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(54) Benævnelse: **VITAMIN K2-INTERMEDIATER**

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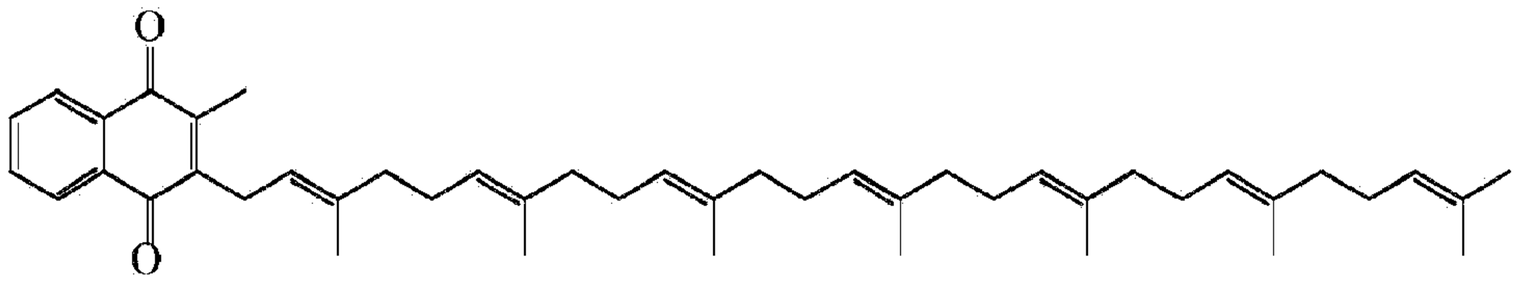
DESCRIPTION

[0001] This application relates to the synthesis of a novel intermediate compound.

[0002] Vitamin K denotes a group of lipophilic and hydrophobic vitamins that are needed for the post-translational modification of certain proteins, mostly required for blood coagulation. Chemically they are 2-methyl-1,4-naphthoquinone derivatives.

[0003] Vitamin K is not a single compound, rather it is a series of related analogues. Vitamin K1 is called phylloquinone and has the systematic name all-E-2-methyl-3-(3,7,11,15-tetramethylhexadec-2-enyl)naphthalene-1,4-dione. Vitamin K2 (menaquinone) is normally produced by bacteria in the intestines, and dietary deficiency is extremely rare unless the intestines are heavily damaged or are unable to absorb the molecule.

[0004] Vitamin K2 is a mixture of different molecules based on a naphthoquinone structure and varying lengths of isoprenoid chains. The compound MK-7 (i.e. 7 isoprenyl groups) is depicted below but other components of the vitamin have different numbers of isoprenoid links. Menaquinones have side chains composed of all-E polyprenyl residues; generally they are designated as MK-n, where n specifies the number of isoprenoid repeating units. The minimum value of n is 2.



MK-7

[0005] All members of the vitamin K group of vitamins share a methylated naphthoquinone ring structure, and vary in the aliphatic side chain attached at the 3-position.

[0006] It is generally accepted that the naphthoquinone is the main functional group of the vitamin, so that the mechanism of action is similar for all K-vitamins. Substantial differences may be expected, however, with respect to intestinal absorption, transport, tissue distribution, and bio-availability when variations in the side chain take place. These differences are caused by the different lipophilicity of the various side chains and by the different food matrices in which they occur.

[0007] A recent paper (Suhara et al., Biorganic Med. Chem Lett. 17 (2007) 1622-1625) suggests the use of certain vitamin K metabolites as biologically active compound which can lead to the development of new drugs based on side-chain modification of the alkyl group. Suhara targets compounds of structure similar to metabolites of vitamin K, i.e. compounds carrying acidic (or other strongly hydrophilic groups) at the terminus of the 3-position side chain. Some of the analogues have apoptosis-inducing properties.

[0008] It is known that γ-carboxylated osteocalcin is involved in the bone remodeling system, and there are strong indications that vitamin K has a beneficial effect on bone diseases such as osteoporosis. There is interest therefore in the investigation of various vitamin K2 type compounds for inhibitory effects on osteoporosis, as potential anti-cancer drugs and for beneficial cardio-vascular activity.

[0009] Whilst vitamin K2 occurs naturally in various vegetables and can be produced by bacteria in the intestines, it is still an interesting synthetic target as isolation of the vitamin from a natural source is complex and concentrations of the vitamin are low. Moreover, synthesis allows the preparation of particular menaquinones rather than the isolation of a mixture of different menaquinones.

