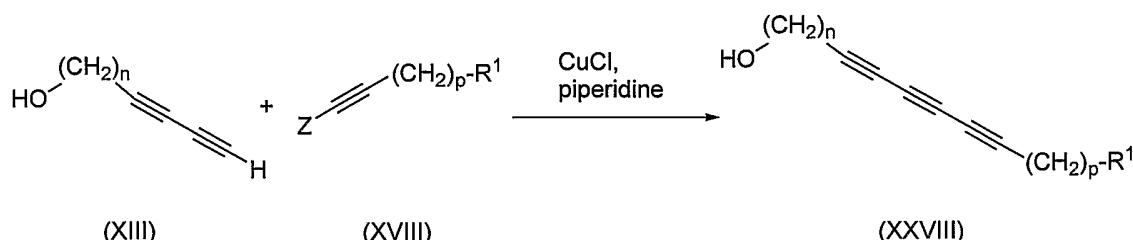


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**Scheme 12:** Preparation of a compound of general formula (XXIII) having a cis configuration at the –ene moiety, where Z and n are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

20

One approach to preparing the yne-yne-yne form of compounds of general formula (XI) might involve the reaction sequence outlined below in Scheme 13 in which a compound of general formula (XXIII) is coupled using an appropriate coupling reaction with a compound of general formula (XVIII) to afford a compound of general formula (XVIII) 25 (i.e. the yne-yne-yne form of general formula (XI)). The Z group in general formula (XVIII) is preferably iodo. The coupling reaction may be performed according to a general procedure outlined in Org. Lett., Vol. 5, No. 20, 3725 – 3728, 2003 in which the compounds to be coupled are combined in degassed piperidine comprising copper chloride.



**Scheme 13:** Preparation of a compound of general formula (XXVIII), where Z, R<sup>1</sup>, n and p are as hereinbefore defined, taking into account any limitations that may be placed on such groups under the reaction conditions employed.

Compounds in accordance with the invention are expected to exhibit a diverse array of bioactivity (i.e. interaction with a biological system to promote a desirable effect). For example, compounds in accordance with the invention have been found to exhibit antimicrobial activity.

By "antimicrobial activity" is meant an agent capable of destroying, inhibiting the growth of, or preventing the growth of microorganisms including bacteria, fungi, protozoae, viruses, yeasts, and algae. As used herein, "antimicrobial" includes, but is not limited to, antibacterials, that is, agents/compounds capable of destroying, inhibiting the growth of, or preventing the growth of bacteria; and antifungals, that is agents capable of destroying, inhibiting the growth of, or preventing the growth of a fungi.

Pathogenic microorganisms have a profound effect on human health and wellbeing. In particular, bacterial and fungal infections are known to cause a diverse array of human, animal or plant disorders. The identification of compounds having antimicrobial activity has been a long-standing and is a potentially never-ending goal of scientists, made all the more difficult by the ability microbes to attain resistance to known antimicrobial agents.

In the context of exhibiting anti-microbial properties, the compounds in accordance with the invention may be used in various applications. For example, the compounds may be used in horticultural and medicinal or pharmaceutical applications. The compounds may also be used to treat the surface of non-biological substrates, for example as an

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antimicrobial surface spray. When used in such applications, the compounds will typically be provided in the form of an antimicrobial composition.

The present invention therefore also provides an antimicrobial composition comprising a  
5 compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material.

It will be appreciated that the nature of the carrier material used in such antimicrobial  
10 compositions may vary depending upon the intended application of the composition. For example, when used in horticultural applications, the carrier material will generally be a plant-compatible carrier material, when used in surface treatment applications (e.g. in the form of an antimicrobial surface spray), the carrier material will typically be compatible with the surface that is to be treated, and when used in medicinal or pharmaceutical  
15 applications, the carrier material will typically be pharmacologically compatible with the intended recipient. By being "compatible" in this context is meant that the carrier material does not result in any degree of unacceptable deleterious effect. For example, in the case of medicinal or pharmaceutical applications, the carrier liquid will be selected such that it does not result in any degree of unacceptable toxicity, including allergenic responses and  
20 disease states in the intended recipient.

Those skilled in the art will be able determine a suitable carrier material for the intended application. The compositions may of course also comprise any other suitable additives.

25 In one embodiment, compounds in accordance with the invention may be used as antimicrobial agents in medicinal or pharmaceutical applications/compositions.

The present invention therefore also provides a method of treating a microbial infection in a subject, said method comprising administering to said subject an effective amount of a  
30 compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds.

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The method of treating a microbial infection in a subject in accordance with the invention will typically comprise administering to the subject a suitable antimicrobial composition in accordance with the invention. In that case, the suitable carrier material will be a pharmacologically compatible carrier material. This and other pharmaceutically acceptable adjuvants are discussed in more detail below.

For medicinal or pharmaceutical applications, the antimicrobial compositions in accordance with the invention will of course be suitable for administration to a subject. By the term "subject" is meant either an animal or human subject. By "animal" is meant primates, livestock animals (including cows, horses, sheep, pigs and goats), companion animals (including dogs, cats, rabbits and guinea pigs), and captive wild animals (including those commonly found in a zoo environment). Laboratory animals such as rabbits, mice, rats, guinea pigs and hamsters are also contemplated as they may provide a convenient test system. Preferably, the subject is a human subject.

15

By the composition or a compound of the invention being "suitable" for administration to a subject is meant that administration of the composition or compound to a subject will not result in any degree of unacceptable toxicity, including allergenic responses and disease states.

20

There is no particular limitation on the mode by which a compound or composition in accordance with the invention can be administered to a subject, but this will generally be by way of oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intrathecal, and intraspinal), inhalation (including vaporisation and nebulisation), topical, rectal and vaginal modes.

As used herein, "treating a microbial infection" can refer to either: prophylactic treatment (e.g. preventing or delaying the onset of the infection, or symptoms thereof, or otherwise diminishing the extent or severity of symptoms before symptoms of the infection are apparent); or therapeutic treatment (e.g. alleviation of one or more symptoms, or halting, reversing or otherwise slowing down the progression of one or more symptoms of the

infection or the severity thereof).

The compounds described herein may be administered in, as appropriate, a treatment or inhibitory effective amount. A treatment effective amount is intended to include an

5 amount which, when administered according to the desired dosing regimen, achieves a desired therapeutic effect, including one or more of: alleviating the symptoms of, preventing or delaying the onset of, inhibiting or slowing the progression of, or halting or reversing altogether the onset or progression of the particular infection being treated.

10 Suitable dosage amounts and dosing regimens to achieve this can be determined by the attending physician and may depend on the particular infection being treated, the severity of the infection as well the general age, health and weight of the subject.

Dosing may occur at intervals of minutes, hours, days, weeks, months or years or  
15 continuously over any one of these periods. Suitable dosages may lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. The dosage may be in the range of 1  $\mu$ g to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage may be in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment,  
20 the dosage may be in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another embodiment, the dosage may be in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per body weight per dosage.

Compounds in accordance with the invention may be administered in a single dose or a  
25 series of doses. While it is possible for such compounds to be administered alone, as described above it is preferable to present the compound(s) as a composition, preferably as a pharmaceutical composition, with one or more pharmaceutically accepted adjuvants.

The present invention therefore further relates to the use of a compound of general formula  
30 (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, in the manufacture of a medicament for treating a

microbial infection in a subject.

Formulation constituents of such compositions are well known to those skilled in the art, see for example, *Remington's Pharmaceutical Sciences*, 18<sup>th</sup> Edition, Mack Publishing, 5 1990. The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, anti-fungal and anti-bacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions may also include other supplementary physiological active agents.

10

The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions include those suitable for oral, rectal, nasal, topical (including dermal, buccal and sublingual), vaginal or parental (including subcutaneous, intramuscular, intravenous and 15 intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient 20 (i.e. compounds in accordance with the invention) with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active 25 ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine 30 the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. inert diluent), preservative disintegrant (e.g. sodium starch glycolate,

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- cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or
- 5 controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.
- 10 Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.
- 15 Compositions suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate,
- 20 polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. Transdermal patches may also be used to administer the compounds of the invention.
- Compositions for rectal administration may be presented as a suppository with a suitable
- 25 base comprising, for example, cocoa butter, glycerin, gelatin or polyethylene glycol.
- Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents 5 and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind 10 previously described.

It should be understood that in addition to the compounds of the invention, the compositions may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include 15 such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil 20 of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium 25 bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

The present invention also relates to prodrugs of compounds of general formulae (I) and (II) hereinbefore defined. Any compound that is a prodrug of a compound of formula (I) 30 and (II) is within the scope and spirit of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo*, either

enzymatically or hydrolytically, to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free thiol or hydroxy group is converted into an ester, such as an acetate, or where a free amino group is converted into an amide. Procedures for acylating the compounds of the 5 invention, for example to prepare ester and amide prodrugs, are well known in the art and may include treatment of the compound with an appropriate carboxylic acid, anhydride or chloride in the presence of a suitable catalyst or base. Other conventional procedures for the selection and preparation of suitable prodrugs are known in the art and are described, for example, in WO 00/23419, *Design of Prodrugs*, Hans Bundgaard, Ed., Elsevier 10 Science Publishers, 1985, and *The Organic Chemistry of Drug Design and Drug Action*, Chapter 8, pp352-401, Academic press, Inc., 1992, the contents of which are incorporated herein by reference.

The present invention also relates to pharmaceutically acceptable salts of compounds of 15 formulae (I) and (II) herein defined. It will be appreciated however that non-pharmaceutically acceptable salts also fall within the scope of the present invention since these may be useful as intermediates in the preparation of pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, 20 nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicyclic sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric 25 acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. In particular, the present invention includes within its scope cationic 30 salts eg sodium or potassium salts.

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Basic nitrogen-containing groups may also be quaternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others to form a salt.

- 5 The present invention also relates to the use of an antimicrobial composition comprising a compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material to treat a microbial infection in a subject.
- 10 The present invention further relates to the use of an antimicrobial composition comprising a compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material to kill microbes.
- 15 Compounds in accordance with the invention are believed to be particularly suitable for use in treating fungal and/or bacterial infections in a subject.

In one embodiment, the present invention also provides an antibacterial and/or antifungal composition comprising a compound of a general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material.

In a further embodiment, the present invention also provides a method of treating a bacterial and/or fungal infection in a subject, said method comprising administering to said subject an effective amount of a compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds.

In another embodiment, the present invention relates to the use of a compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, in the manufacture of a medicament for treating

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a bacterial and/or fungal infection in a subject.

In a further embodiment, the present invention relates to the use of an antibacterial and/or antifungal composition comprising a compound of general formula (I) and/or (II) as 5 hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material to treat a bacterial and/or fungal infection in a subject.

In another embodiment, the present invention relates to the use of an antibacterial and/or 10 antifungal composition comprising a compound of general formula (I) and/or (II) as hereinbefore defined, and/or a pharmaceutically acceptable salt or prodrug of one or both of the compounds, and a suitable carrier material to treat kill bacteria and/or fungi.

Compounds in accordance with the invention have been found to exhibit both Gram- 15 positive and Gram-negative antibacterial properties.

There are numerous bacteria that are known and to cause infections in a subject. Compounds in accordance with the invention are believed to exhibit broad spectrum 20 antibacterial activity.

Compounds in accordance with the invention are believed to be particularly effective against bacteria that include, but are not limited to, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes* and *Methicillin-resistant Staphylococci* (MRSA). 25

*Straphylococcus aureus* is known to cause a range of infections ranging from minor skin infections, such as pimples, impetigo, boils, cellulitis folliculitis, furuncles, carbuncles, scalded skin syndrome and abscesses, to life-threatening infections, such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), and septicaemia.

30 *Pseudomonas aeruginosa* is renowned for infecting the pulmonary tract, urinary tract,

burns, wounds, and also for causing other blood infections. *Pseudomonas aeruginosa* may also cause community acquired pneumonias, as well as ventilator-associated pneumonias. This bacteria is naturally resistant to a large range of antibiotics and can demonstrate additional resistance after unsuccessful treatment.

5

*Escherichia coli* is known to cause gastroenteritis, urinary tract infections, and neonatal meningitis. This bacteria is also known to be responsible for causing peritonitis, mastitis, septicemia and Gram-negative pneumonia.

- 10    *Streptococcus pyogenes* can give rise to numerous infections ranging from mild superficial skin infections to life-threatening systemic infections. Examples of mild infections include pharyngitis ("strep throat") and localised skin infection ("impetigo"). Erysipelas and cellulitis are characterised by the multiplication and lateral spread of *Streptococcus pyogenes* in deep layers of the skin. *Streptococcus pyogenes* invasion and multiplication in  
15    the fascia can lead to necrotizing fasciitis, a potentially life-threatening condition that often requires in surgical treatment.

- MRSA is a resistant variation of the common bacterium *Staphylococcus aureus*. MRSA has evolved an ability to survive treatment with  $\beta$ -lactam antibiotics, including penicillin,  
20    methicillin, and cephalosporins. MRSA is especially troublesome in hospital-associated (nosocomial) infections.

- Compounds in accordance with the invention have been found to exhibit excellent antibacterial properties against *Pseudomonas aeruginosa* including MRSA and  
25    *Streptococcus pyogenes*.

Bacterial infections that compounds in accordance with the invention may be used to treat include, but are not limited to, those mentioned above.

- 30    Compounds in accordance with the invention are believed to exhibit broad spectrum antifungal activity.

Compounds in accordance with the invention are believed to be particularly suitable for treating mycosis in a subject. Types of mycoses that compounds in accordance with the invention might be used to treat, include, but are not limited to superficial mycoses,  
5 cutaneous mycoses, subcutaneous mycoses and systemic mycoses.

Fungal species that compounds in accordance with the invention exhibit antifungal properties against include, but are not limited to, *Candida*.

10 *Candida* is the most common fungal pathogen known to give rise to infections in a subject. *Candida* is known to be responsible for the condition in a subject known a Candidiasis. Candidiasis usually occurs as an infection in an immuno-compromised subject or is usually precipitated by some predisposing condition. The infection can take the form of superficial infections, through Candidaemia to deep-seated systemic infections. In healthy  
15 subjects, *Candida* exists commensally in a variety of body locations such as the oral cavity, gastrointestinal tract, anus and groin. In the commensal state, *Candida* species do not cause disease. However, physiological changes that leave the subject host immuno-compromised may allow *Candida* to evade immune defences and over-grow cavities and infect tissues. Antifungal compounds such as those in accordance with the invention  
20 function to kill and/or suppress the growth of *Candida* fungal, thus preventing the establishment of the diseased or infected state.

25 *Candida* species that compounds in accordance with the invention exhibit antifungal properties against include, but are not limited to, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis* and *Candida parapsilosis*.

Fungal infections that compounds in accordance with the invention may be used to treat include, but are not limited to, those mentioned above.

30 It will be appreciated that a subject may develop a microbial infection as a result of coming into contact with a substrate on which bacteria and/or fungi reside. The compositions in

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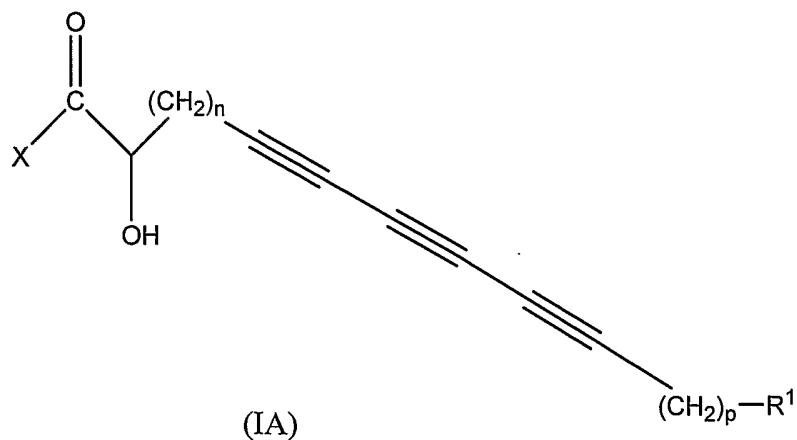
accordance with the invention can of course also be used to kill bacteria and/or fungi on a substrate, for example by being provided in the form of an antimicrobial surface spray.

Compounds in accordance with the invention may also be polymerised to provide unique  
5 polymers such as polyacetylenes.

Accordingly, the present invention also provides polymers comprising a polymerised residue of one or more compounds of general formula (I) or (II) as hereinbefore defined. By the polymer comprising a "polymerised residue" of one or more compounds of general  
10 formula (I) or (II) is meant that the compounds take part in a polymerisation reaction so as to form part of a polymer chain.

The present invention further provides a method of preparing a polyacetylene, said method comprising polymerising one or more compounds of general formula (I) or (II) as  
15 hereinbefore defined.

The present invention also provides a method of preparing a polytriacetylene, said method comprising polymerising one or more compounds of general formula (IA):



20 wherein X, n, p and R<sup>1</sup> are as hereinbefore defined.

It will be appreciated that compounds of general formula (IA) are a subset of compounds of general formula (I).

Compounds in accordance with the invention may be conveniently polymerised using techniques known in the art for polymerising diacetylene compounds. For example, crystallisation and Langmuir-Blodgett techniques may be employed.

5

Langmuir-Blodgett techniques have been used in the art to prepare monolayer and multilayer PDA films. It is expected that similar techniques can be used in preparing PTA's. Thus, this would typically involve spreading a thin layer of triyne monomer on a water surface in a solvent such as chloroform. Solvent can then rapidly evaporate, to cause 10 the monomers to align with respect to each other and the water surface. A substrate (such as glass or mica) may then be brought upwards through the surface of the water, while a computer controlled movable barrier compresses the layer of monomer on the surface of the water so as to keep a constant pressure. This can result in the deposition of a highly ordered monolayer of monomers onto the substrate. This process can be repeated to build 15 up several layers. These layers can then be photopolymerised to form extremely thin films of PTA on the substrate.

PTA's formed using Langmuir-Blodgett techniques are expected to have limited application as they are typically formed on a substrate. The resulting polymer can then be 20 difficult to remove for use independent of the substrate. Polymerisation of the triyne compounds in crystalline form may advantageously overcome this problem. In order to obtain PTA's using this technique, it is necessary to obtain precursor crystal phases of the triyne compounds having a suitable molecular packing. The triyne compounds may be crystallised from an appropriate solvent, from the melt, or from the vapour, so as to 25 provide the monomer crystal phase that can be polymerised.

Where solvent crystallisation is employed, a variety of solvents may be used. For example, solvents such as alkyl esters of monocarboxylic acids, alkyl alcohols, paraffins, olefins, benzene, alkylated benzenes, ethers, ketones, petroleum ether, halogenated 30 hydrocarbons, and water may be used. Examples of specific solvents include, but are not limited to, ethylacetate, methyl propionate, methanol, ethanol, butanol, isopropanol,

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hexane, heptane, 1,4-dimethylheptane, toluene, xylene, trimethylbenzene, ethyl ether, isopropyl ether, 1,2-dimethoxyethane, tetrahydrofuran, dioxane, acetone, ethylmethylketone, chloroform, dichloromethane, trichloroethane, and mixtures thereof.

5 Crystallisation may, for example, be conducted at room temperature by the evaporation of solutions containing from about 0.0001 to about 0.5, and preferably about 0.002 to about 0.2, parts by weight of triyne monomer per parts by weight of solvent or solvent blend.

10 Other conventional recrystallisation techniques may also be used, such as sublimation or by cooling a saturated solution to sufficiently low temperature (typically at or above room temperature) where crystallisation occurs.

Suitable crystals may also be grown from the melt using conventional techniques known in the art.

15 The crystalline form of the triyne compounds may then be polymerised by subjecting the monomeric crystals to actinic radiation, heat or mechanical stress. When polymerised by heat, the monomeric crystals will typically be subjected to a temperature below the melting point of the crystals and the decomposition temperature of the resulting polymer.

20 Examples of actinic radiation include, but are not limited to, visible, ultra violet, and gamma radiation.

25 The resulting polyacetylenes may be purified by using a suitable solvent to extract any non-polymerised triyne compounds.

Polyacetylenes formed using the crystallisation technique may advantageously be liquid phase processable in that they may be either melt processable, solution processable or both.

30 The present invention will hereinafter be further described with reference to the following non-limiting Examples.

## EXAMPLES

### General

5 Proton NMR spectra were obtained on *Bruker AV400* and *Bruker AV200* spectrometer, operating at 400 MHz and 200 MHz. All spectra were obtained at 23°C unless specified. Chemical shifts are reported in parts per million (ppm) on the δ scale and relative to the chloroform peak at 7.26 ppm (<sup>1</sup>H) or the TMS peak at 0.00 ppm (<sup>1</sup>H). Oven dried glassware was used in all reactions carried out under an inert atmosphere (either dry  
10 nitrogen or argon). All starting materials and reagents were obtained commercially unless otherwise stated. Removal of solvents “under reduced pressure” refers to the process of bulk solvent removal by rotary evaporation (low vacuum pump) followed by application of high vacuum pump (oil pump) for a minimum of 30 min. Analytical thin layer chromatography (TLC) was performed on plastic-backed Merck Kieselgel KG60F<sub>254</sub> silica  
15 plates and visualised using short wave ultraviolet light, potassium permanganate or phosphomolybdate dip. Flash chromatography was performed using 230-400 mesh Merck Silica Gel 60 following established guidelines under positive pressure. Tetrahydrofuran and dichloromethane were obtained from a solvent dispensing system under an inert atmosphere. All other reagents and solvents were used as purchased.

20

### Method for the antimicrobial activity assay

#### *Materials and Methods – bacteria assay*

Tests were preformed by comparing growth of bacteria in standard broth culture with and  
25 without the addition of each compound (1 μMolar in broth) after incubation for 18 hours at 37°C. The amount of bacterial growth was measured by comparing the optical density (OD<sub>595</sub>) of control broths (without compound) and test broth (containing compound). Any reduction in the OD<sub>595</sub> indicates that the compound inhibited bacterial growth. The percentage reduction gives an indication of the level of antimicrobial activity. These tests  
30 were performed in duplicates.

- 44 -

The bacteria tested were as follows:

1. *Staphylococcus aureus* ATCC 25923
2. *Pseudomonas aeruginosa* ATCC 27853
3. *Escherichia coli* ATCC 25922
- 5 4. *Streptococcus pyogenes* ATCC 19615
5. MRSA – 5, a clinical isolate

#### ***Materials and Methods – fungi assay***

##### ***Fungal strains***

Yeast strains were maintained on solidified YEPD (1% yeast extract, 2% glucose, 1.5% agar) and stored at 4°C. Cells were prepared as fresh inoculations in solid YEPD at 30°C prior to their utilisation. Candida strains employed in this study consisted of the clinical isolates, American Type Culture Collection (ATCC) strains, . *albicans* 90028, *C. glabrata* 90030, *C. krusei* 6258, *C. tropicalis* 750 and *C. parapsilosis*.

##### ***Compound and antifungal drug stocks***

15 Compounds were freshly prepared as 100 mM stock solutions in dimethylsulphoxide (DMSO). Ketoconazole (Sigma, St. Louis, MO, USA) was solubilized in methanol. DMSO and methanol comprised <1% of the total test volume. Growth curves were determined using concentrations of DMSO, ethanol and methanol equal to those present in test solutions to verify that they did not inhibit the growth of Candida.

##### **20 *Growth inhibition assays of yeast***

Yeast strains were inoculated at a low cell density in YEPD to achieve a starting optical density at A<sub>595</sub> of 0.1. The yeast inocula (100 µl) were then added to each well of a 96-well microplate (Nunc, Wiesbaden, Germany). Test compounds were then added as two-fold serial dilutions down from 1 mM concentrations. A growth control was included in

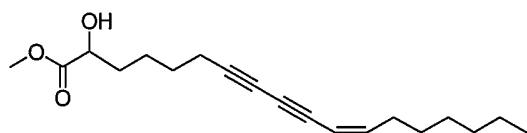
- 45 -

the same microplate. The microplate was incubated in a microplate shaker at 28°C, and the  $A_{595}$  was measured at 0 and 20 h using a microplate reader (Labsystem Multiscan Ascent). Each sample was assayed in triplicate. Absorbance values were averaged and plotted against the drug and compound concentration, and the concentration required to 5 inhibit 50% growth (IC<sub>50</sub>) was calculated.

### Example 1

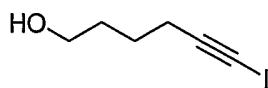
#### 2-Hydroxy-octadec-11-ene-7,9-diynoic acid methyl ester

10



#### Part A: Synthesis of 6-Iodo-hex-5-yn-1-ol

15

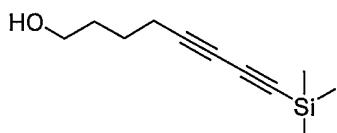


To a solution of 5-hexyn-1-ol (1 ml, 0.89 g, 9.07 mmol) in MeOH (10 ml) was added an aqueous solution (2 ml) of KOH (1.27 g, 22.7 mmol) and the mixture was stirred for 10 min at 0°C. Iodine (2.53 g, 9.98 mmol) was added in one portion and the mixture was then 20 warmed to room temperature. After stirring for 3 h, the mixture was diluted with H<sub>2</sub>O (15 ml) and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 25 ml). The combined organic layers were concentrated to give a residue which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) and washed with saturated aqueous solutions of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (15 ml) and NaCl (15 ml). Purification by flash-chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 90:10) afforded the title 25 compound (1.23 g, 61 %) as a yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.51 – 1.72 (4H, m), 2.42 (2H, t, J = 6.8 Hz), 3.70 (2H, t, J = 6.2 Hz).

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**Part B: Synthesis of 8-Trimethylsilyl-octa-5, 7-diyn-1-ol**



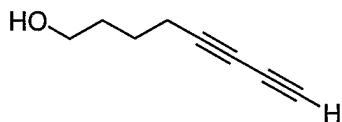
5

To a solution of trimethylsilylacetylene (0.50 ml, 0.34 g, 3.51 mmol) and 6-iodo-5-hexyn-1-ol (0.30 g, 1.34 mmol) in degassed piperidine (2 ml), cooled at 0°C, was added CuCl (0.01 g, 0.14 mmol) and the mixture was stirred at room temperature for 30 min. Saturated aqueous NH<sub>4</sub>Cl solution (6 ml) was added and the reaction mixture was extracted with Et<sub>2</sub>O (3 x 10 ml). Combined organic layers were washed with brine (2 x 25 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification by flash-chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 95:5) afforded the title compound (0.22 g, 87 %) as a yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.15 (9H, s), 1.59 – 1.71 (4H, m), 2.00 (1H, broad, s), 2.32 (2H, t, J = 6.7 Hz), 3.63 (2H, t, J = 6.1 Hz).

15

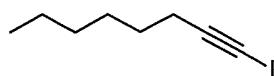
**Part C: Synthesis of Octa-5, 7-diyn-1-ol**



20 To a solution of 8-trimethylsilyl-octa-5, 7-diyn-1-ol (4.31 g, 22.63 mmol) in dry THF (100 ml) was added tetrabutylammonium fluoride (TBAF) (1 M in THF, 22.63 mmol, 22.63 ml) at -78 °C and the mixture was stirred for 10 min at the same temperature. The mixture was slowly brought to 0°C, stirred for additional 10 min, quenched with water (200 ml) and extracted with Et<sub>2</sub>O (3 x 100 ml). The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> 25 and concentrated under vacuum. The product (2.68 g, 97 %) was immediately used in the next reaction step without further purification.

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**Part D: Synthesis of 1-Iodo-oct-1-yne**

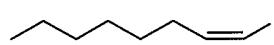


5 N-BuLi (1.6 M in hexane, 25.34 ml, 40.55 mmol) was added slowly to a solution of oct-1-yne (4.61 ml, 3.44g, 31.19 mmol) in dry THF at -20°C under argon and was stirred for 1 h. The mixture was then cooled to -40°C and treated with iodide (10.29 g, 40.55 mmol). After stirring for 12 h at room temperature the reaction mixture was quenched with saturated NH<sub>4</sub>Cl (100 ml) solution and extracted with ethyl acetate (3 x 50 ml). The combined  
10 organic layers were washed with saturated aqueous sodium thiosulfate solution (100 ml), and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent left a colourless oil (7.00 g, 95%) which was used without further purification.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.88 (3H, t, *J* = 7.5 Hz), 1.32 – 1.59 (8H, m), 2.35 (2H, t, *J* = 6.9 Hz).

15

**Part E: Synthesis of 1-Iodo-oct-1-ene**



20 To 114 ml of a 0.5 M 9-BBN (9-borabicyclo [3.3.1] nonane)/THF solution (57 mmol) was added 12.21 g (51.68 mmol) of 1-iodo-oct-1-yne via syringe under argon. After stirring at room temperature for 6 h, the THF was completely removed under vacuum and replaced with 150 ml of pentane. Acetic acid (4.01 ml, 4.21 g, 56.84 mmol) was added via syringe and the mixture stirred for 2h. Ethanolamine (7.53 ml, 7.64 g, 125.07 mmol) was added via  
25 syringe. The best results were obtained when a small part of the ethanolamine (10 %) was added and the mixture stirred for a few minutes to allow the formation of a solid precipitate. The rest of the ethanolamine was then slowly added (10-15 min). The reaction mixture was poured onto a short silica gel column (pentane) and the product (8.74 g, 71 %) was eluted with pentane. Colourless 1-iodo-oct-1-ene (8.74 g, 71 %) was obtained after  
30 removal of pentane in vacuum.

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.89 (3H, t, J = 6.6 Hz), 1.21 – 1.55 (8H, m), 2.10 – 2.17 (2H, m), 6.13 – 6.20 (2H, m).

**Part F: Synthesis of Hexadec-9-ene-5, 7-diyn-1-ol**

5

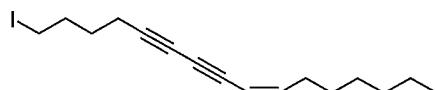


A mixture of (Z)-1-iodo-oct-1-ene (8.08 g, 33.95 mmol), octa-5, 7-diyn-1-ol (2.76 g, 22.63 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.58 g, 2.26 mmol) and CuI (0.43 g, 2.26 mmol) in degassed 10 piperidine (35 ml) was stirred at room temperature for 4 h. Et<sub>2</sub>O (250 ml) was added and the resulting solution was washed with saturated aqueous NH<sub>4</sub>Cl solution (2 x 200 ml) and saturated aqueous NaCl solution (2 x 200 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuum. Purification by flash chromatography (ethyl acetate/hexane 1:3) gave the title compound (3.42 g, 65 %) as a yellow oil.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.88 (3H, t, J = 7.0 Hz), 1.21 – 1.46 (8H, m), 1.59 – 1.74 (4H, m), 2.32 (2H, qd, J = 7.3 Hz, J = 1.1 Hz), 2.39 (2H, t, J = 6.2 Hz), 3.67 (2H, t, J = 6.4 Hz), 5.46 (1H, d, J = 10.8 Hz), 6.03 (1H, dt, J = 10.8 Hz, J = 7.5 Hz).

**Part G: Synthesis of 1-iodo-hexadec-9-ene-5, 7-diyne**

20



To a solution of hexadec-9-ene-5, 7-diyn-1-ol (1.81 g, 7.75 mmol) PPh<sub>3</sub> (2.24 g, 8.53 mmol) and imidazole (0.63 g, 9.30 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added I<sub>2</sub> (2.07 g, 8.14 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was

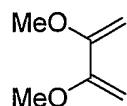
- 49 -

purified by flash silica gel column chromatography (gradient eluent: 0 % - 2 % ethyl acetate in hexane) to provide the title compound (2.31 g, 87 %) as a pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.89 (3H, t, J = 6.9 Hz), 1.22 – 1.46 (8H, m), 1.67 (2H, quint, J = 6.9 Hz), 1.95 (2H, quint, J = 7.7 Hz), 2.32 (2H, qd, J = 7.2 Hz, J = 1.2 Hz),  
 5 2.39 (2H, t, J = 6.2 Hz), 3.20 (2H, t, J = 6.9 Hz), 5.45 (1H, d, J = 10.7 Hz), 6.02 (1H, dt, J = 10.7 Hz, J = 7.6 Hz).

#### Part H: Synthesis of 2, 3-Dimethoxy-1,3-butadiene-diene

10

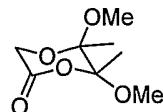


A mixture of biacetyl (17.2 g, 0.2 mol), absolute methanol (25 ml, 1.25 mol), trimethyl orthoformate (63.6 g, 0.6 mol) and concentrated sulfuric acid (95 drops) was refluxed for 10 h. The excess of reagents were distilled off and the remaining liquid was vacuum-  
 15 distilled. Ammonium dihydrogenphosphate (25 mg) and a few crystals of hydroquinone were added and the liquid was heated at 100 deg to 110 deg. Methanol slowly distilled over, together with some remaining orthoformate. The temperature was raised (160 deg to 170 deg) and the colourless oily liquid collected between 129 deg and 132 deg (17.3 g or 76 % of crude diene). Redistillation gave 2,3-dimethoxy-1, 3-butadiene (15.5 g, 68 %), b.  
 20 p. 132 deg – 132.5 deg.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 3.57 (6H, s), 4.02 (2H, d, J = 1.5 Hz), 4.57 (2H, d, J = 1.5 Hz)

#### Part I: Synthesis of ( $\pm$ ) 5,6-Dimethoxy-5,6-dimethyl-[1, 4]dioxane-2-one

25



Triphenylphosphine hydrobromide (165 mg, 0.48 mmol) was added to a stirred solution of hydroxy-acetic acid (270 mg, 3.55 mmol) and 2,3-dimethoxy-1,3-butadiene (490 mg, 2.29

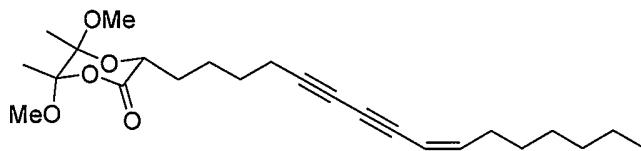
- 50 -

mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at room temperature. After 3 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (20 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give the lactone as a white solid (559 mg, 83 %).

5   <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.38 (3H, s), 1.49 (3H, s), 3.30 (3H, s), 3.43 (3H, s), 4.14 (1H, d, J = 17.6 Hz), 4.28 (1H, d, J = 17.6)

**Part J: Synthesis of 3-Hexadec-9-ene-5,7-diynyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one**

10

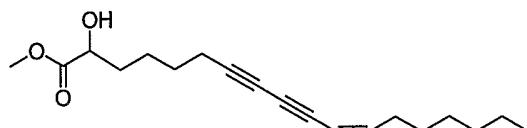


Lithium bis(trimethylsilyl)amide (LHMDS) (1M in THF, 1.3 ml) was added to a stirred solution of 5,6-Dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (263 mg, 1.38 mmol) in THF 15 (7 ml) at -78 deg. After 15 min 1-Iodo-hexadec-9-ene-5,7-diyn (1.42 g, 4.15 mmol) was added and the solution stirred at -78 deg for 1 h and then warmed to -20 deg for 2.5 h. The reaction was quenched at -20 deg with acetic acid (0.194 ml, 2.76 mmol), Et<sub>2</sub>O (20 ml) was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O-petrol 8:1) to give the 20 lactone as a colourless oil 0.27 g (0.67 mmol, 49 %).

25   <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.89 (3H, t, J = 7.1 Hz), 1.22 – 1.62 (18H, m), 1.37 (3H, s), 1.48 (3H, s), 1.89 (2H, quart, J = 6.3 Hz), 2.28 – 2.39 (4H, m,), 3.30 (3H, s), 3.41 (3H, s), 4.13 (1H, t, J = 5.8 Hz), 5.45 (1H, d, J = 10.7 Hz), 6.02 (1H, dt, J = 10.7 Hz, J = 7.6 Hz)

25

**Part K: Synthesis of 2-Hydroxy-octadec-11-ene-7,9-diynoic acid methyl ester**



- 51 -

3-Hexadec-9-ene-5,7-diynyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.27 g, 0.67 mmol) was dissolved in a 0.3 M solution of trimethylsilyl chloride (4.00 mmol, 0.44 g, 0.51 ml) in Methanol (15 ml) and stirred at room temperature for 25 min. The reaction was  
 5 concentrated in vacuo and purified via column chromatography (ethyl acetate/hexane 1:3) giving the pure product in 91 % yield (0,61 mmol, 186 mg).

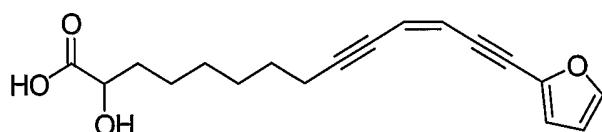
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.97 (3H, t, J = 7.2 Hz), 1.22 – 1.87 (14H, m), 2.26 – 2.39 (4H, m), 2.47-2.87 (1H, broad), 3.79 (3H, s), 4.19 (1H, dd, J<sup>1</sup> = 4.1, J<sup>2</sup> = 7.1), 5.45 (1H, d, J = 10.8 Hz), 6.02 (1H, dt, J = 10.8 Hz, J = 7.5 Hz).

10

### Example 2

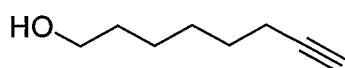
#### (Z)-14-(furan-2-yl)-2-hydroxytetradeca-11-en-9,13-diynoic acid

15



#### Part A: Synthesis of Oct-7-yn-1-ol

20



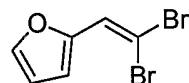
Lithium metal (6.33 g, 912 mmol) was cut in small pieces and added under stirring to 1.3-diaminopropane (440ml) under nitrogen. The mixture was heated to 50 deg until the lithium had reacted completely (disappearance of dark blue colour of the mixture). After  
 25 that 3-octyn-1-ol (10g, 79.2 mmol) was added. The mixture was stirred at 50 – 60 deg for 5 h then over night at 40 deg. The reddish orange reaction mixture was cooled and slowly poured into 1200 ml of ice water with constant stirring. It was extracted with chloroform (3 x 300 ml). The combined organic layers were washed with saturated brine (2 x 300 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield crude Oct-7-  
 30 yn-1-ol as an orange oil.

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- The crude product (23.5 g) was dissolved in a 1:1 mixture of water and THF solution (940 ml) containing dissolved silver nitrate (32.9 g, 0.194 mol). The mixture was stirred at room temperature overnight. Most of the THF was removed by rotary evaporator to increase the size of the precipitate. The mixture was poured into an equal volume of 5 acetone and stirred for 5 min. The white precipitate was filtered and washed with a small volume of acetone. The precipitate was dissolved with warm 1.6 M HNO<sub>3</sub>. The resulting solution was cooled and extracted with dichloromethane (3 x equal volume). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give pure oct-7-yn-1-ol (12g, 48% yield).
- 10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.2 – 1.8 (m, 8 H), 1.90 – 1.97 (m, 1 H), 2.10 – 2.30 (m, 2 H), 3.64 (t, 2 H, J = 6.6 Hz)

**Part B: Synthesis of 2-(2, 2-dibromovinyl)furan**

15



Triphenylphosphine (65.40 g, 0.249 mol), carbon tetrabromide (82.27 g, 0.248 mol), and zinc dust (19.2 g, 0.294 mol) were placed in a well dried flask. Anhydrous dichloromethane (600 ml) was added under nitrogen and the mixture was stirred for 41 h at 20 room temperature. Then furfural (9.57 g, 99.6 mmol) was added slowly to the stirred mixture (cooled to 0 deg). After stirring for 6 h at room temperature, hexane (600 ml) was added to the stirred reaction mixture resulting in two layers. The top layer was filtered through Celite leaving the lower sticky layer in the flask. The volume of filtrate (hexane) was reduced under reduced pressure. The solid was removed by filtration and the filtrate 25 was concentrated to give crude 2-(2, 2-dibromovinyl)furan as a brown oil. The crude product was purified by column chromatography using a short column (SiO<sub>2</sub>, petroleum spirit) giving the pure product (14.2 g, 57% yield).

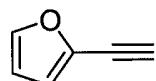
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 6.44 -6.50 (m, 1 H), 6.95 (d, 1H, J = 3.4 Hz), 7.38 – 7.46 (m, 2 H)

30

- 53 -

**Part C: Synthesis of 2-ethynylfuran**

5

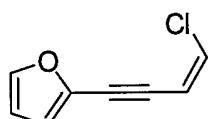


A 1.6 M ether solution of methyllithium (20.84 ml, 33.35 mmol) was added dropwise to a solution of 2-(2, 2-dibromovinyl)furan (3.0 g, 11.91 mmol) in dry ether (100 ml) cooled at -78 deg under argon. After stirring for 1 h at -78 deg, the mixture was allowed to warm up to room temperature and was stirred over night. The reaction mixture was carefully quenched with half saturated aqueous ammonium chloride solution (150 ml) and the layers were separated. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated to yield 2-ethynylfuran as a brown oil (0.52 g, 47%). The material was used immediately in the next step without any further purification.