[0010] Various individuals have synthesised the menaquinone compounds which form part of vitamin K2 or components thereof. The first synthesis of menaquinones, reported by Isler et al., Helv. Chim Acta 1958, 41, 786-807, used a nonstereospecific approach. Tso and Chen, J Chem Res 1995, 104-105 describes a one pot synthesis of vitamin K although he concentrates on the formation of the naphthoquinone ring as opposed to the side chain of the molecule. His chemistry involves the reaction of 3-substituted isobenzofuranones with vinylic sulphones to form the naphthoquinone ring structure.

[0011] Suhara et al, Bioorg Med Chem Lett 17, (2007) 1622-1625, describe various syntheses of menaquinone analogues in which the terminal methyl group is converted to a hydroxyl, aldehyde or acid group.

[0012] Naruta, J Org Chem 1980, 45, 4097-4104, describes the synthesis of some vitamin K2 analogues using trialkylallylstannane chemistry to bond the preformed side-chain to the naphthoquinone group.

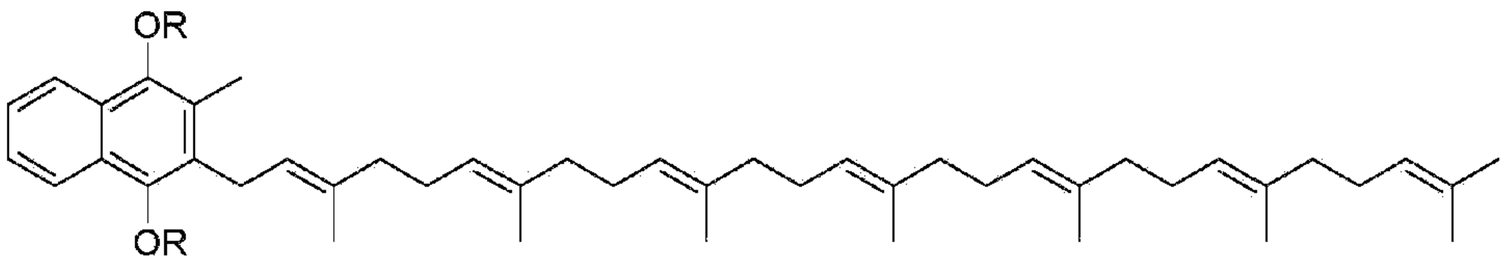
[0013] US 4089873 describes the preparation of menaquinones using a copper-mediated coupling reaction.

[0014] US 4199531 describes the preparation of quinones using arylsulfonyl/halogen coupling chemistry.

[0015] The present inventors have devised a synthetic strategy for the formation of MK-7 and other menaquinones. The method utilises Kumada or Suzuki chemistry to connect a side chain to the naphthoquinone ring. The side chain can be further manipulated, e.g. using Biellmann chemistry to produce the desired compounds.

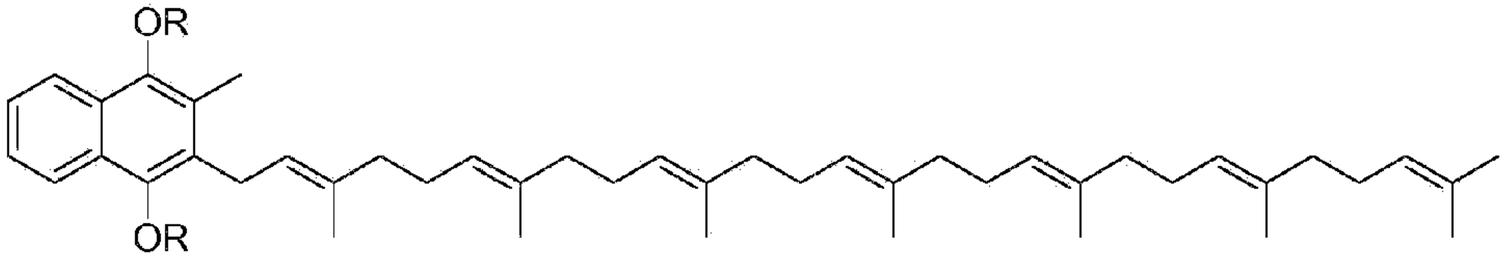
[0016] The process described herein allows formation of menaquinones in high yield and crucially with stereochemical integrity. In particular, the inventors do not see any presence of Z-isomers during their reactions. A key intermediate in the above reactions, shown below, is new and forms the key aspect of the invention. The invention therefore provides a compound of

formula:



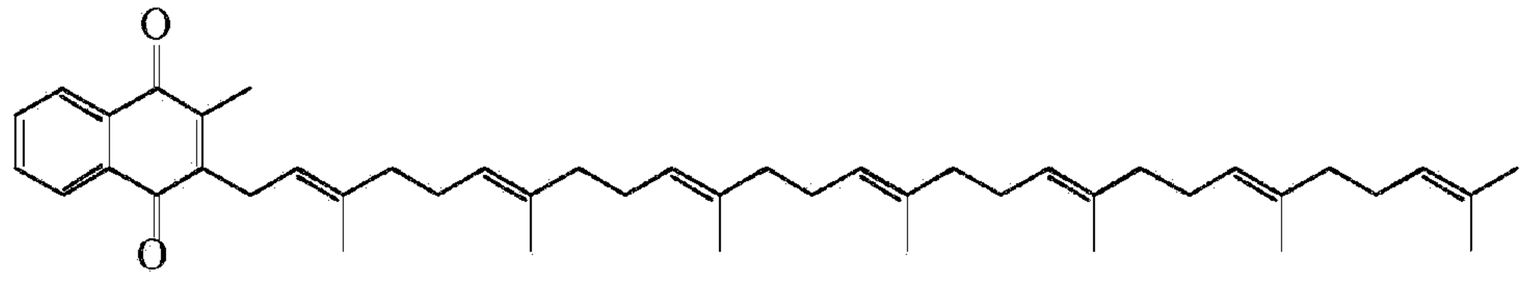
wherein R is ethyl.

[0017] The invention furthermore provides a process for the preparation of MK-7 comprising converting a compound



wherein R is an ethyl group;

into MK-7:

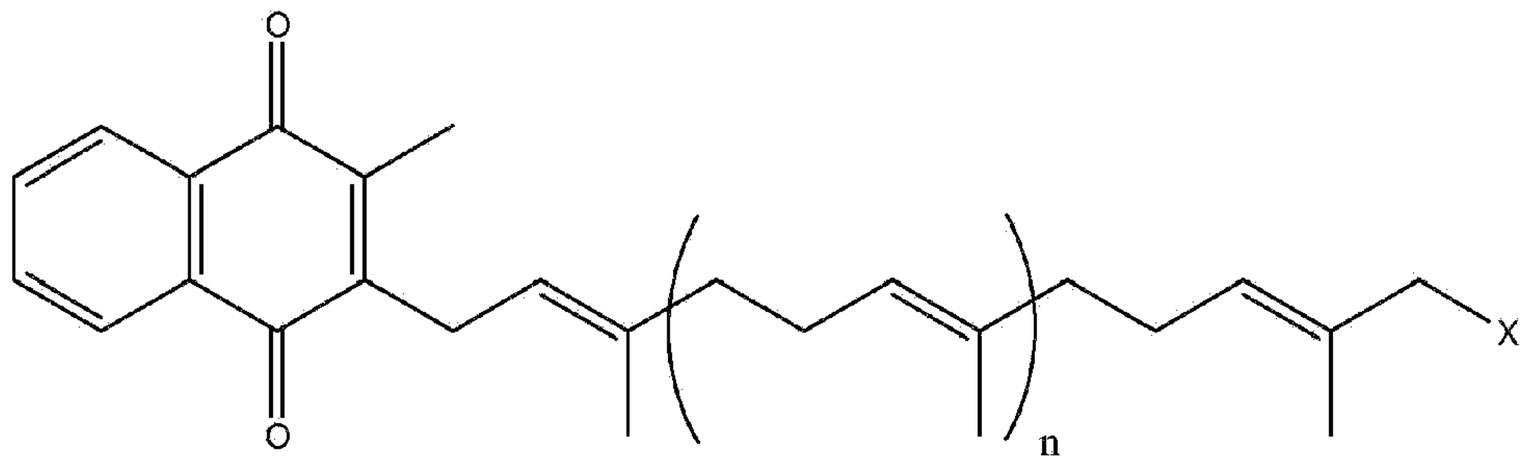


.