10      <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 3.38 (s, 1 H), 6.38 (dd, 1H, J = 3.4 Hz, J = 1.9 Hz),  
15      6.65 (d, 1 H, J = 3.3 Hz), 7.39 (m, 1 H)

**Part D: Synthesis of (Z)-2-(4-chlorobut-3-en-1-ynyl)furan**

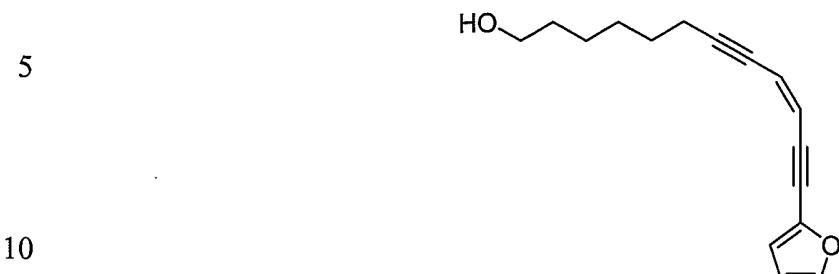
20



To a solution of Pd(PPh<sub>3</sub>)<sub>4</sub> (1.35 g, 1.16 mmol), cis-1,2-dichloroethylene (10 g, 103.16 mmol), butylamine (10.24 ml, 103.16 mmol) and 2-ethynylfuran (2.147 g, 23.31 mmol) in dry ether (250 ml) was added CuI (0.44 g, 2.33 mmol) under argon. The mixture was stirred over night at room temperature. The whole reaction mixture was concentrated and used immediately in the next step without any further purification.

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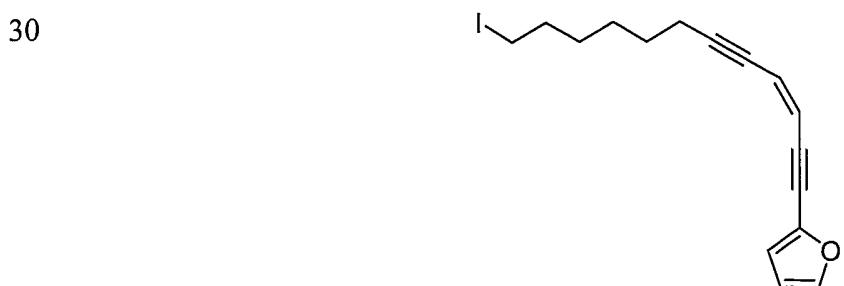
**Part E: Synthesis of (*Z*)-12-(furan-2-yl)dodeca-9-en-7,11-diyn-1-ol**



(*Z*)-2-(4-chlorobut-3-en-1-ynyl)furan (23.31 mmol) was stirred in piperidine (35 ml) under argon while  $\text{PdCl}_2(\text{PhCN})_2$  (0.224 g, 0.58 mmol) and oct-7-yn-1-ol (1.47 g, 11.66 mmol) were added successively. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with half saturated aqueous ammonium chloride solution (150 ml) and extracted with ether (3 x 150 ml). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography ( $\text{SiO}_2$ , 15% ethyl acetate in petroleum spirit) giving a brown oil (1.22 g). The oil was dissolved in methanol (30 ml) and stirred with activated charcoal (60 mg) for 1 h. The mixture was filtered through celite. After removal of methanol the pure (*Z*)-12-(furan-2-yl)dodeca-9-en-7,11-diyn-1-ol was obtained as a pale brown oil (1.09 g, 38%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta[\text{ppm}] = 1.34 - 1.65$  (m, 8 H), 2.45 (td, 2 H,  $J = 6.9$  Hz,  $J = 2.1$  Hz), 3.62 (t, 2 H,  $J = 6.6$  Hz), 5.86 (dt, 1 H,  $J = 10.9$  Hz,  $J = 2.2$  Hz), 5.96 (d, 1 H,  $J = 10.9$  Hz), 6.41 (dd, 1 H,  $J = 3.4$  Hz,  $J = 1.9$  Hz), 6.60 - 6.63 (m, 1 H), 7.41 - 7.43 (m, 1 H)

**Part F: Synthesis of (*Z*)-2-(12-iodododeca-3-en-1,5-diynyl)furan**

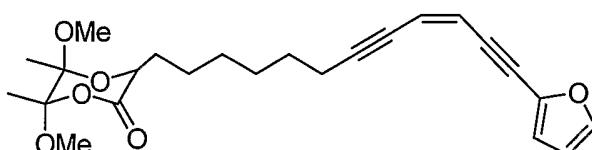


- 55 -

- To a solution of (Z)-12-(furan-2-yl)dodeca-9-en-7,11-diyn-1-ol (1.03 g, 4.25 mmol), PPh<sub>3</sub> (1.23 g, 4.68 mmol) and imidazole (0.35 g, 5.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (150 ml) was added I<sub>2</sub> (1.13 g, 4.463 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h
- 5 before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (150 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Gradient eluent 0% to 2% petroleum spirit) to provide the iodide in as a pale brown oil (1.07 g, 72%).
- 10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.16 – 1.66 (m, 6 H), 1.76 – 1.85 (m, 2H), 2.45 (td, 2H, J = 6.8 Hz, J = 2.0 Hz), 3.16 (t, 2H, J = 7.0 Hz), 5.86 (dt, 1H, J = 10.8 Hz, J = 2.2 Hz), 5.96 (d, 1 H, J = 10.9 Hz), 6.42 (dd, 1 H, J = 3.4 Hz, J = 1.9 Hz), 6.60 – 6.63 (m, 1 H), 7.42 – 7.44 (m, 1 H)

15 **Part G: Synthesis of (Z)-3-(12-(furan-2-yl)dodeca-9-en-7,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

20



- Lithium bis(trimethylsilyl)amide (1M in THF, 1.04 ml, 1.04 mmol) was added to a stirred solution of 5,6-Dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (180 mg, 0.94 mmol) in THF (10 ml) at -78 deg. After 15 min (Z)-2-(12-iodododeca-3-en-1,5-diynyl)furan (990 mg,
- 25 2.81 mmol) was added and the solution was stirred at -78 deg for 15 min and then transferred into a cooling bath and stirred at -20 deg for 3 h. The reaction was quenched at -20 deg with acetic acid (0.12 ml, 2.068 mmol), Et<sub>2</sub>O (20 ml) was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated giving a brown oil. The crude product was
- 30 purified by column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as a pale yellow oil 65 mg (17%).

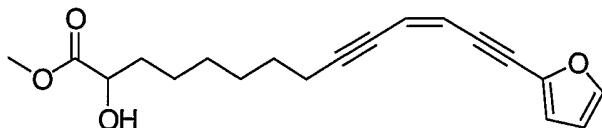
- 56 -

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 1.3 – 1.6 (m, 8 H; 1.48, s, Me, 1.38, s, Me), 1.75 – 1.95 (m, 2 H), 2.35 – 2.5 (m, 2 H), 3.29 (s, 3 H), 3.4 (s, 3 H), 4.13 (t, 1 H, J = 5.9 Hz), 5.85 (dt, 1 H, J = 10.9 Hz, J = 2.0 Hz), 5.96 (d, 1 H, J = 10.9 Hz), 6.41 (dd, 1 H, J = 3.4 Hz, J = 1.9 Hz), 6.59 – 6.63 (m, 1 H), 7.41 – 7.44 (m, 1 H)

5

**Part H: Synthesis of (Z)-methyl 14-(furan-2-yl)-2-hydroxytetradeca-11-en-9, 13-diynoate**

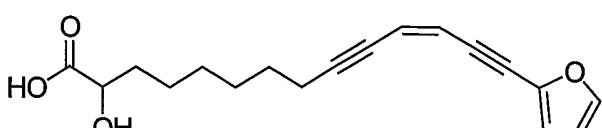
10



(Z)-3-(12-(furan-2-yl)dodeca-9-en-7,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (28 mg, 0.068 mmol) was dissolved in a 0.3 M solution of TMSCl in MeOH (1.5 ml, 0.45 mmol) under argon. The solution was stirred for 30 min at room temperature and then 15 concentrated under reduced pressure giving (Z)-methyl 14-(furan-2-yl)-2-hydroxytetradeca-11-en-9, 13-diynoate (21 mg) as an oil. The product was used without further purification

20

**Part I: Synthesis of (Z)-14-(furan-2-yl)-2-hydroxytetradeca-11-en-9, 13-diynoic acid**



25 The (Z)-methyl 14-(furan-2-yl)-2-hydroxytetradeca-11-en-9, 13-diynoate (21 mg, 0.067 mmol) was stirred in a 2:1 mixture of water and THF (10 ml) under argon. Then lithium hydroxide monohydrate (6.3 mg, 0.15 mmol) was added at 0 deg. The mixture was stirred at room temperature over night before it was acidified with 1 N HCl (pH 1). It was extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried over 30 Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give (Z)-14-(furan-2-yl)-2-hydroxytetradeca-11-en-9, 13-diynoic acid as an oil (19.6 mg).

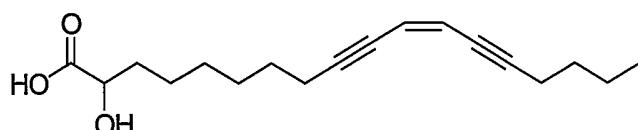
- 57 -

<sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz): δ[ppm] = 1.00 – 1.90 (m, 10 H), 2.36 – 2.5 (m, 2 H), 4.12 (dd, 1 H, J = 4.2 Hz, J = 7.6 Hz), 5.93 – 6.03 (m, 1 H), 6.08 (d, 1 H, 10.9 Hz), 6.5 – 6.57 (m, 1 H), 6.72 (d, 1 H, J = 3.3 Hz), 7.60 – 7.67 (m, 1 H)

## 5 Example 3

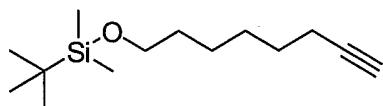
### (Z)-1, 3-dihydroxynonadeca-12-en-10, 14-diyn-2-one

10



### Part A: Synthesis of tert-butyldimethyl(oct-7-nyloxy)silane

15

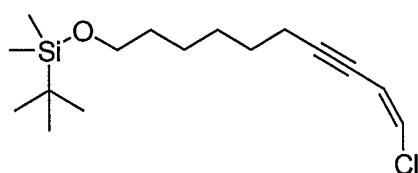


To a stirred solution of Oct-7-yn-1-ol (2.0 g, 15.85 mmol) in dry THF (175 ml) was added imidazole (2.37 g, 34.87 mmol) followed by tert-butyldimethylsilylchloride (2.63 g, 17.42 mmol) under nitrogen. The mixture was stirred for 16 h at room temperature before water (100 ml) and petroleum spirit (200 ml) were added. The layers were separated and the aqueous phase was extracted with petroleum spirit. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated to give the protected alcohol. The crude product was purified by column chromatography (SiO<sub>2</sub>, 0 – 5% ethyl acetate in petroleum spirit) to give the pure tert-butyldimethyl(oct-7-nyloxy)silane as a colourless oil (2.75 g, 70%).

25     <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.04 (s, 6 H), 0.89 (s, 9 H), 1.3 – 1.59 (m, 8 H), 1.9 – 1.97 (m, 1 H), 2.18 (td, 2 H, J = 7.0 Hz, J = 2.5 Hz), 3.60 (t, 2 H, J = 6.5 Hz)

### Part B: Synthesis of (Z)-tert-butyl(10-chlorodec-9-en-7-nyloxy)dimethylsilane

30



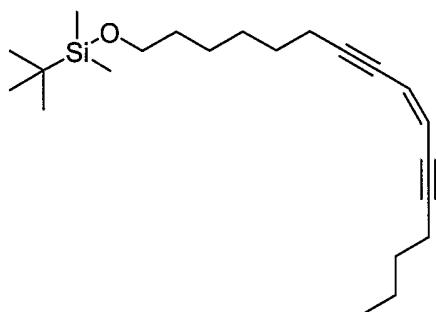
- 58 -

To a solution of Pd(PPh<sub>3</sub>)<sub>4</sub> (1.37 g, 1.19 mmol), cis-1,2-dichloroethylene (10 g, 103.16 mmol), butylamine (10.24 ml, 103.16 mmol) and tert-butyldimethyl(oct-7-nyloxy)silane (3 g, 12.48 mmol) in dry ether (250 ml) was added CuI (0.45 g, 2.38 mmol) under argon.

5 The mixture was stirred over night at room temperature. The whole reaction mixture was concentrated and used immediately in the next step without any further purification.

**Part C: Synthesis of (Z)-tert-butyl(hexadeca-9-en-7,11-diynyloxy)dimethylsilane**

10



15

(Z)-tert-butyl(10-chlorodec-9-en-7-nyloxy)dimethylsilane (12.48 mmol) was stirred in piperidine (30 ml) under argon while PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.24 g, 0.62 mmol) and hex-1-yne (2.05 g, 24.96 mmol) were added successively. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with half saturated aqueous

20 ammonium chloride solution (150 ml) and extracted with ether (3 x 150 ml). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield crude product as a brown oil. The crude product was purified by column chromatography (SiO<sub>2</sub>, 1% ethyl acetate in petroleum spirit) giving the pure (Z)-tert-butyl(hexadeca-9-en-7,11-diynyloxy)dimethylsilane as pale yellow oil (1.46 g, 34%).

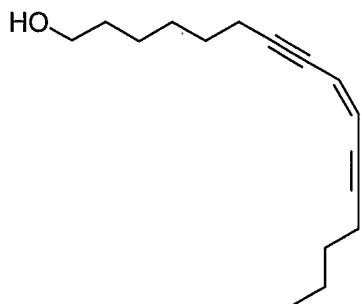
25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.04 (s, 6 H), 0.85 – 0.93 (m, 3 H), 0.89 (s, 3 Me), 1.16 – 1.62 (m, 12 H), 2.19 – 2.46 (m, 4 H), 3.55 – 3.65 (m, 2 H), 5.72 (br, 1.66 H, cis), 5.88 (br, 0.34 H, trans)

30

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**Part D: Synthesis of (Z)-hexadeca-9-en-7,11-diyn-1-ol**

5



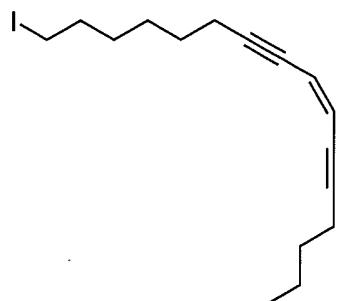
To a stirred solution of (Z)-tert-butyl(hexadeca-9-en-7,11-diynyloxy)dimethylsilane (3.06 g, 8.83 mmol) in methanol (350 ml) was added acidic resin Dowex 50WX8. The mixture was stirred over night at room temperature then filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , 15% ethyl acetate in petroleum spirit) to give (Z)-hexadeca-9-en-7,11-diyn-1-ol as a pale yellow oil (0.9 g, 44% yield).

15      $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ [ppm] = 0.92 (t, 3 H,  $J$  = 7.2 Hz), 1.35 – 1.65 (m, 12 H), 2.29 – 2.35 (m, 0.6 H, trans), 2.37 – 2.43 (m, 3.4 H, cis), 3.62 – 3.67 (m, 2 H), 5.72 (m, 1.7 H, cis), 5.88 (m, 0.3 H, trans)

**Part E: Synthesis of (Z)-16-iodohexadeca-7-en-5,9-diyne**

20

25



To a solution of (Z)-hexadeca-9-en-7,11-diyn-1-ol (0.81 g, 3.49 mmol),  $\text{PPh}_3$  (1.01 g, 3.83 mmol) and imidazole (0.29 g, 4.19 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (150 ml) was added  $\text{I}_2$  (0.93 g, 3.67 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it 30 was quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (150 ml). The organic phase was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 ml). The combined organic

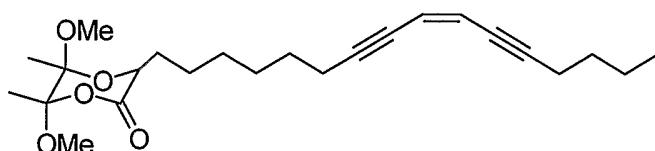
- 60 -

phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , Gradient eluent 2%ethyl acetate in petroleum spirit) to provide iodide in as a pale brown oil (0.82 g, 69%).

- <sup>1</sup>H-NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ [ppm] = 0.93 (t, 3 H,  $J$  = 7.3 Hz), 1.33 – 1.62 (m, 10 H),  
 5 1.79 – 1.89 (m, 2 H), 2.3 – 2.36 (m, 0.6 H, trans), 2.37 – 2.44 (m, 3.4 H, cis), 3.19 (t, 2 H,  $J$  = 7.0 Hz), 5.68 – 5.77 (m, 1.7 H, cis), 5.87 – 5.9 (m, 0.3 H, trans)

**Part F: Synthesis of (Z)-3-(hexadeca-9-en-7,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

10



- 15 Lithium bis(trimethylsilyl)amide (1M in THF, 0.76 ml, 0.76 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (130 mg, 0.69 mmol) in THF (10 ml) at -78 deg. After 15 min (Z)-16-iodohexadeca-7-en-5,9-diyn (712 mg, 2.08 mmol) was added and the solution was stirred at -78 deg for 15 min and then transferred into a cooling bath and stirred at -20 deg for 3 h. The reaction was quenched at -20 deg  
 20 with acetic acid (0.09 ml, 1.52 mmol),  $\text{Et}_2\text{O}$  (20 ml) was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated giving a brown oil. The crude product was purified by column chromatography ( $\text{SiO}_2$ , 7% EtOAc in petroleum spirit) to give the lactone as a pale yellow oil 14 mg (5%).

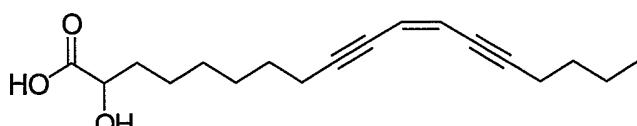
- 25 <sup>1</sup>H-NMR ( $\text{CDCl}_3$ , 200 MHz):  $\delta$ [ppm] = 0.92 (t, 3 H,  $J$  = 7.1 Hz), 1.14 – 1.7 (m, 12 H), 1.38 (s, 3 H), 1.48 (s, 3 H), 1.75 – 1.95 (m, 2 H), 2.25 – 2.45 (m, 4 H), 3.29 (s, 3 H), 3.41 (s, 3 H), 4.13 (t, 1 H,  $J$  = 5.9 Hz), 5.69 – 5.74 (m, 1.74 H, cis), 5.86 – 5.89 (m, 0.26 H, trans)

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**Part G: Synthesis of (Z)-1,3-dihydroxynonadeca-12-en-10,14-diyn-2-one**

5



(Z)-3-(hexadeca-9-en-7,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (5 mg, 0.012 mmol) was dissolved in a 9:1 mixture of THF and water (5 ml) and stirred at room temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml) and washed with a 2.5 M aqueous NaOH solution (5 ml). The aqueous phase was extracted 10 with dichloromethane twice. The combined organic phase were washed with 3M HCl (2 x), and brine (2 x), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give (Z)-1,3-dihydroxynonadeca-12-en-10,14-diyn-2-one (3 mg, 86% yield) as oil.

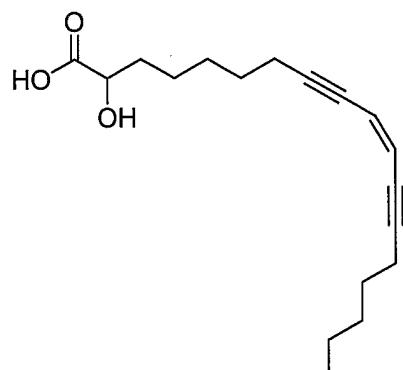
<sup>1</sup>H-NMR ( $(\text{CD}_3)_2\text{CO}$ , 400 MHz):  $\delta$ [ppm] = 0.92 (t, 3 H,  $J$  = 7.1 Hz), 1.15 – 1.9 (m, 14 H), 2.25 – 2.45 (m, 4 H, cis and trans), 4.11 – 4.17 (m, 1 H), 5.77 (s, 1.78 H, cis), 5.89 (s, 0.22 H, trans)

15

**Example 4**

**(Z)-2-hydroxyoctadeca-10-en-8, 12-diynoic acid**

20

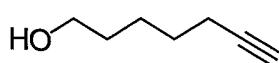


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**Part A: Synthesis of hept-6-yn-1-ol**

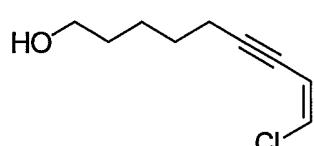


- 5    Lithium metal (8.1 g, 1.17 mol) was cut in small pieces and was added to 1,3-diaminopropane (490 ml) under stirring and under nitrogen. The mixture was heated to 50 deg until the lithium had reacted completely (disappearance of dark blue colour of the mixture). Then 3-heptyn-1-ol (10g, 89.2 mmol) was added. The mixture was stirred at 50 – 60 deg for 3 h then over night at 40 deg. The reddish orange reaction mixture was cooled  
10    and slowly poured into 1200 ml of ice water under constant stirring. It was extracted with chloroform (3 x 300 ml). The combined organic layers were washed with saturated brine (2 x 300 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield crude hept-6-yn-1-ol as an orange oil (10.4 g).
- 15    The crude product was dissolved in a 1:1 mixture of water and THF (940 ml) containing dissolved silver nitrate (32.9 g, 0.194 mol). The mixture was stirred at room temperature overnight. THF was removed by rotary evaporator.. The mixture was poured into an equal volume of acetone and stirred for 5 min. The white precipitate was filtered and washed with a small volume of cooled acetone. The precipitate was dissolved with warm 1.6 M  
20    HNO<sub>3</sub> (1 litre). The resulting solution was cooled and extracted with dichloromethane (3 x equal volume). The combined organic layers were washed with saturated brine (3 x 200 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated giving pure hept-6-yn-1-ol as a pale yellow oil (4.8 g, 48% yield).
- 25    <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.4 – 1.62 (m, 6 H), 1.94 (t, 1 H, J = 2.5 Hz), 2.17 – 2.24 (m, 2 H), 3.65 (t, 2 H, J = 6.4 Hz)

**Part B: Synthesis of (Z)-9-chloronon-8-en-6-yn-1-ol**

30

To a solution of Pd(PPh<sub>3</sub>)<sub>4</sub>



(1.49 g, 1.29 mmol), cis-1,2-

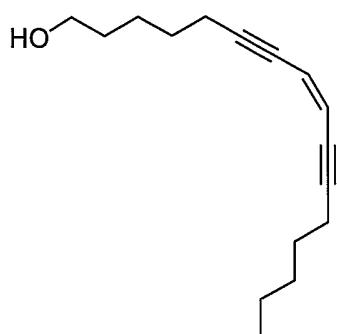
- 63 -

dichloroethylene (7.52 g, 77.57 mmol), butylamine (7.7 ml, 77.57 mmol) and hept-6-yn-1-ol (2.9 g, 25.85 mmol) in dry ether (150 ml) was added CuI (0.49 g, 2.59 mmol) under argon. The mixture was stirred over night at room temperature. The whole reaction mixture was concentrated and used immediately in the next step without any further purification.

5

**Part C: Synthesis of (Z)-hexadeca-8-en-6,10-diyn-1-ol**

10



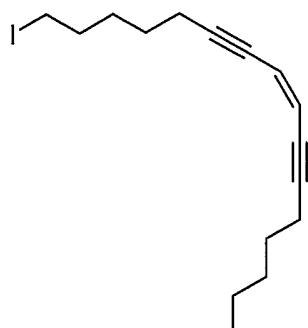
15 (Z)-9-chloronon-8-en-6-yn-1-ol (25.85 mmol) was stirred in piperidine (40 ml) under argon while  $\text{PdCl}_2(\text{PhCN})_2$  (0.5 g, 1.29 mmol) and hept-1-yne (2.98 g, 31.03 mmol) were added successively. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with half saturated aqueous ammonium chloride solution (150 ml) and extracted with ether (3 x 150 ml). The combined organic extracts were dried over  
20  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography ( $\text{SiO}_2$ , 15% ethyl acetate in petroleum spirit) giving the pure (Z)-hexadeca-8-en-6,10-diyn-1-ol as brown oil (1.2 g, 20%).

<sup>1</sup>H-NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ [ppm] = 0.91 (t, 3 H, J = 7.2 Hz), 1.2 – 1.7 (m, 12 H), 2.25  
25 – 2.5 (m, 4 H), 3.63 – 3.69 (m, 2 H), 5.69 – 5.77 (m, 1.64 H, cis), 5.87 – 5.9 (m, 0.36 H, trans)

- 64 -

**Part D: Synthesis of (Z)-1-iodohexadeca-8-en-6,10-divyne**

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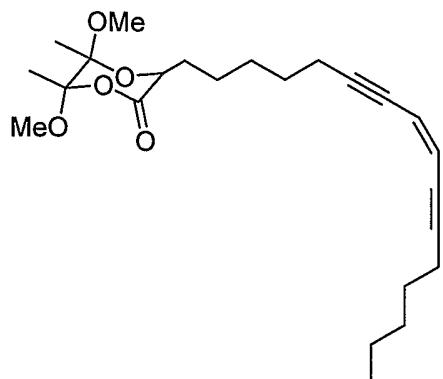
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To a solution of (Z)-hexadeca-8-en-6,10-diyn-1-ol (1.13 g, 4.87 mmol), PPh<sub>3</sub> (1.4 g, 5.35 mmol) and imidazole (0.4 g, 5.84 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (150 ml) was added I<sub>2</sub> (1.3 g, 5.11 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (150 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Gradient eluent 2% ethyl acetate in petroleum spirit) to provide the iodide in as a pale brown oil (1.4 g, 84%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.91 (t, 3 H, J = 7.2 Hz), 1.2 – 1.65 (m, 10 H), 1.86 (pant, 2 H, J = 7.1 Hz), 2.28 – 2.45 (m, 4 H), 3.19 (t, 0.36 H, trans, J = 7.0 Hz), 3.20 (t, 1.64 H, cis, J = 7.1 Hz), 5.69 – 5.77 (m, 1.64 H, cis), 5.88 – 5.9 (m, 0.36 H, trans)

**Part E: Synthesis of (Z)-3-(hexadeca-8-en-6,10-divynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

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- 65 -

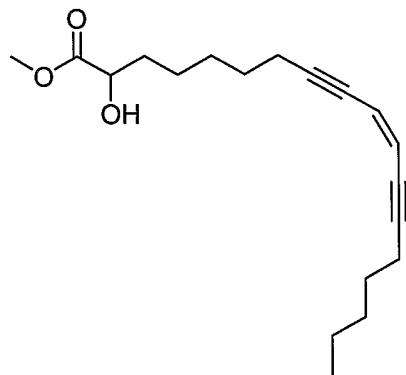
Lithium bis(trimethylsilyl)amide (1M in THF, 1.34 ml, 1.34 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (230 mg, 1.22 mmol) in THF (10 ml) at -78 deg. After 15 min (Z)-1-iodohexadeca-8-en-6,10-diyne (1.25 g, 3.65 mmol) 5 was added and the solution stirred at -78 deg for 15 min and then transferred into a cooling bath and stirred at -20 deg for 3 h. The reaction was quenched at -20 deg with acetic acid (0.15 ml, 2.68 mmol), Et<sub>2</sub>O (20 ml) was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether layers were concentrated giving a brown oil. The crude product was purified by column 10 chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as a pale yellow oil 152 mg (31%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.91 (t, 3 H, J = 7.1 Hz), 1.14 – 1.66 (m, 12 H), 1.39 (s, 3 H), 1.48 (s, 3 H), 1.8 – 1.96 (m, 2 H), 2.26 – 2.45 (m, 4 H), 3.30 (s, 3 H), 3.42 (s, 3 H), 4.15 (t, 1 H, J = 5.9 Hz), 5.7 – 5.74 (m, 1.5 H, cis), 5.86 – 5.89 (m, 0.5 H, trans)

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**Part F: Synthesis of (Z)-methyl 2-hydroxyoctadeca-10-en-8,12-dynoate**

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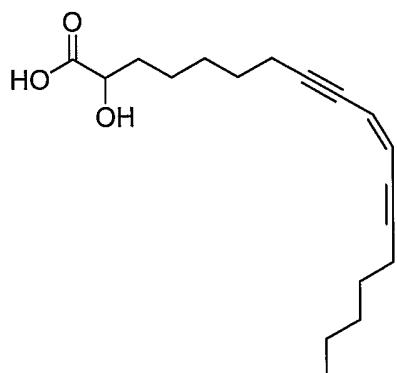
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(Z)-3-(hexadeca-8-en-6,10-diyynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one ( 40 mg, 0.099 mmol) was dissolved in a 0.3 M solution of TMSCl in MeOH (2 ml, 0.6 mmol) under argon. The solution was stirred at room temperature for 30 min and then concentrated under reduced pressure giving (Z)-methyl 2-hydroxyoctadeca-10-en-8,12- 30 diynoate (30 mg) as oil. The product was used without further purification.

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**Part G: Synthesis of (Z)-2-hydroxyoctadeca-10-en-8,12-diynoic acid**

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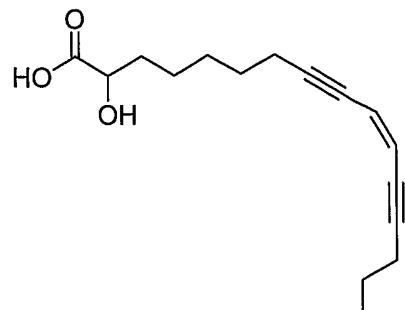
(Z)-methyl 2-hydroxyoctadeca-10-en-8,12-diynoate (30 mg, 0.098 mmol) was stirred in a 2:1 mixture of water and THF (10 ml) under argon. Then lithium hydroxide monohydrate (9.1 mg, 0.216 mmol) was added at 0 deg. The mixture was stirred at room temperature over night before 1 N HCl (25 ml) was added. The mixture was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give (Z)-2-hydroxyoctadeca-10-en-8,12-diynoic acid as oil (27.5 mg).

<sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz): δ[ppm] = 0.91 (t, 3 H, J = 7.1 Hz), 1.25 – 1.75 (m, 14 H), 2.3 – 2.44 (m, 4 H), 4.10 - 4.18 (m, 1 H), 5.78 (s, 1.54 H, cis), 5.90 (s, 0.46 H, trans).

**Example 5**

**(Z)-2-hydroxyhexadeca-10-en-8,12-diynoic acid**

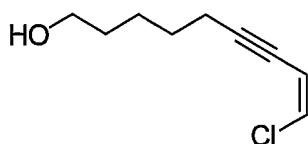
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**Part A: Synthesis of (Z)-9-chloronon-8-en-6-yn-1-ol**

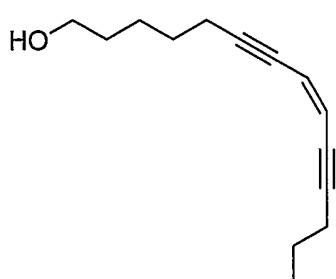
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To a solution of  $\text{Pd}(\text{PPh}_3)_4$  (1.55 g, 1.34 mmol), cis-1,2-dichloroethylene (8.0 g, 82.53 mmol), butylamine (8.19 ml, 82.53 mmol) and hept-6-yn-1-ol (3.0 g, 26.75 mmol) in dry ether (200 ml) was added CuI (0.51 g, 2.68 mmol) under argon. The mixture was stirred over night at room temperature. The whole reaction mixture was concentrated and used immediately in the next step without any further purification.

**Part B: Synthesis of (Z)-tetradeca-8-en-6,10-diyn-1-ol**

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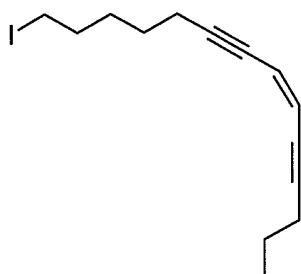
(*Z*)-9-chloronon-8-en-6-yn-1-ol (26.75 mmol) was stirred in piperidine (40 ml) under argon while  $\text{PdCl}_2(\text{PhCN})_2$  (0.51 g, 1.34 mmol) and pent-1-yne (2.19 g, 32.1 mmol) were added successively. The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with half saturated aqueous ammonium chloride solution (150 ml) and extracted with ether (3 x 150 ml). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography ( $\text{SiO}_2$ , 20% ethyl acetate in petroleum spirit) giving the pure (*Z*)-tetradeca-8-en-6,10-diyn-1-ol as a brown oil (3.1 g, 56%).

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.03 (t, 3 H, J = 7.3 Hz), 1.4 – 1.72 (m, 8 H), 2.25 – 2.48 (m, 4 H), 3.59 – 3.72 (m, 2 H), 5.66 – 5.8 (m, 1.85 H, cis), 5.87 – 5.91 (m, 0.15 H, trans)

5 Part C: Synthesis of (Z)-14-iodotetradeca-6-en-4,8-diyne

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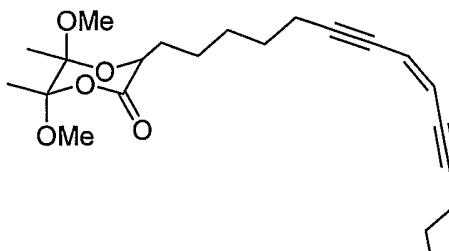


To a solution of (Z)-tetradeca-8-en-6,10-diyne-1-ol (2.91 g, 14.24 mmol), PPh<sub>3</sub> (4.11 g, 15.67 mmol) and imidazole (1.16 g, 17.09 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (400 ml) was added I<sub>2</sub> 15 (3.79 g, 14.95 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (250 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Gradient eluent 2% ethyl 20 acetate in petroleum spirit) to provide the iodide as a pale brown oil (3.7 g, 83%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 1.03 (t, 3 H, J = 7.3 Hz), 1.44 – 1.70 (m, 6 H), 1.76 – 1.96 (m, 2 H), 2.25 – 2.49 (m, 4 H), 3.19 (t, 2 H, J = 7.0 Hz), 5.66 – 5.81 (m, 1.88 H, cis), 5.87 – 5.91 (m, 0.12 H, trans)

25 Part D: Synthesis of (Z)-5,6-dimethoxy-5,6-dimethyl-3-(tetradeca-8-en-6,10-diy vinyl)-1,4-dioxan-2-one

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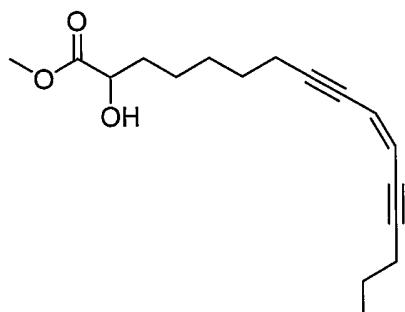
Lithium bis(trimethylsilyl)amide (1M in THF, 3.9 ml, 3.9 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (750 mg, 3.93 mmol) in THF (20 ml) at -78 deg. After 15 min (Z)-14-iodotetradeca-6-en-4,8-diyne (3.7 g, 11.78 mmol) 5 was added and the solution stirred at -78 deg for 15 min and then transferred into a cooling bath and stirred at -20 deg for 3 h. The reaction was quenched at -20 deg with acetic acid (0.45 ml, 7.86 mmol), Et<sub>2</sub>O (50 ml) was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether layers was concentrated giving a brown oil. The crude product was purified by column 10 chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as a pale yellow oil 480 mg (32%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 1.03 (t, 3 H, J = 7.3 Hz), 1.35 – 1.7 (m, 8 H), 1.39 (s, 3 H), 1.48 (s, 3 H), 1.78 – 1.96 (m, 2 H), 2.24 – 2.46 (m, 4 H), 3.30 (s, 3 H), 3.42 (s, 3 H), 4.13 – 4.2 (m, 1 H), 5.69 – 5.75 (m, 1.8 H, cis), 5.86 – 5.9 (m, 0.2 H, trans)

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#### Part E: Synthesis of (Z)-methyl 2-hydroxyhexadeca-10-en-8,12-dynoate

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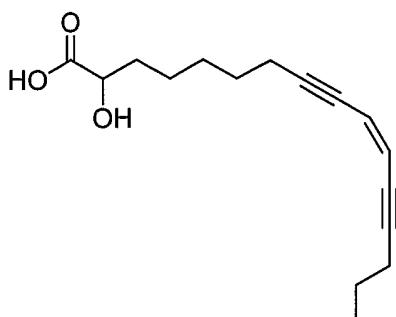


(Z)-5,6-dimethoxy-5,6-dimethyl-3-(tetradeca-8-en-6,10-diylyn)-1,4-dioxan-2-one (142 mg, 25 0.378 mmol) was dissolved in a 0.3 M solution of TMSCl in MeOH (8 ml, 2.4 mmol) under argon. The solution was stirred for 30 min at room temperature and then concentrated under reduced pressure giving (Z)-methyl 2-hydroxyhexadeca-10-en-8,12-dynoate (104 mg) as oil. The product was used without further purification.

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**Part F: Synthesis of (Z)-2-hydroxyhexadeca-10-en-8,12-diynoic acid**

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10 (Z)-methyl 2-hydroxyhexadeca-10-en-8,12-diynoate (104 mg, 0.376 mmol) was stirred in a 2:1 mixture of water and THF (30 ml) under argon. Lithium hydroxide monohydrate (35 mg, 0.83 mmol) was added at 0 deg. The mixture was stirred at room temperature over night before 1 N HCl (100 ml) was added. The reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, 15 filtered and concentrated under reduced pressure to give (Z)-2-hydroxyhexadeca-10-en-8,12-diynoic acid as an oil (98.2 mg).

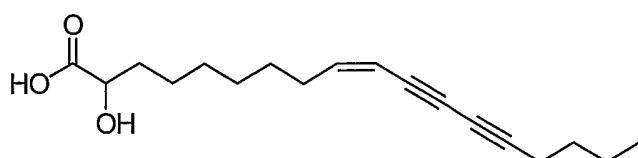
<sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz): δ[ppm] = 1.01 (t, 3 H, J = 7.4 Hz), 1.35 – 1.75 (m, 10 H), 2.25 – 2.45 (m, 4 H), 4.15 (dd, 1 H, J = 4.2 Hz, J = 7.6 Hz), 5.77 (s, 1.84 H, cis), 5.89 (s, 0.16 H, trans)

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**Example 6**

(Z)-2-hydroxyoctadeca-9-en-11,13-diynoic acid

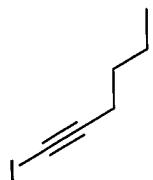
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**Part A: Synthesis of 1-iodohex-1-yne**

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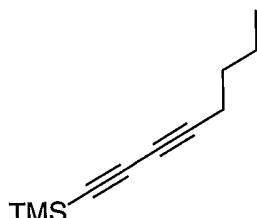
A 1.6 M solution of n-butyl lithium in hexane (79.13 ml, 126.61 mmol) was added slowly to a solution of 1-hex-1-yne (8 g, 97.39 mmol) in dry THF (250 ml) at -20 °C under argon and stirred for 1 h. The reaction mixture was then cooled to -40 °C and treated with iodine (32.13 g, 126.61 mmol). After stirring for 12 h at room temperature the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (500 ml) and extracted with ethyl acetate (2 x 200 ml). The combined organic layers were washed with saturated sodium thiosulfate solution (2 x 100 ml) and saturated brine (2 x 20 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure giving 1-iodohex-1-yne as a pale brown oil in quantitative yield. The material was used in the next step without any further purification.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.90 (t, 3 H, J = 7.0 Hz), 1.3 – 1.6 (m, 4 H), 2.36 (t, 2 H, 6.9 Hz)

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**Part B: Synthesis of trimethyl(octa-1,3-diynyl)silane**

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A solution of trimethylsilylacetylene (9.9 g, 100.94 mmol) and 1-iodohex-1-yne (7.0 g, 33.65 mmol) in degassed piperidine (50 ml) was cooled to 0°C under argon. Copper (I) chloride (0.33 g, 3.37 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h of stirring the reaction mixture was quenched with half

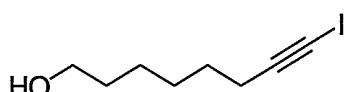
- 72 -

saturated aqueous ammonium chloride solution (150 ml) and extracted with diethyl ether (2 x 100 ml). The combined organic layers were washed with saturated brine (2 x 75 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO<sub>2</sub>, PET-spirit) to give trimethyl(octa-1,3-5 diynyl)silane (3.5 g, 58%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.18 (s, 9 H), 0.86 – 0.96 (m, 3 H), 1.3 – 1.6 (m, 4 H), 2.27 (t, 2 H, J = 6.8 Hz)

#### Part C: Synthesis of 8-iodooct-7-yn-1-ol

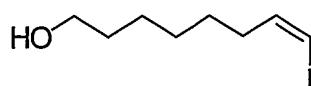
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To a solution of oct-7-yn-1-ol (2.29 g, 18.15 mmol) in MeOH (20 ml) was added an aqueous solution of KOH (2.55 g, 45.36 mmol) in water 4 ml) at 0 deg. After 10 minutes I<sub>2</sub> (5.07 g, 19.97 mmol) was added in one portion and the mixture was then warmed to room temperature. After being stirred at room temperature overnight the mixture was diluted with water (50 ml) and the aqueous layer was extracted with ether (3 x 70 ml). The combined organic layers were washed with saturated brine (2 x 30 ml) and half saturated aqueous sodiumthiosulphate solution (2 x 30 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated giving a pale yellow oil (3.87 g, 83%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 1.1 – 1.7 (m, 8 H), 2.36 (t, 2 H, J = 6.8 Hz), 3.64 (t, 2 H, J = 6.5 Hz)

25    Part D: Synthesis of (Z)-8-iodooct-7-en-1-ol



A mixture of 8-iodooct-7-yn-1-ol (1.4 g, 5.55 mmol), p-toluenesulfonhydrazide (2.07 g, 11.11 mmol) and sodium acetate (1.37 g, 16.66 mmol) were refluxed in a 1:1 mixture of water and THF (150 ml) overnight. The reaction mixture was cooled to room temperature

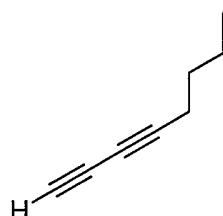
- 73 -

and diluted with half saturated aqueous ammonium chloride solution (300 ml) and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO<sub>2</sub>, 15% ethyl acetate in PET-spirit) to give (Z)-8-5 iodooct-7-en-1-ol as a pale yellow oil (0.8 g, 56%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 1.3 – 1.7 (m, 8 H), 2.05 – 2.25 (m, 2 H), 3.65 (t, 2 H, J = 6.5 Hz), 6.09 – 6.23 (m, 2 H)

#### **Part E: Synthesis of octa-1,3-diyne**

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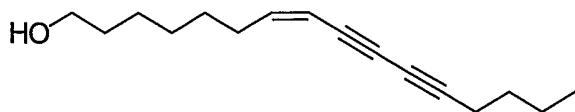


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A solution of trimethyl(octa-1,3-diyynyl)silane (2.2 g, 12.34 mmol) in 50 ml of methanol was treated with potassium carbonate (1.88 g, 13.57 mmol) under argon at room temperature for 1 h. The mixture was quenched with half saturated aqueous ammonium chloride solution (150 ml) and extracted with ether (3 x 75 ml). The combined organic layers were washed with saturated brine (2 x 75 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure giving the product which was used in the next step without any further purification.

#### **Part F: Synthesis of (Z)-hexadeca-7-en-9,11-diyne-1-ol**

25



Crude octa-1,3-diyne (12.34 mmol) was stirred in degassed piperidine (25 ml) while octa-30 1,3-diyne (0.79 g, 3.12 mmol) was added followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.24 g, 0.34 mmol) under argon. The mixture was cooled to 0°C and copper (I) iodide (78 mg, 0.41 mmol) was

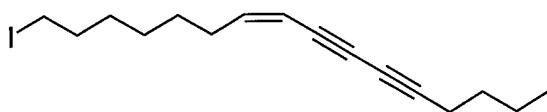
- 74 -

added. The reaction was stirred at 0°C for 5 min and then allowed to warm to room temperature overnight. The reaction mixture was diluted with diethyl ether (100 ml). The resulting solution was washed with half saturated aqueous ammonium chloride solution (2 x 100 ml) and saturated brine (2 x 100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, gradient eluent 1 - 15 % ethyl acetate in PET-spirit) to give (Z)-hexadeca-7-en-9,11-diyn-1-ol as brown oil (0.66 g, 90%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.85 – 1.00 (m, 3 H), 1.3 – 1.7 (m, 12 H), 2.25 – 2.44 (m, 4 H), 3.65 (t, 2 H, J = 6.5 Hz), 5.42 – 5.52 (m, 1 H), 6.02 (dt, 1 H, J = 10.8 Hz, J = 7.5 Hz)

#### Part G: Synthesis of (Z)-16-iodohexadeca-9-en-5,7-diyne

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To a solution of (Z)-hexadeca-7-en-9,11-diyn-1-ol (0.6 g, 2.58 mmol), PPh<sub>3</sub> (0.75 g, 2.84 mmol) and imidazole (0.21 g, 3.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (75 ml) was added I<sub>2</sub> (0.69 g, 2.71 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Gradient eluent 0% to 2% ethyl acetate in petroleum spirit) to provide (Z)-16-iodohexadeca-9-en-5,7-diyne as a pale yellow oil (0.57 g, 65%).

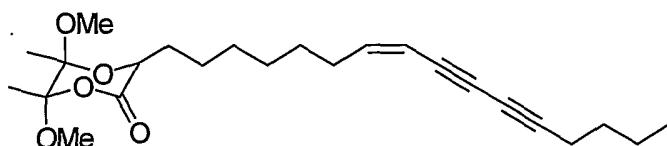
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.86 – 0.98 (m, 3 H), 1.2 – 1.64 (m, 10 H), 2.2 – 2.5 (m, 4 H), 3.19 (t, 2 H, J = 7.0 Hz), 5.42 – 5.53 (m, 1 H), 6.01 (dt, 1 H, J = 10.8 Hz, J = 7.5 Hz)

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**Part H: Synthesis of (Z)-3-(hexadeca-7-en-9,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

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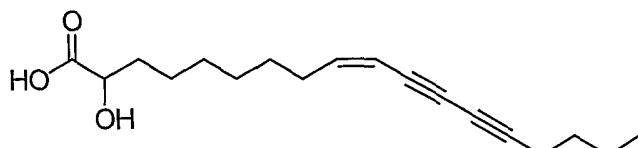


Lithium bis(trimethylsilyl)amide (1M in THF, 0.52 ml, 0.52 mmol) was added to a stirred  
10 solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (98 mg, 0.52 mmol) in THF  
(10 ml) at -78°C. After 15 min (Z)-16-iodohexadeca-9-en-5,7-diyne (0.53 g, 1.55 mmol)  
was added and the solution stirred at -78°C for 15 min and then transferred into a cooling  
bath and stirred at -20°C for 3 h. The reaction was quenched at -20°C deg with acetic acid  
15 (0.06 ml, 1.04 mmol), Et<sub>2</sub>O was added and the precipitated salts removed by filtration  
through a plug of silica. The salt was washed with ether. The combined ether was  
concentrated giving a yellow oil. The crude product was purified by column  
chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as a pale yellow  
oil 9 mg, 5%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.85 – 0.98 (m, 3 H), 1.2 – 1.65 (m, 12 H), 1.39 (s,  
20 3 H), 1.48 (s, 3 H), 1.78 – 1.96 (m, 2 H), 2.22 – 2.42 (m, 4 H), 4.15 (t, 1 H, J = 5.9 Hz),  
5.40 – 5.51 (m, 1 H), 6.01 (dt, 1 H, J = 10.8 Hz, J = 7.5 Hz)

**Part I: Synthesis of (Z)-2-hydroxyoctadeca-9-en-11,13-diynoic acid**

25



(Z)-3-(hexadeca-7-en-9,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (12 mg,  
30 0.029 mmol) was dissolved in a 9:1 mixture of THF and water (5 ml) and stirred at room  
temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml)

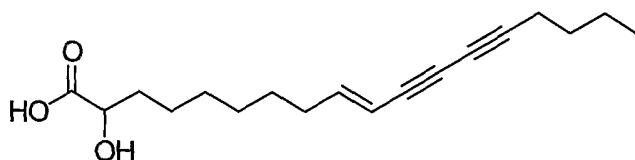
- 76 -

and washed with 2.5 M aqueous NaOH solution (5 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl (2 x), and brine (2 x), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give (Z)-2-hydroxyoctadeca-9-en-11,13-dynoic acid (7.7 mg, 91%) as an oil.

- 5      $^1\text{H-NMR}$  ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz):  $\delta$ [ppm] = 0.91 (t, 3 H, J = 7.2 Hz), 1.2 – 1.9 (m, 14 H), 2.26 – 2.42 (m, 4 H), 4.08 – 4.19 (m, 1 H), 5.54 (d, 1 H, J = 10.8 Hz), 6.1 – 6.2 (m, 1 H)

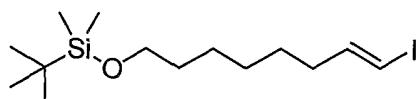
### Example 7

10   (E)-2-hydroxyoctadeca-9-en-11,13-dynoic acid



15

**Part A: Synthesis of (E)-tert-butyl(8-iodooct-7-enyloxy)dimethylsilane**



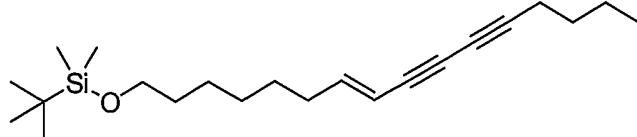
- 20   To a stirred solution of tert-butyldimethyl(oct-7-ynyloxy)silane (6 g, 24.95 mmol) in dry THF (350 ml) was added half of the amount of Cp<sub>2</sub>Zr(H)Cl (4 g, 15.51 mmol) at room temperature under argon. After stirring for 20 min, the other half of Cp<sub>2</sub>Zr(H)Cl was added and the mixture was stirred for 20 more min, then iodine (6.3 g, 24.95 mmol) was added until a dark red colour became permanent. The mixture was diluted with hexane (1.2 L) and the zirconium salts were filtered on a pad of Celite. The filtrate was washed with half saturated aqueous sodiumthiosulphate solution (3 x 300 ml), saturated brine (2 x 300 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give (E)-tert-butyl(8-iodooct-7-enyloxy)dimethylsilane as pale brown oil (7.36 g, 80%).
- 25

- 1      $^1\text{H-NMR}$  (CDCl<sub>3</sub>, 200 MHz):  $\delta$ [ppm] = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.1 – 1.7 (m, 8 H), 1.95 – 2.15 (m, 2 H), 3.59 (t, 2 H, J = 6.4 Hz), 5.97 (dt, 1 H, J = 14.3 Hz, J = 7.4 Hz), 6.51 (dt, 1 H, J = 14.3 Hz, J = 7.1 Hz)

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**Part B: Synthesis of (E)-tert-butyl(hexadeca-7-en-9,11-diynyoxy)dimethylsilane**

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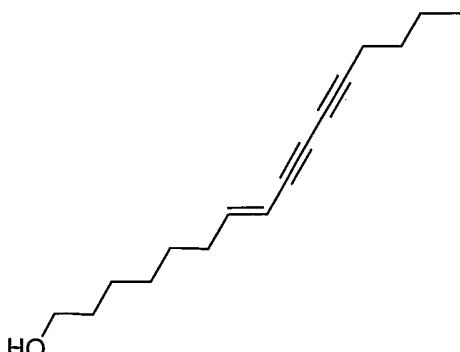
The freshly prepared octa-1,3-diyne (46.26 mmol) was stirred in degassed piperidine (150 ml) under argon while (E)-tert-butyl(8-iodooct-7-enyloxy)dimethylsilane (5.68 g, 15.42 mmol) was added followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.2 g, 1.7 mmol). The mixture was cooled to 10 0°C and copper (I) iodide (0.38 g, 2.0 mmol) was added. The reaction was stirred at 0°C for 5 min and then allowed to warm to room temperature overnight. The reaction mixture was diluted with diethyl ether (250 ml). The resulting solution was washed with half saturated aqueous ammonium chloride solution (2 x 300 ml) and saturated brine (2 x 300 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, 1% ethyl acetate in PET-spirit) to give (Z)-hexadeca-7-en-9,11-diyn-1-ol as brown oil (4.76 g, 89%).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.04 (s, 6 H), 0.85 – 0.95 (m, 3 H), 0.88 (s, 9 H), 1.2 – 1.6 (m, 12 H), 2.02 – 2.18 (m, 2 H), 2.24 – 2.38 (m, 2 H), 3.58 (t, 2 H, J = 6.4 Hz), 20 5.39 – 5.54 (m, 1 H), 6.27 (dt, 1 H, J = 15.9 Hz, J = 7.1 Hz)

**Part C: Synthesis of (E)-hexadeca-7-en-9,11-diyn-1-ol**

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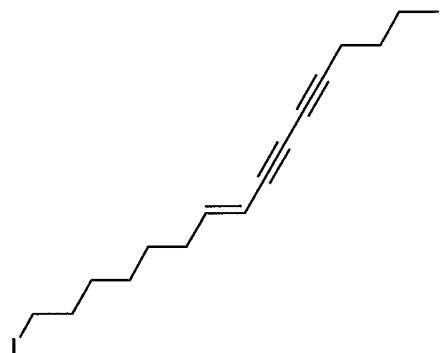
To a stirred solution of (E)-tert-butyl(hexadeca-7-en-9,11-diynyloxy)dimethylsilane (4.51 g, 13.0 mmol) in methanol (500 ml) was added acidic resin Dowex 50WX8. The mixture was stirred over night at room temperature, then filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, 5 15% ethyl acetate in petroleum spirit) to give (E)-hexadeca-7-en-9,11-diyn-1-ol as a pale brown oil (2.16 g, 72% yield).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.9 (t, 3 H, J = 7.2 Hz), 1.1 -1.65 (m, 12 H), 2.06 – 2.16 (m, 2 H), 2.31 (t, 2 H, J = 6.8 Hz), 3.58 – 3.67 (m, 2 H), 5.48 (d, 1 H, J = 15.8 Hz), 6.2 – 6.31 (m, 1 H)

10

**Part D: Synthesis of (E)-16-iodohexadeca-9-en-5,7-diyne**

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20

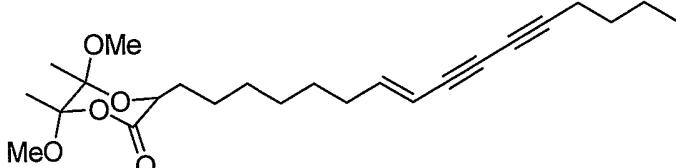
To a solution of (E)-hexadeca-7-en-9,11-diyn-1-ol (1.85 g, 7.96 mmol), PPh<sub>3</sub> (2.30 g, 8.76 mmol) and imidazole (0.65 g, 9.55 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added I<sub>2</sub> (2.12 g, 8.36 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (120 ml). The organic phase was separated 25 and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, Gradient eluent 0% to 2% ethyl acetate in petroleum spirit) to provide (E)-16-iodohexadeca-9-en-5,7-diyne as a pale yellow oil (2.1 g, 76%).

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.91 (t, 3 H, J = 7.2 Hz), 1.2 – 1.58 (m, 10 H), 1.76 – 1.88 (m, 2 H), 2.08 – 2.16 (m, 2 H), 2.31 (t, 2 H, J = 6.8 Hz), 3.18 (t, 2 H, J = 7.0 Hz), 5.45 – 5.52 (m, 1 H), 6.25 (dt, 1 H, J = 15.9 Hz, J = 7.1 Hz)

5 **Part E: Synthesis of (E)-3-(hexadeca-7-en-9,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

10



15

Lithium bis(trimethylsilyl)amide (1M in THF, 1.81 ml, 1.81 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (0.34 g, 1.81 mmol) in THF (15 ml) at -78°C. After 15 min the reaction mixture was warmed to -70°C and (E)-16-iodohexadeca-9-en-5,7-diynne (1.86 g, 5.43 mmol) was added. The solution was stirred between -70°C and -60°C for 1.5 h and then warmed to -20°C and stirred for 2.5 h. The reaction was quenched at -20°C with acetic acid (0.21 ml, 3.62 mmol), Et<sub>2</sub>O was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated giving a yellow oil. The crude product was purified by column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as a colourless oil 160 mg, 22%).

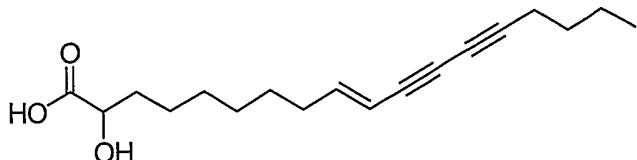
20

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.91 (t, 3 H, J = 7.2 Hz), 1.24 – 1.56 (m, 12 H), 1.39 (s, 3 H), 1.48 (s, 3 H), 1.82 – 1.9 (m, 2 H), 2.06 – 2.15 (m, 2 H), 2.31 (t, 2 H J = 6.9 Hz), 3.30 (s, 3 H), 3.41 (s, 3 H), 4.14 (t, 1 H, J = 5.9 Hz), 5.44 – 5.51 (m, 1 H), 6.26 (dt, 1 H, J = 15.9 Hz, J = 7.1 Hz)

25

**Part F: Synthesis of (E)-2-hydroxyoctadeca-9-en-11,13-diynoic acid**

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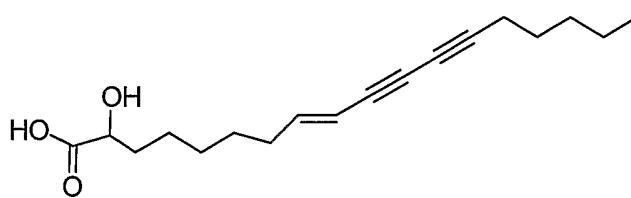
(E)-3-(hexadeca-7-en-9,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (20 mg, 0.053 mmol) was dissolved in a 9:1 mixture of THF and water (3 ml) and stirred at room temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml) 5 and washed with a 2.5 M aqueous NaOH solution (3 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl twice, and brine twice, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give (Z)-2-hydroxyoctadeca-9-en-11,13-diynoic acid (4.1mg, 52%) as a pale brown oil.

<sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz):  $\delta$  = 0.9 (t, 3 H, J = 7.3 Hz), 1.26 – 1.65 (m, 12 H), 1.69 – 10 1.76 (m, 2 H), 2.11 – 2.18 (m, 2 H), 2.34 (t, 2 H, J = 7.1 Hz), 4.05 (dd, 1 H, J = 7.5 Hz, J = 4.2 Hz), 5.55 – 5.62 (m, 1 H), 6.30 (dt, 1 H, J = 15.9 Hz, J = 7.1 Hz)

### Example 8

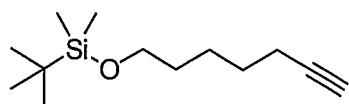
15 **Synthesis of (E)-2-hydroxyoctadeca-8-en-10,12-diynoic acid**

20



**Part A: Synthesis of tert-butyl(hept-6-vnyloxy)dimethylsilane**

25



To a stirred solution of hept-6-yn-1-ol (5.3 g, 47.25 mmol) in dry THF (450 ml) was added imidazole (7.08 g, 103.95 mmol) followed by tert-butyldimethylsilylchloride (7.83 g, 30 51.97 mmol) under nitrogen. The mixture was stirred for 16 h at room temperature before water (200 ml) and hexane (250 ml) were added. The layers were separated and the

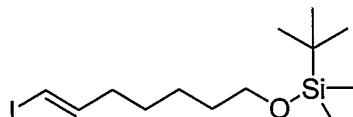
- 81 -

aqueous phase was extracted with hexane. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated to give the protected alcohol. The crude product was purified by column chromatography (SiO<sub>2</sub>, 0 – 1.5% ethyl acetate in petroleum spirit) to give the pure tert-butyl(hept-6-yloxy)dimethylsilane as a colourless oil (8.23 g, 77%).

5 The product was used immediately in the next reaction step.

**Part B: Synthesis of (E)-tert-butyl(7-iodohept-6-enyloxy)dimethylsilane**

10

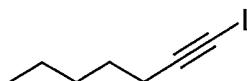


To a stirred solution tert-butyl(hept-6-yloxy)dimethylsilane (3.91 g, 17.27 mmol) in dry THF (450 ml) was added the half of the amount of Cp<sub>2</sub>Zr(H)Cl (2.76 g, 10.70 mmol) at room temperature under argon. After stirring for 20 min, the other half of Cp<sub>2</sub>Zr(H)Cl was added and the mixture was stirred for 20 more min, then iodine (4.38 g, 17.27 mmol) was added until a dark red colour became permanent. The mixture was diluted with hexane (800 ml) and the zirconium salts were filtered on a pad of Celite. The filtrate was washed with half saturated aqueous sodium thiosulphate solution (2 x 300 ml), saturated brine (2 x 300 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was chromatographed (SiO<sub>2</sub>, 2% ethyl acetate in pet. Spirit) to give (E)-tert-butyl(7-iodohept-6-enyloxy)dimethylsilane as pale brown oil (4.39 g, 72%).

15  
20  
25

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.07 (s, 6 H), 0.91 (s, 9 H), 1.15 – 1.73 (m, 6 H), 1.95 – 2.15 (m, 2 H), 3.61 (t, 2 H, J = 6.6 Hz), 5.99 (dt, 1 H, J<sup>1</sup> = 14.5 Hz, J<sup>2</sup> = 1.4 Hz), 6.53 (dt, 1 H, J = 14.3 Hz, J = 7.1 Hz)

**Part C: Synthesis of 1-iodohept-1-yne**

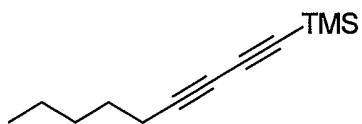


30 A 1.6 M solution of n-butyl lithium in hexane (25.34 ml, 40.55 mmol) was added slowly to a solution of hept-1-yne (3 g, 31.19 mmol) in dry THF (150 ml) at -20°C under argon and

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stirred for 1 h. The reaction mixture was then cooled to -40°C and treated with iodine (10.29 g, 40.55 mmol). After stirring for 12 h at room temperature the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (200 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic layers were washed with 5 saturated sodium thiosulfate solution (2 x 50 ml) and saturated brine (2 x 20 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure giving 1-iodohept-1-yne as a pale brown oil in quantitative yield. The material was used in the next step without any further purification.

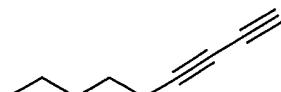
#### 10 **Part D: Synthesis of trimethyl(nona-1,3-diynyl)silane**



15 A solution of trimethylsilylacetylene (14.1 g, 143.2 mmol) and 1-iodohept-1-yne (10.6 g, 47.73 mmol) in degassed piperidine (70 ml) was cooled to 0°C under argon. Copper (I) chloride (0.47 g, 4.77 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h of stirring the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (250 ml) and extracted with diethyl ether 20 (2 x 200 ml). The combined organic layers were washed with saturated brine (2 x 100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, pentane) to give of trimethyl(nona-1,3-diynyl)silane as colourless oil (6.6 g, 72%). The product was used immediately in the next step.

25

#### **Part E: Synthesis of nona-1,3-diyne**



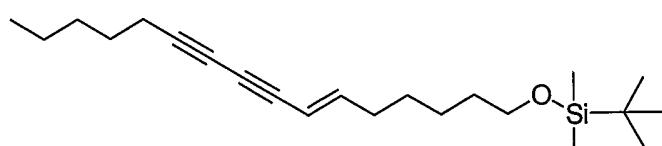
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A solution of trimethyl(nona-1,3-diynyl)silane (6.38 g, 33.17 mmol) in methanol (150 ml) was treated with potassium carbonate (5.04 g, 36.48 mmol) under argon at room temperature for 1 h. The mixture was quenched with half saturated aqueous ammonium chloride solution (400 ml) and extracted with ether (3 x 150 ml). The combined organic layers were washed with saturated brine (2 x 100 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure giving the product which was used in the next step without any further purification.

**Part F: Synthesis of (E)-tert-butyl(hexadeca-6-en-8,10-diynyoxy)dimethylsilane**

10

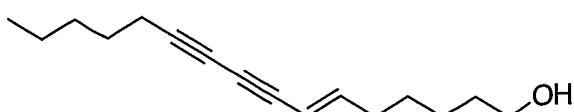


15 Crude nona-1,3-diyne (33.17 mmol) was stirred in degassed piperidine (100ml) while (E)-tert-butyl(7-iodohept-6-enyloxy)dimethylsilane (4.25 g, 12 mmol) was added followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.93 g, 1.32 mmol) under argon. The mixture was cooled to 0°C and copper (I) iodide (0.3 g, 1.56 mmol) was added. The reaction was stirred at 0°C for 5 min and then allowed to warm to room temperature overnight. The reaction mixture was diluted with 20 diethyl ether (200ml). The resulting solution was washed with half saturated aqueous ammonium chloride solution (2 x 200 ml) and saturated brine (2 x 200 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, gradient eluent 0 - 1 % ethyl acetate in PET-spirit) to give (E)-tert-butyl(hexadeca-6-en-8,10-diynyoxy)dimethylsilane as a brown oil (3.6 g, 86%).

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ = 0.04 (s, 6 H), 0.85 – 0.95 (m, 3 H), 0.88 (s, 9 H), 1.18 – 1.63 (m, 12 H), 2.04 – 2.22 (m, 2 H), 2.26 – 2.41 (m, 2 H), 3.62 (t, 2 H, J = 6.7 Hz), 5.39 – 5.54 (d, 1 H, J = 15.8 Hz), 6.29 (dt, 1 H, J = 15.9 Hz, J = 7.1 Hz)

**Part G: Synthesis of (E)-hexadeca-6-en-8,10-diyn-1-ol**

30

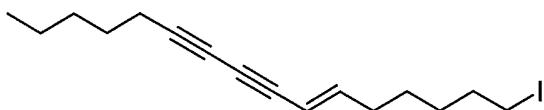


To a stirred solution of (E)-tert-butyl(hexadeca-6-en-8,10-diynyloxy)dimethylsilane (3.5 g, 10.1 mmol) in methanol (400 ml) was added acidic resin Dowex 50WX8. The mixture was stirred over night at room temperature, then filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO<sub>2</sub>, 5 15% ethyl acetate in petroleum spirit) to give (E)-hexadeca-6-en-8,10-diyn-1-ol as a pale brown oil (1.92 g, 82% yield).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.87 (tr, 1H, J = 7.1 Hz), 1.18 – 1.59 (m, 12H), 2.08 – 2.13 (m, 2H), 2.27 (tr, 2H, J = 7.1 Hz), 3.61 (dd, 2H, J<sup>1</sup> = 11.5 Hz, J<sup>2</sup> = 6.4 Hz), 5.46 (d, 1H, J = 15.9 Hz), 6.23 (dtr, 1H, J<sup>1</sup> = 15.9 Hz, J<sup>2</sup> = 7.1 Hz)

#### Part H: Synthesis of (E)-1-iodohexadeca-6-en-8,10-diyne

15



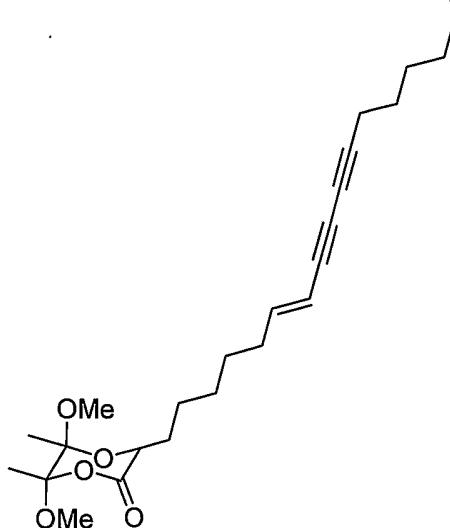
To a solution of (E)-hexadeca-6-en-8,10-diyn-1-ol (1.75 g, 7.53 mmol), PPh<sub>3</sub> (2.17 g, 8.27 mmol) and imidazole (0.62 g, 9.04 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added I<sub>2</sub> (2.0 g, 7.91 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (120 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 2% ethyl acetate in petroleum spirit) to provide (E)-1-iodohexadeca-6-en-8,10-diyne as a pale yellow oil (2.1 g, 80%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.90 (tr, 3H, J = 7.1 Hz), 1.23 – 1.46 (m, 6H), 1.49 – 1.60 (m, 4H), 1.82 (quint, 2H, J = 7.1 Hz), 2.11 – 2.16 (m, 2H), 2.31 (tr, 2H, J = 7.0 Hz), 3.17 (tr, 2H, J = 7.0 Hz), 5.49 (d, 1H, J = 15.8 Hz), 6.25 (dtr, 1H, J<sup>1</sup> = 15.8 Hz, J<sup>2</sup> = 7.1 Hz)

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**Part I: Synthesis of (E)-3-(hexadeca-6-en-8,10-divinyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

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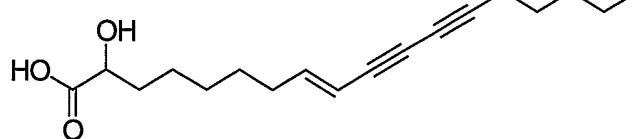
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- 15     Lithium bis(trimethylsilyl)amide (1M in THF, 0.59 ml, 0.59 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (0.1 g, 0.54 mmol) in THF (10 ml) at -78°C. After 15 min the reaction mixture was warmed to -50°C and (E)-1-iodohexadeca-6-en-8,10-diyne (0.55g, 1.61 mmol) was added. The solution was stirred between -50°C for 1 h and then warmed to -20°C and stirred for 2.5 h. The reaction was  
 20     quenched at -20°C with acetic acid (0.2 ml, 3.52 mmol), Et<sub>2</sub>O was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether layers was concentrated giving a yellow oil. The crude product was purified by column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as colourless oil (10 mg, 4.7%).
- 25     <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.89 (tr, 3H, J = 7.1 Hz), 1.22 – 1.59 (m, 18H), 1.83 – 1.89 (m, 2H), 2.08 – 2.14 (m, 2H), 2.30 (tr, 2H, J = 7.0 Hz), 3.30 (s, 3H), 3.41 (s, 3H), 4.14 (tr, 1H, J = 6.1 Hz), 5.47 (d, 1H, J = 15.9 Hz), 6.25 (dtr, 1H, J<sup>1</sup> = 15.9 Hz, J<sup>2</sup> = 7.1 Hz)

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**Part J: Synthesis of (E)-2-hydroxyoctadeca-8-en-10,12-diynoic acid**

5



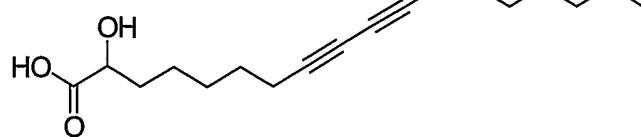
(E)-3-(hexadeca-6-en-8,10-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (4 mg, 0.01 mmol) was dissolved in a 9:1 mixture of THF and water solution (3 ml) and stirred at room temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml) and washed with 2.5 M aqueous NaOH solution (3 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl twice, and brine twice, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give (E)-2-hydroxyoctadeca-8-en-10,12-diynoic acid (1.6 mg, 55%) as a pale brown oil.

$^1\text{H-NMR}$  (( $\text{CD}_3$ )<sub>2</sub>CO, 400 MHz):  $\delta$ [ppm] = 0.77 (tr, 3 H,  $J$  = 7.0 Hz), 1.04 – 1.78 (m, 14H), 2.00 – 2.07 (m, 2H), 2.21 (tr, 2H,  $J$  = 7.0 Hz), 2.43 – 3.21 (br, 2H), 4.00 (dd, 1H,  $J^1$  = 7.5 Hz,  $J^2$  = 4.2 Hz), 5.46 (d, 1H,  $J$  = 15.8 Hz), 6.13 – 6.25 (m, 1H)

20 **Example 9**

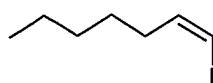
**(Z)-2-hydroxyoctadeca-12-en-8,10-diynoic acid**

25



**Part A: Synthesis of (Z)-1-iodohept-1-ene**

30

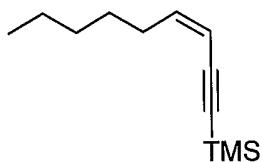


To a stirred solution of 0.5 M 9-BBN in THF (108 ml, 54.04 mmol) was added a solution of 1-iodohept-1-yne (10 g, 45.03 mmol) in THF (50 ml) via syringe under argon. After stirring at room temperature overnight the THF was completely removed under reduced pressure. Pentane (150 ml) was added to the resulting residue and treated with acetic acid 5 (3.1 ml, 54.04 mmol) via syringe. The mixture was stirred for 10 min. Ethanolamine (0.6 ml, 10% of total amount) was added and stirred for 5 min. The rest of the ethanolamine (5.9 ml) was then added slowly (10 – 15 min). The reaction mixture was then passed through a silica column and eluted with pentane to give (Z)-1-iodohept-1-ene which was used immediately in the next reaction step.

10

**Part B: Synthesis of (Z)-trimethyl(non-3-en-1-ynyl)silane**

15

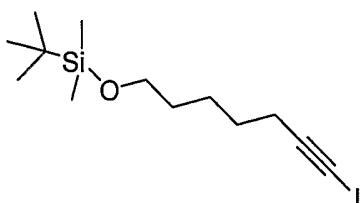


(Z)-1-iodohept-1-ene (7 g, 31.24 mmol) was stirred in degassed piperidine (250ml) while trimethylsilylacetylene (9.2 g, 93.72 mmol) was added followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2.41 g, 3.44 mmol) under argon. The mixture was cooled to 0°C and copper (I) iodide (0.77 g, 20 4.06 mmol) was added. The reaction was stirred at 0°C for 5 min and then allowed to warm to room temperature overnight. The reaction mixture was diluted with diethyl ether (500ml). The resulting solution was washed with half saturated aqueous ammonium chloride solution (2 x 800 ml) and saturated brine (2 x 500 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO<sub>2</sub>, gradient eluent 0 - 1 % ethyl acetate in PET-spirit) to give (Z)-trimethyl(non-3-en-1-ynyl)silane as brown liquid (5.1 g, 84%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.20 (s, 9H), 0.90 (tr, 3H, J = 6.5 Hz), 1.21 – 1.53 9m, 6H), 2.23 – 2.40 (m, 2H), 5.47 (d, 1H, J = 10.9 Hz), 5.95 (dtr, 1H, J<sup>1</sup> = 10.9 Hz, J<sup>2</sup> = 7.3 Hz)

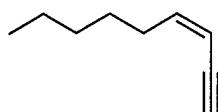
**Part C: Synthesis of tert-butyl(7-iodohept-6-ynyoxy)dimethylsilane**

5



A 1.6 M solution of n-butyl lithium in hexane (10.76 ml, 17.2 mmol) was added slowly to a solution of tert-butyl(hept-6-ynyoxy)dimethylsilane (3 g, 13.25 mmol) in dry THF (200 ml) at -20 °C under argon and stirred for 1 h. The reaction mixture was then cooled to -10 °C and treated with iodine (4.37 g, 17.22 mmol). After stirring for 16 h at room temperature the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (400 ml) and extracted with ether (3 x 200 ml). The combined organic layers were washed with half saturated sodium thiosulfate solution (2 x 150 ml) and saturated brine (2 x 100 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure giving 1-iodohex-1-yne as a pale yellow oil (4.64 g) in quantitative yield. The material was used in the next step without any further purification.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.07 (s, 6H), 0.91 (s, 9H), 1.35 – 1.68 (m, 6H), 2.37 (tr, 2H, J = 6.6 Hz). 3.61 (tr, 2H, J = 5.9 Hz)

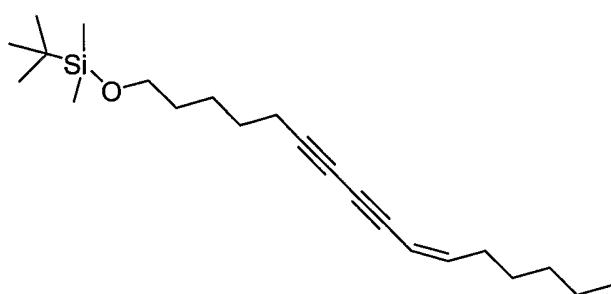
**20 Part D: Synthesis of (Z)-non-3-en-1-yne**

25 A solution of (Z)-trimethyl(non-3-en-1-ynyl)silane (5.0 g, 25.72 mmol) in methanol (120 ml) was treated with potassium carbonate (3.91 g, 28.29 mmol) under argon at room temperature for 1 h. The mixture was quenched with half saturated aqueous ammonium chloride solution (400 ml) and extracted with ether (3 x 100 ml). The combined organic layers were washed with saturated brine (2 x 50 ml), dried over MgSO<sub>4</sub>, filtered and 30 concentrated under reduced pressure giving the product which was used in the next step without any further purification.

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**Part E: Synthesis of (Z)-tert-butyl(hexadeca-10-en-6,8-diynyoxy)dimethylsilane**

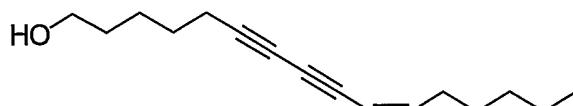
5



- 10 A solution of freshly prepared (*Z*)-non-3-en-1-yne (25.72 mmol) and tert-butyl(7-iodohept-6-yloxy)dimethylsilane (3.63 g, 10.29 mmol) in degassed piperidine (30 ml) was cooled to 0°C under argon. Copper (I) chloride (0.1 g, 1.03 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h of stirring the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (100 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic layers were washed with saturated brine (2 x 75 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO<sub>2</sub>, gradient eluent 0 – 5% ethyl acetate in petroleum spirit) to give (*Z*)-tert-butyl(hexadeca-10-en-6,8-diynyoxy)dimethylsilane as pale brown oil (2.7 g, 75%).
- 15
- 20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ[ppm] = 0.07 (s, 6H), 0.80 – 0.96 (m, 12H), 1.20 – 1.67 (m, 12H), 2.24 – 2.40 (m, 4H), 3.61 (tr, 2H, J = 6.0 Hz), 5.46 (d, 1H, J = 10.8 Hz), 6.03 (dtr, 1H, J<sup>1</sup> = 10.8 Hz, J<sup>2</sup> = 7.5 Hz)

**Part F: Synthesis of (*Z*)-hexadeca-10-en-6,8-diyn-1-ol**

25



- To a stirred solution of (*Z*)-tert-butyl(hexadeca-10-en-6,8-diynyoxy)dimethylsilane (3.14 g, 9.06 mmol) in methanol (400 ml) was added acidic resin Dowex 50WX8. The mixture 30 was stirred for over night at room temperature, then filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash

- 90 -

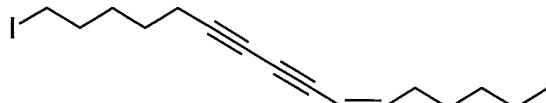
chromatography ( $\text{SiO}_2$ , 15% ethyl acetate in petroleum spirit) to give (*Z*)-hexadeca-10-en-6,8-diyn-1-ol as a pale yellow oil (1.45 g, 69%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz):  $\delta$  = 0.88 (tr, 3H,  $J$  = 6.9 Hz), 1.14 – 1.78 (m, 12H), 2.20 – 2.46 (m, 4H), 3.60 – 3.75 (m, 2H), 5.46 (d, 1H,  $J$  = 10.8 Hz), 6.03 (dtr, 1H,  $J^1$  = 10.8 Hz,  $J^2$  = 7.5 Hz)

5

#### Part G: Synthesis of (*Z*)-16-iodohexadeca-6-en-8,10-diyne

10



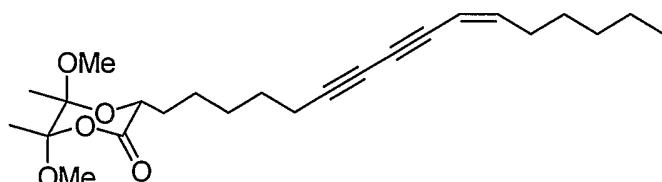
To a solution of (*Z*)-hexadeca-10-en-6,8-diyn-1-ol (1.34 g, 5.77 mmol),  $\text{PPh}_3$  (1.66 g, 6.34 mmol) and imidazole (0.47 g, 6.92 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (150 ml) was added  $\text{I}_2$  (1.54 g, 6.06 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it

15 was quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (120 ml). The organic phase was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 100 ml). The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 2% ethyl acetate in petroleum spirit) to provide (*Z*)-16-iodohexadeca-6-en-8,10-diyne as a pale yellow oil (1.5 g, 76%).

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ [ppm] = 0.89 (tr, 3H,  $J$  = 6.9 Hz), 1.24 – 1.66 (m, 10H), 1.85 (quint, 2H,  $J$  = 7.1 Hz), 2.28 – 2.38 (m, 4H), 3.19 (tr, 2H,  $J$  = 7.0 Hz), 5.56 (d, 1H,  $J$  = 10.7 Hz), 6.04 (dtr, 1H,  $J^1$  = 10.7 Hz,  $J^2$  = 7.5 Hz)

#### Part H: Synthesis of (*Z*)-3-(hexadeca-10-en-6,8-diynyl)-5,6-dimethoxy-5,6-dimethyl-25 1,4-dioxan-2-one

30



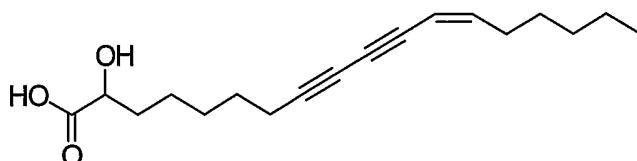
Lithium bis(trimethylsilyl)amide (1M in THF, 1.55 ml, 1.55 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (0.27 g, 1.41 mmol) in THF (10 ml) at -78°C. After 15 min the reaction mixture was warmed to -70°C and (Z)-16-5 iodohexadeca-6-en-8,10-diyne (1.45g, 4.24 mmol) was added. The solution was stirred at -70°C for 1 h and then warmed to -20°C and stirred for 2.5 h. The reaction was quenched at -20°C with acetic acid (0.19 ml, 3.24 mmol). Et<sub>2</sub>O was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated giving a yellow oil. The crude product was purified by 10 column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as pale yellow oil (0.15 g, 26%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.89 (tr, 3H, J = 6.9 Hz), 1.26 – 1.64 (m, 18H), 1.83 – 1.95 (m, 2H), 2.28 – 2.35 (m, 4H), 3.31 (s, 3H), 3.42 (s, 3H), 4.15 (tr, 1H, J = 5.9 Hz), 5.46 (d, 1H, J = 10.8 Hz), 6.03 (dtr, 1H, J<sup>1</sup> = 10.8 Hz, J<sup>2</sup> = 7.5 Hz)

15

#### Part I: Synthesis of (Z)-2-hydroxyoctadeca-12-en-8,10-diynoic acid

20



(Z)-3-(hexadeca-10-en-6,8-diynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (45 mg, 0.11 mmol) was dissolved in a 9:1 mixture of THF and water (10 ml) and stirred at room temperature for 45 min. The reaction mixture was diluted with dichloromethane (30 ml) 25 and washed with 2.5 M aqueous NaOH solution (10 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl twice, and brine twice, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give (Z)-2-hydroxyoctadeca-12-en-8,10-diynoic acid (29.3 mg, 91%) as a pale brown oil.

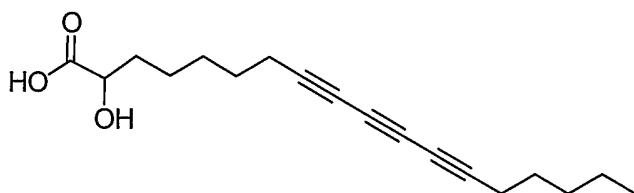
<sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>CO, 400 MHz): δ[ppm] = 0.89 (tr, 3H, J = 6.5 Hz), 1.22 – 1.85 (m, 14 H), 30 2.25 – 2.44 (m, 4H), 2.61 – 3.56 (br, 2H), 4.14 (dd, 1H, J<sup>1</sup> = 7.5 Hz, J<sup>2</sup> = 4.2 Hz), 5.53 (d, 1H, J = 10.8 Hz), 6.13 (dtr, 1H, J<sup>1</sup> = 10.8 Hz, J<sup>2</sup> = 7.6 Hz)

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**Example 10**

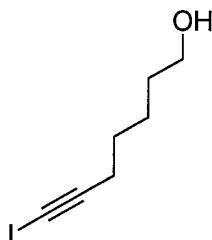
**2-hydroxyoctadeca-8,10,12-triynoic acid**

5



10    **Part A: Synthesis of 7-iodohept-6-yn-1-ol**

15



To a solution of hept-6-yn-1-ol (5 g, 44.58 mmol) in MeOH (50 ml) was added an aqueous solution of KOH (6.25 g, 111.44 mmol) in 10 ml of water at 0°C. After 10 minutes I<sub>2</sub> (12.44 g, 49.03 mmol) was added in one portion and the mixture was then 20 warmed to room temperature. After being stirred at room temperature overnight the mixture was diluted with water (100 ml) and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic layers were concentrated to give a yellow oil residue. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) which was washed with saturated brine (100 ml) and half saturated aqueous sodiumthiosulphate solution (100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, 25 filtered and concentrated. The crude product was chromatographed (SiO<sub>2</sub>, gradient eluent 5 – 20% ethyl acetate in petroleum spirit) giving a pale yellow oil (9.8 g, 77%).

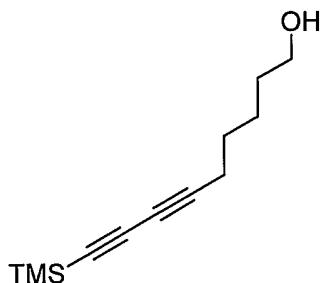
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 1.41 – 1.74 (m, 6H), 2.38 (tr, 2H, J = 6.8 Hz), 3.64 (tr, 2H, J = 6.4 Hz)

30

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**Part B: Synthesis of 9-(trimethylsilyl)nona-6,8-diyn-1-ol**

5



10 A solution of trimethylsilylacetylene (10.19 g, 103.72 mmol) and 7-iodohept-6-yn-1-ol (9.43 g, 39.6 mmol) in degassed piperidine (55 ml) was cooled to 0°C under argon. Copper (I) chloride (0.39 g, 3.96 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h of stirring the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (200 ml) and extracted with diethyl ether (3 x 200 ml). The combined organic layers were washed with saturated brine (2 x 100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO<sub>2</sub>, 2% ethyl acetate in petroleum spirit) to give 9-(trimethylsilyl)nona-6,8-diyn-1-ol as brown oil (8.2 g, 99 %).

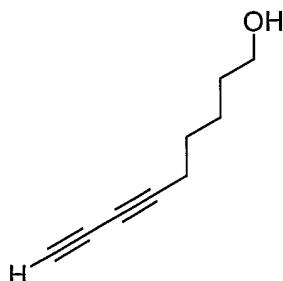
15

1 H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.18 (s, 9H), 1.39 – 1.67 (m, 6H), 2.30 (tr, 2H, J = 6.5 Hz), 3.54 – 3.71 (m, 2H)

20

**Part C: Synthesis of nona-6,8-diyn-1-ol**

25



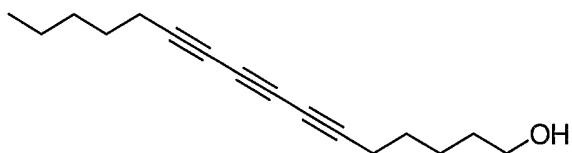
30 To a stirred solution of 9-(trimethylsilyl)nona-6,8-diyn-1-ol (4 g, 19.2 mmol) in dry THF (150 ml) under argon was added 1.0 M tetrabutylammoniumfluoride (TBAF) in THF

- 94 -

(28.8ml, 28.8 mmol) at 0°C. The mixture was stirred at room temperature for 3 h before it was diluted with water (500 ml). The aqueous phase was extracted with diethyl ether (3 x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a brown oil which was immediately used for next step without  
5 purification.

#### **Part D: Synthesis of hexadeca-6,8,10-triyn-1-ol**

10

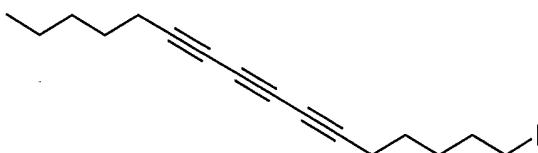


A solution of nona-6,8-diyn-1-ol (19.2 mmol) and 1-iodohept-1-yne (4.69 g, 21.12 mmol) in pyrrolidine (30 ml) under argon was treated with copper (I) iodide (0.37 g, 1.92 mmol)  
15 in small portions at 0°C. Then the reaction mixture was allowed to warm to room temperature. After 1 h of stirring the mixture was quenched with half saturated aqueous ammonium chloride solution (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with saturated brine (50 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by  
20 column chromatography (SiO<sub>2</sub>, 2.5% ethyl acetate in dichloromethane) to give hexadeca-6,8,10-triyn-1-ol as pale yellow oil (0.71 g, 16%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.90 (tr, 3H, J = 6.9 Hz), 1.12 – 1.68 (m, 12 H), 2.18 – 2.37 (m, 4H), 3.57 – 3.73 (m, 2H)

25 **Part E: Synthesis of 1-iodohexadeca-6,8,10-triyne**

30 To a solution of hexadeca-6,8,10-triyn-1-ol (0.65 g, 2.84 mmol), PPh<sub>3</sub> (0.82 g, 3.12 mmol) and imidazole (0.23 g, 3.41 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added I<sub>2</sub> (0.76 g, 2.98



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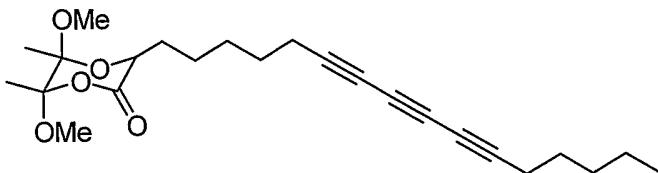
mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 ml). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 5% ethyl acetate in petroleum spirit) to provide 1-iodohexadeca-6,8,10-triyne as a colourless oil (0.64 g, 66%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.90 (tr, 3H, J = 7.1 Hz), 1.24 – 1.43 (m, 6H), 1.45 – 1.62 (m, 4H), 1.84 (quint, 2H, J = 7.0 Hz), 2.21 – 2.32 (m, 4H), 3.18 (tr, 2H, J = 7.0 Hz)

10

**Part F: Synthesis of 3-(hexadeca-6,8,10-triynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one**

15



Lithium bis(trimethylsilyl)amide (1M in THF, 0.69 ml, 0.69 mmol) was added to a stirred solution of 5,6-dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (0.12 g, 0.63 mmol) in THF (10 ml) at -78°C. After 15 min the reaction mixture was warmed to -50°C and 1-iodohexadeca-6,8,10-triyne (0.64 g, 1.88 mmol) was added. The solution was stirred at -50°C for 1 h and then warmed to -20°C and stirred for 2.5 h. The reaction was quenched at -20°C with acetic acid (0.08 ml, 1.45 mmol). Et<sub>2</sub>O was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated giving a yellow oil. The crude product was purified by column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as pale yellow oil (24 mg, 4%).

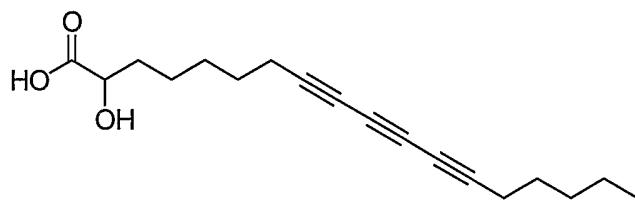
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz): δ = 0.90 (tr, 3H, J = 7.1 Hz), 1.21 – 1.60 (m, 18 H), 1.85 – 1.92 (m, 2H), 2.21 – 2.32 (m, 4H), 3.31 (s, 3H), 3.42 (s, 3H), 4.15 (tr, 1H, J = 5.9 Hz)

30

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**Part G: Synthesis of 2-hydroxyoctadeca-8,10,12-triynoic acid**

5



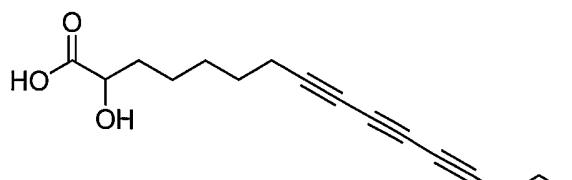
3-(hexadeca-6,8,10-triynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (5 mg, 0.012 mmol) was dissolved in a 9:1 mixture of THF and water (3 ml) and stirred at room 10 temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml) and washed with 2.5 M aqueous NaOH solution (3 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl twice, and brine twice, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give 2-hydroxyoctadeca-8,10,12-triynoic acid (2.2 mg, 67%) as a pale brown oil.

15  $^1\text{H-NMR}$  (( $\text{CD}_3)_2\text{CO}$ , 400 MHz):  $\delta$ [ppm] = 0.76 (tr, 3H,  $J$  = 7.0 Hz), 1.07 – 1.75 (m, 14H), 2.05-2.34 (m, 4H), 4.00 (dd, 1H,  $J^1$  = 7.3 Hz,  $J^2$  = 4.2 Hz)

**Example 11**

20 **2-hydroxyhexadeca-8,10,12-triynoic acid**

25



**Part A: Synthesis of tetradeca-6,8,10-triyn-1-ol**

30



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A solution of freshly prepared nona-6,8-diyn-1-ol (20.64 mmol) and 1-iodopent-1-yne (4.4 g, 22.71 mmol) in degassed piperidine (30 ml) was cooled to 0°C under argon. Copper (I) chloride (0.2 g, 2.06 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 1 h of stirring the reaction mixture was quenched with half saturated aqueous ammonium chloride solution (120 ml) and extracted with diethyl ether (3 x 150 ml). The combined organic layers were washed with saturated brine (2 x 75 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, 25% ethyl acetate in petroleum spirit) to give tetradeca-6,8,10-triyn-1-ol as a pale brown oil (2.0 g, 48%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.96 (tr, 3H, J = 7.3 Hz), 1.09 – 1.64 (m, 8H), 2.19 – 2.33 (m, 4H), 3.62 (tr, 2H, J = 6.3 Hz)

**Part B: Synthesis of 14-iodotetradeca-4,6,8-triyne**

15



To a solution of tetradeca-6,8,10-triyn-1-ol (2.0 g, 9.89 mmol), PPh<sub>3</sub> (2.85 g, 10.88 mmol) and imidazole (0.81 g, 11.87 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added I<sub>2</sub> (2.64 g, 10.38 mmol) in small portions at -10°C. The solution was stirred at -10°C for 1 h before it was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (200 ml). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 5% ethyl acetate in petroleum spirit) to provide 14-iodotetradeca-4,6,8-triyne as a colourless oil (2.6 g, 84%).

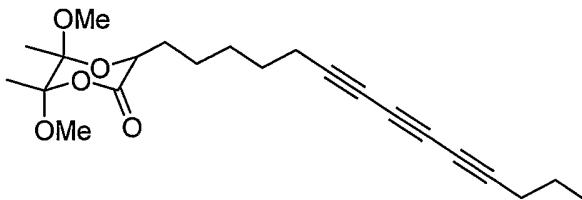
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.95 (tr, 3H, J = 7.4 Hz), 1.38 – 1.63 (m, 6H), 1.80 (quint, 2H, J = 7.0Hz), 2.12 – 2.35 (m, 4H), 3.15 (tr, 2H, J = 6.9 Hz)

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**Part C: Synthesis of 5,6-dimethoxy-5,6-dimethyl-3-(tetradeca-6,8,10-triynyl)-1,4-dioxan-2-one**

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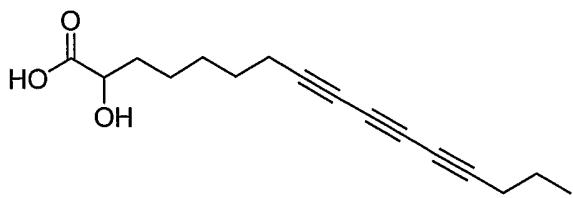
Lithium bis(trimethylsilyl)amide (1M in hexane, 2.64 ml, 2.64 mmol) was added to a stirred solution of 5,6-Dimethoxy-5,6-dimethyl-[1, 4] dioxan-2-one (0.53 g, 2.78 mmol) in THF (20 ml) at -78°C. After 15 min 14-iodotetradeca-4,6,8-triyne (2.60 g, 8.33 mmol) was added and the solution was stirred at -78°C for 1 h and then warmed to -20°C and stirred for 2.5 h. The reaction was quenched at -20°C with acetic acid (0.32 ml, 5.56 mmol). Et<sub>2</sub>O was added and the precipitated salts removed by filtration through a plug of silica. The salt was washed with ether. The combined ether was concentrated. The crude product was purified by column chromatography (SiO<sub>2</sub>, 7% EtOAc in petroleum spirit) to give the lactone as pale yellow oil (300 mg, 29%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.98 (tr, 3H, J = 7.3 Hz), 1.22 – 1.65 9m, 14H), 1.79 – 1.196 (m, 2H), 2.18 – 2.35 (m, 4H), 3.31 (s, 3H), 3.41 (s, 3H), 4.14 (tr, 1H, J = 5.9 Hz)

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**Part D: Synthesis of 2-hydroxyhexadeca-8,10,12-triynoic acid**

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3-(hexadeca-6,8,10-triynyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (7 mg, 0.019 mmol) was dissolved in a 9:1 mixture of THF and water (5 ml) and stirred at room temperature for 45 min. The reaction mixture was diluted with dichloromethane (20 ml) and washed with 2.5 M aqueous NaOH solution (5 ml). The aqueous phase was extracted with dichloromethane twice. The combined organic phase were washed with 3M HCl

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twice, and brine twice, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give 2-hydroxyhexadeca-8,10,12-triynoic acid (4.2 mg, 85%) as a pale brown oil.

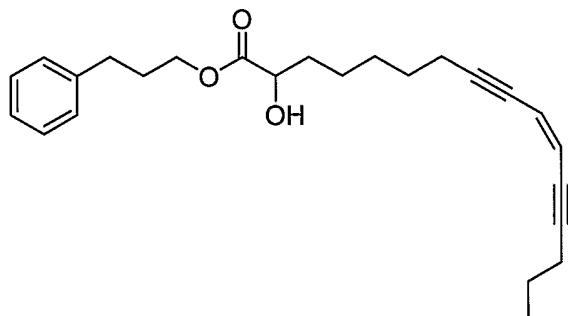
$^1\text{H-NMR}$  ( $\text{d}6$ -acetone, 400 MHz):  $\delta$ [ppm] = 0.85 (tr, 3H,  $J$  = 7.4 Hz), 1.23 – 1.72 (m, 10 H), 2.13 – 2.30 (m, 4H), 2.59 – 3.48 (br, 2H), 4.01 (dd, 1H,  $J^1$  = 7.5 Hz,  $J^2$  = 4.1 Hz)

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**Example 12**

**(Z)-3-phenylpropyl 2-hydroxyhexadeca-10-en-8,12-dynoate**

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15

5,6-Dimethoxy-5,6-dimethyl-3-((Z)-tetradeca-8-en-6,10-diynyl) [1,4]dioxan-2-one (0.02 g, 0.06 mmol) was dissolved in a 0.50 M solution of TMS chloride in 3-phenyl propan-1-ol (5 ml, 2.5 mmol) and heated to 80°C for 80 h. The reaction was diluted with saturated aqueous  $\text{NaHCO}_3$  (20 ml), the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 ml), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give the crude product. The crude product was purified through column chromatography ( $\text{SiO}_2$ , EtOAc-petrol, 9:1) to give the ester as a yellow oil 0.01 g (0.03 mmol, 50 %).

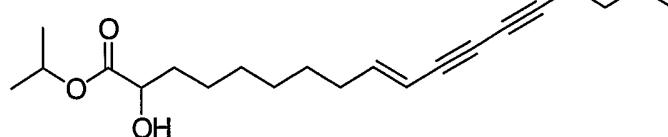
20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz):  $\delta$ [ppm] = 1.02 (tr, 3H,  $J$  = 7.2 Hz), 1.13 – 1.29 (m, 4H), 1.39 – 2.10 (m, 8H), 2.30 – 2.44 (m, 4H), 2.66 – 2.76 (m, 2H), 4.11 – 4.27 (m, 3H), 5.75 (s, 2H), 7.12 – 7.37 (m, 5H)

- 100 -

**Example 13**

**(E)-isopropyl 2-hydroxyoctadeca-9-en-11,13-diynoate**

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3-((E)-hexadeca-7-en-9,11-diyynyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.02 g, 10 0.05 mmol) was dissolved in a 0.50 M solution of TMS chloride in <sup>i</sup>PrOH (5 ml, 2.5 mmol) and heated to reflux at 80°C for 64 h. The reaction was diluted with saturated aqueous NaHCO<sub>3</sub> (20 ml), the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 ml), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the ester as a yellow oil (0.01 g, 0.03 mmol, 60 %).

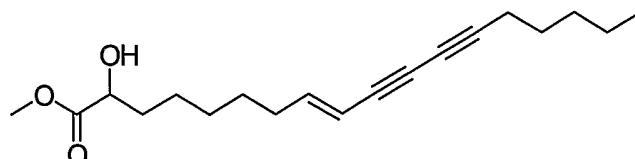
15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.88 (tr, 3H, J = 7.1 Hz), 1.14 – 1.85 (m, 16 H), 2.03 – 2.13 (m, 2H), 2.23 – 2.34 (m, 2H), 2.71 (d, 1H, J = 4.5 Hz), 4.03 – 4.14 (m, 1H), 5.03 – 5.12 (m, 1H), 5.44 (d, 1H, J = 15.9 Hz), 6.23 (dtr, 1H, J<sup>1</sup> = 15.9 Hz, J<sup>2</sup> = 6.9 Hz)

**Example 14**

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**(E)-methyl 2-hydroxyoctadeca-8-en-10,12-diynoate**

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3-((E)-heptadeca-7-en-9,11-diyynyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.01 mg, 0.03 mmol) was dissolved in a 0.5 M solution of TMS-chloride in MeOH (5 ml, 2.5 mmol) and stirred at room temperature for 30 min. The reaction was diluted with saturated aqueous NaHCO<sub>3</sub> (20 ml), the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 ml), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the ester as a yellow oil in quantitative yield..

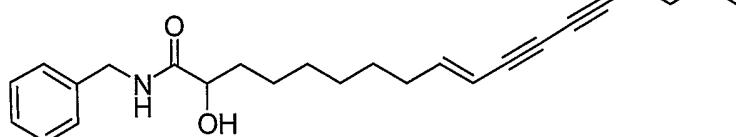
- 101 -

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.87 (tr, 3H, J = 7.0 Hz), 1.13 – 1.81 (m, 14 H), 2.06 – 2.11 (m, 2H), 2.28 (tr, 2H, J = 7.0 Hz), 2.65 (d, 1H, J = 5.6 Hz), 3.76 (s, 3H), 4.13 – 4.17 (m, 1H), 5.44 (d, 1H, J = 15.8 Hz), 6.22 (dtr, 1H, J<sup>1</sup> = 15.8 Hz, J<sup>2</sup> = 7.1 Hz)

5    **Example 15**

**(E)-N-benzyl-2-hydroxyoctadeca-9-en-11,13-diynamide**

10



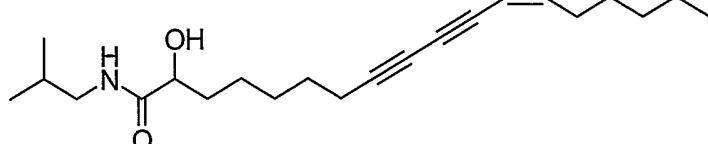
3-((E)-hexadeca-7-en-9,11-diynyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.01 mg, 0.03 mmol) was dissolved in benzylamine (5 ml) and stirred at room temperature for 15 120 h. The reaction was concentrated in vacuo. The crude amide was purified through column chromatography (SiO<sub>2</sub>, EtOAc-petrol, 1:5) to give the amide as a yellow oil 0.01 g (0.01 mmol, 33 %).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ[ppm] = 0.88 (tr, 3H, J = 7.3 Hz), 1.16 – 1.89 (m, 14 H), 2.02 – 2.12 (m, 2H), 2.28 (tr, 2H, J = 6.8 Hz), 4.11 – 4.18 (m, 1H), 4.45 (d, 2H, J = 5.9 Hz), 5.44 (d, 1H, J = 15.8 Hz, ), 6.22 (dtr, 1H, J<sup>1</sup> = 15.8 Hz, J<sup>2</sup> = 7.1 Hz), 6.63 – 6.76 (m, 1H), 7.20 – 7.36 (m, 5H) .

**Example 16**

25    **(Z)-2-hydroxy-N-isobutyloctadeca-12-en-8,10-diynamide**

30



3-((Z)-hexadeca-10-en-6,8-diynyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.03 mg, 0.07 mmol) was dissolved in benzylamine (2 ml) and stirred at room temperature for

- 102 -

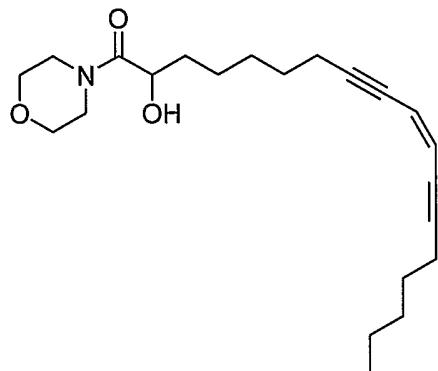
120 h. The reaction was concentrated in vacuo. The crude amide was purified through column chromatography ( $\text{SiO}_2$ , EtOAc-petrol, 2:3) to give the amide as a yellow oil 0.01 g (0.04 mmol, 57 %).

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta[\text{ppm}] = 0.81 - 0.93$  (m, 9H), 1.23 – 1.92 (m, 15H), 2.27 – 2.40 (m, 4H), 2.42 – 2.54 (m, 1H), 3.06 – 3.19 (m, 2H), 4.09 – 4.16 (m, 1H), 5.46 (d, 1H,  $J = 10.8$  Hz), 6.03 (dtr, 1H,  $J^1 = 10.8$  Hz,  $J^2 = 7.5$  Hz), 6.37 – 6.54 (m, 1H)

### Example 17

#### 10 (Z)-2-hydroxy-1-morpholinoctadeca-10-en-8,12-diyn-1-one

15



3-((Z)-hexadeca-8-en-6,10-diynyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (0.02 g, 20 0.04 mmol) was dissolved in morpholine (5 ml) and stirred at room temperature for 48 h. The reaction was concentrated in vacuo to yield the amide as a colourless oil (0.03 mmol, 0.01 g, 75 %).

1  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta[\text{ppm}] = 0.87$  (tr, 3H,  $J = 7.2$  Hz), 1.19 – 1.74 (m, 14H), 2.34–2.40 (m, 4H), 3.51 – 3.77 (m, 8H), 4.36 (tr, 1H,  $J = 7.1$  Hz), 5.69 (s, 2H)

25

The following compounds were tested (antibacterial assay and antifungal assay) as described in the materials and methods section

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Compound	Structure	Compound	Structure
1		12	
2		13	
3		14	
4		15	
5		16	
6		17	
7		18	
8		19	
9		20	
10		21	
11			

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### Antibacterial Assay Data

The amount of bacterial growth was measured by comparing the optical density (OD<sub>595</sub>) of control broths (without compound) and test broth (containing compound). Shown here is  
 5 the % reduction in the OD<sub>595</sub> of the test broth which indicates the level of antimicrobial activity.

Compound	<i>S. aureus</i> ATCC 25923	<i>Pseudomonas aeruginosa</i> ATCC 27853	<i>Escherichia coli</i> 25922	<i>Streptococcus pyogenes</i> ATCC 19615	MRSA clinical isolate
1	100.00	100.00	84.88	97.62	100.00
2	95.69	99.27	97.48	98.07	97.61
3	95.79	100.00	62.60	100.00	99.08
4	101.23	100.00	63.57	100.00	101.84
5	41.23	80.56	-19.77	42.97	3.68
6	60.51	85.94	-37.02	9.18	-14.18
7	-	99.17	30.23	48.64	87.85
8	100.00	98.59	75.97	100.00	100.00
9	96.51	94.27	100.00	59.64	100.00
10	100.00	100.00	100.00	100.00	100.00
11	69.54	100.00	36.82	100.00	100.00
12	40.38	88.89	54.37	94.40	33.85
13	46.15	100	55.34	84.80	56.15
14	45.19	99.26	52.43	100.00	100.00
15	39.42	98.52	66.99	69.60	60.80
16	54.81	100.00	53.40	100.00	83.08
17	31.73	94.07	62.14	79.20	30.77
18	31.15	93.33	57.28	99.20	27.69
19	41.35	85.19	69.90	93.60	36.92
20	66.35	89.63	64.08	100.00	31.54
21	55.77	95.56	77.67	90.40	41.85

These results show that most compounds are very active against gram-positive and gram-  
 10 negative bacteria.

Most compounds were active against Ps. aeruginose, an organism which is generally resistant to many traditional antimicrobials and infections are difficult to treat.

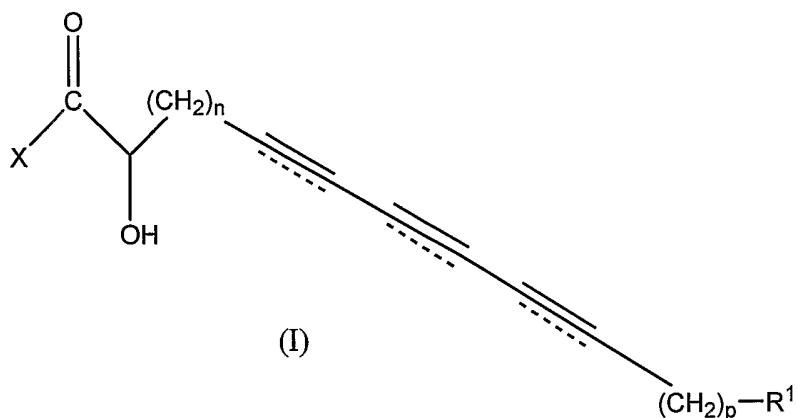
**Antifungal Assay Data**

Number of compound	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. tropicalis</i>	<i>C. krusei</i>	<i>C. parapsilosis</i>
Ketoconazole	~8 µM	~15µM	~2 µM	2-4 µM	<2 µM
1	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	500-1000 µM
2	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	500-1000 µM
3	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
4	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
5	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
6	500-1000 µM	~500 µM	500-1000 µM	500-1000 µM	~250 µM
7	500-1000 µM	500-1000µM	500-1000 µM	500-1000 µM	~2 µM
8	> 1-2 mM	500-1000 µM	-	~1000 µM	2-4 µM
9	> 1-2 mM	500-1000 µM	500-1000 µM	500-1000 µM	2-4 µM
10	500-1000 µM	500-1000 µM	500-1000 µM	500-1000 µM	125-250 µM
11	> 1-2 mM	1-2 mM	> 1-2 mM	> 1-2 mM	~30 µM
12	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
13	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
14	~1000 µM	~500 µM	~1000 µM	> 1-2 mM	> 1-2 mM
15	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
16	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
17	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
18	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
19	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
20	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM
21	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM	> 1-2 mM

- 5 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.
- 10 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

## CLAIMS

1. A compound of general formula (I)



5

wherein X is OR<sup>2</sup> or NR<sup>2</sup>R<sup>3</sup>, where R<sup>2</sup> and R<sup>3</sup> are each independently selected from H and an organic substituent or form together with N a heterocyclyl substituent;

R<sup>1</sup> is selected from H and an organic substituent;

10 n is an integer from 2 to 15;

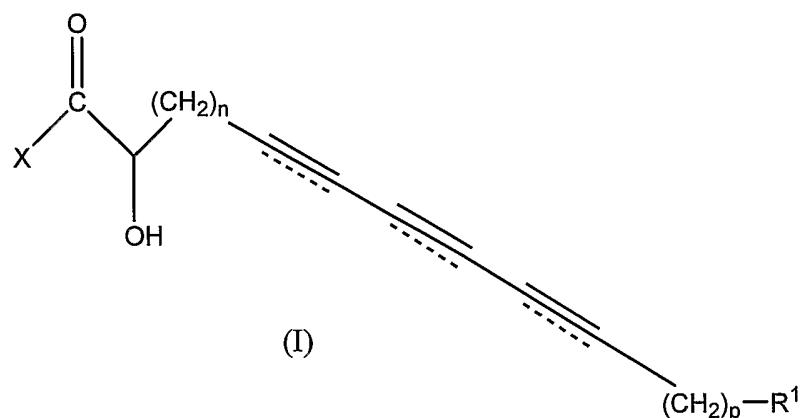
p is an integer from 0 to 15; and

each  group represents a double or triple bond with at least two of such groups being triple bonds.

15 2. The compound according to claim 1, wherein R<sup>1</sup> is selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted alkylthio, 20 optionally substituted alkynylthio, optionally substituted alkynylthio, optionally substituted arylthio, optionally substituted acyl, sulfoxide, sulfonyl, sulfonamide, amino, amido, carboxy ester, amino acid, and a peptide.

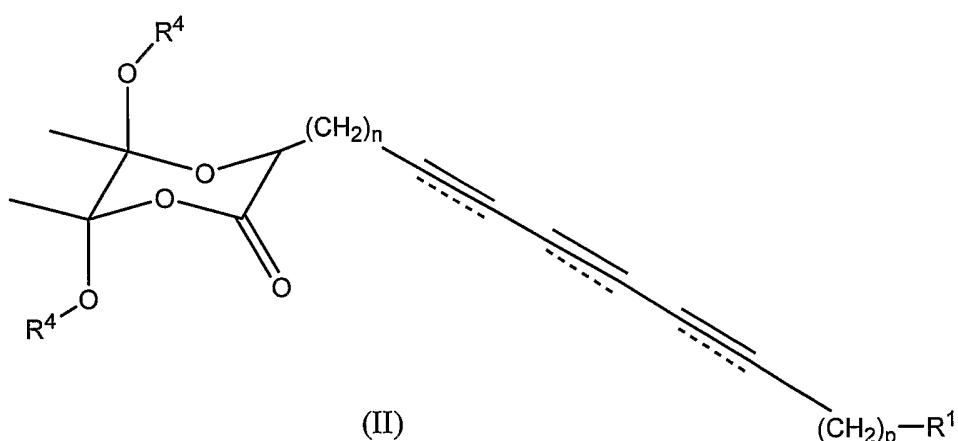
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11. A method of preparing a compound of general formula (I)



5

said method comprising the diacetal deprotection of a compound of general formula (II)



- 10 wherein X is  $\text{OR}^2$  or  $\text{NR}^2\text{R}^3$ , where  $\text{R}^2$  and  $\text{R}^3$  are each independently selected from H and an organic substituent or form together with N a heterocyclyl substituent;  
 $\text{R}^1$  is selected from H and an organic substituent;  
 $\text{R}^4$  is selected from H and an organic substituent;  
n is an integer from 2 to 15;  
15 p is an integer from 0 to 15; and

each group represents a double or triple bond with at least two of such

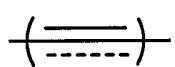
- 107 -

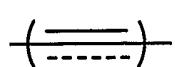
3. The compound according to claim 1 or 2, wherein R<sup>2</sup> and R<sup>3</sup> are each independently selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, and optionally 5 substituted heteroaryl.

4. The compound according to any one of claims 1 to 3, wherein n is an integer from 3 to 15.

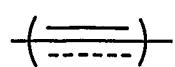
10 5. The compound according to any one of claims 1 to 4, wherein p is 0.

6. The compound according to any one of claims 1 to 5, wherein R<sup>1</sup> is an optionally substituted alkyl group.

15 7. The compound according to any one of claims 1 to 6, wherein relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>-moiety in formula (I) the three  groups represent an yne-yne-yne structure.

8. The compound according to any one of claims 1 to 6, wherein relative to the 20 proximity of the -(CH<sub>2</sub>)<sub>n</sub>-moiety in formula (I) the three  groups represent an yne-yne-ene structure.

9. The compound according to any one of claims 1 to 6, wherein relative to the 25 proximity of the -(CH<sub>2</sub>)<sub>n</sub>-moiety in formula (I) the three  groups represent an ene-yne-yne structure.

10. The compound according to any one of claims 1 to 6, wherein relative to the proximity of the -(CH<sub>2</sub>)<sub>n</sub>-moiety in formula (I) the three  groups represent an yne-ene-yne structure.

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groups being triple bonds.

12. The method according to claim 11, wherein R<sup>4</sup> is selected from H, optionally substituted alkyl, optionally substituted alkene, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted trialkylsilyl.  
5
13. The method according to claim 11 or 12, wherein the compound of formula (I) is selected from a compound according to any one of claims 1 to 10.
- 10 14. A method of treating a microbial infection in a subject, said method comprising administering to said subject an effective amount of a compound of general formula (I) as defined in claim 1, and/or a compound of general formula (II) as defined in claim 11, and/or a pharmaceutically acceptable salt or prodrug of one or both of said compounds.
- 15 15. The method according to claim 14, wherein the compound administered is a compound of general formula (I) as defined in any one of claims 1 to 10, and/or a pharmaceutically acceptable salt or prodrug thereof.
16. The method according to claim 14 or 15, wherein the microbial infection is a  
20 bacterial and/or fungal infection.
17. The method according to claim 14, 15 or 16, wherein the microbial infection is caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Methicillin-resistant Staphylococci* (MRSA) and/or *Candida*.  
25
18. An antimicrobial composition comprising a compound of general formula (I) as defined in claim 1, and/or a compound of general formula (II) as defined in claim 11, and/or a pharmaceutically acceptable salt or prodrug of one or both of said compounds, and a carrier material.

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19. The antimicrobial composition according to claim 18, wherein the compound is of general formula (I) as defined in any one of claims 1 to 10, and/or a pharmaceutically acceptable salt or prodrug thereof.
- 5 20. The antimicrobial composition according to claim 18 or 19 in the form of an antibacterial and/or antifungal composition.
21. Use of an antimicrobial composition according to claim 18, 19 or 20 to kill microbes.
- 10 22. Use according to claim 21, wherein the microbes are bacteria and/or fungi.
23. Use according to claim 21 or 22, wherein the microbes are selected from one or more of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Methicillin-resistant Staphylococci* (MRSA) and *Candida*.
- 15 24. Use of an antimicrobial composition according to claim 18, 19 or 20 to treat a microbial infection in a subject.
- 20 25. Use according to claim 24, wherein the compound used is of general formula (I) as defined in any one of claims 1 to 10, and/or a pharmaceutically acceptable salt or prodrug thereof.
26. Use according to claim 24 or 25, wherein the microbial infection is a bacterial and/or fungal infection.
- 25 27. Use according to claim 24, 25 or 26, wherein the microbial infection is caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Methicillin-resistant Staphylococci* (MRSA) and/or *Candida*.

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28. Use of a compound of general formula (I) as defined in claim 1, and/or a compound of general formula (II) as defined in claim 11, and/or a pharmaceutically acceptable salt or prodrug of one or both of said compounds, in the manufacture of a medicament for treating a microbial infection in a subject.

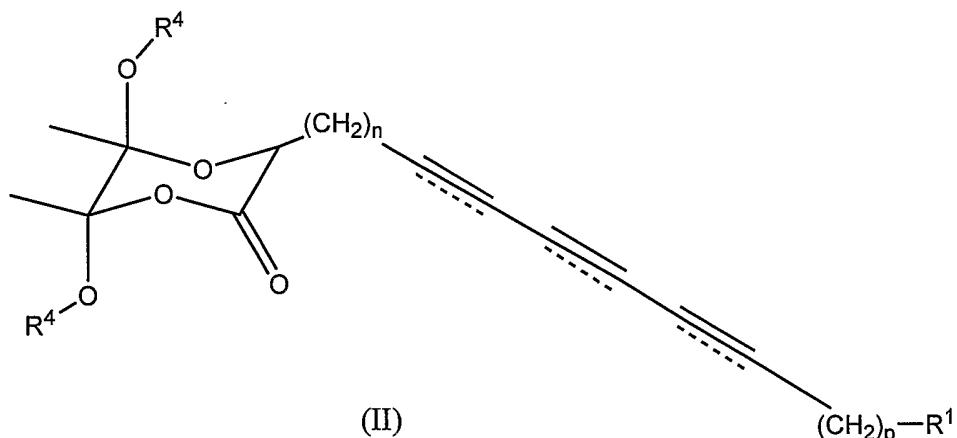
5

29. Use according to claim 28, wherein the compound used is of general formula (I) as defined in any one of claims 1 to 10, and/or a pharmaceutically acceptable salt or prodrug thereof.

10 30. Use according to claim 28 or 29, wherein the microbial infection is a bacterial and/or fungal infection.

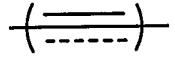
15 31. Use according to claim 28, 29 or 30, wherein the microbial infection is caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Methicillin-resistant Staphylococci* (MRSA) and/or *Candida*.

32. A compound of general formula (II)



20 20 wherein  $R^1$  is selected from H and an organic substituent;  
 $R^4$  is selected from H and an organic substituent;  
n is an integer from 1 to 15;  
p is an integer from 0 to 15; and

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each  group represents a double or triple bond with at least two of such groups being triple bonds.

33. A polymer comprising a polymerised residue of one or more compounds of general  
5 formula (I) as defined in claim 1, and/or of general formula (II) as defined in claim 11.

34. A method of preparing a polyacetylene, said method comprising polymerising one or more compounds of general formula (I) as defined in claim 1, and/or of general formula (II) as defined in claim 11.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU2009/000290

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

<i>C07C 57/00</i> (2006.01)	<i>A61K 31/201</i> (2006.01)	<i>C07C 69/732</i> (2006.01)
<i>A01N 37/06</i> (2006.01)	<i>A61K 31/231</i> (2006.01)	<i>C07C 235/28</i> (2006.01)
<i>A01N 37/18</i> (2006.01)	<i>A61K 31/341</i> (2006.01)	<i>C07D 307/54</i> (2006.01)
<i>A01N 43/08</i> (2006.01)	<i>A61K 31/357</i> (2006.01)	<i>C07D 319/12</i> (2006.01)
<i>A01N 43/32</i> (2006.01)	<i>A61P 31/00</i> (2006.01)	<i>C08F 138/00</i> (2006.01)
<i>A61K 31/16</i> (2006.01)	<i>A61P 31/04</i> (2006.01)	<i>C08F 238/00</i> (2006.01)
<i>A61K 31/165</i> (2006.01)	<i>C07C 57/18</i> (2006.01)	

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 CA, MEDLINE, BIOSIS, WPIDS, EPODOC: structure search based on formulas I and II and keyword search using keywords based on antimicrobial agents, antifungal agents, anti-bacterial agents, alkynes, polyalkyne, polyacetylene, polyyne, diyne, triyne, antimicrobial, antibiotic, antibacterial, antifungal, fungicide.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Cambie, R. C. et al. Chemistry of the Higher Fungi. Part XIV. Polyacetylenic Metabolites of <i>Poria sinuosa</i> Fr. J. Chem. Soc. (1963) pages 2056-2064 See page 2056, compounds (IX) and (X) and page 2063, lines 9-15, 38-42	1-3, 5-7, 9 4, 8, 10, 14-31
P,Y	WO 2008/031157 A1 (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION) 20 March 2008 See page 61, line 14 – page 62, line 24; page 84, lines 5-12; and claims 18 and 30	1-34

Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 22 April 2009	Date of mailing of the international search report 07 MAY 2009
Name and mailing address of the ISA/AU <b>AUSTRALIAN PATENT OFFICE</b> PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer <b>KATE HOLDEN</b> AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6225 6129

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2009/000290

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Zgoda, J. R. et al. Polyacetylene Carboxylic Acids from <i>Mitrophora celebica</i> . <i>J. Nat. Prod.</i> (2001) Vol. 64, No. 10, pages 1348-1349 See page 1348, compounds 1 & 2 and page 1349, left col. lines 3-12	4, 8, 10, 14-31
A	Avato, P. et al. Antimicrobial Activity of Polyacetylenes from <i>Bellis perennis</i> and their Synthetic Derivatives. <i>Planta Medica</i> (1997) Vol. 63, pages 503-507 See page 503, compounds 1-5; page 506, Table 2; and page 505, right col. line 57- page 506, line 8.	1-34
A	EP 0 293 131 A2 (MERCK & CO. INC.) 30 November 1988 See page 2, formula (I) and lines 40-42	1-34

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2009/000290

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	2008031157	AU	2007295948
EP	0293131	JP	1079169
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
END OF ANNEX			