[0018] The Kumada, Suzuki, and Bielmann reactions discussed below enable the preparation of the intermediate shown above. Processes or compounds which do not relate to the intermediate above or which do not relate to the process for the formation of MK-7 from this intermediate are not within the scope of the invention but are included to enable the invention.

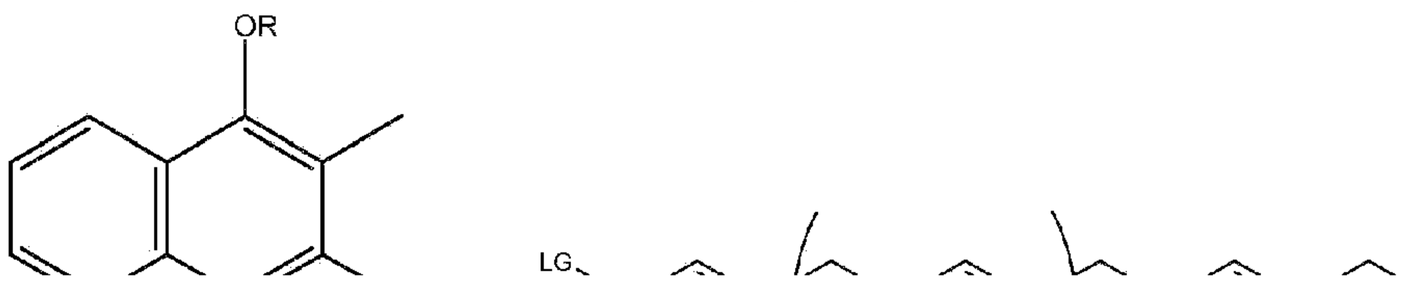
KUMADA

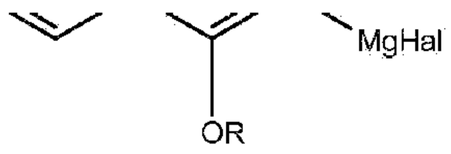
[0019] A compound of formula (I)



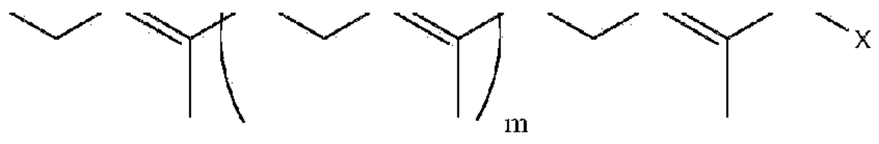
(I)

may be prepared by a process comprising a step in which (i) a compound of formula (II) is reacted with a compound of formula (III)





(II)



(III)

wherein R is an alkyl group;

LG is a leaving group;

m is an integer of from 0 to 8;

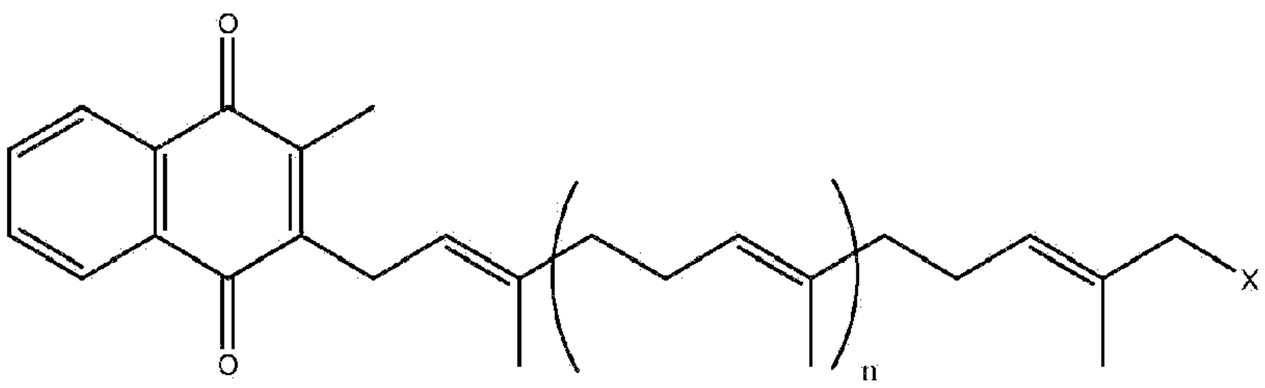
n is an integer of from 0 to 9; and

X is hydrogen, halide, hydroxyl, or protected hydroxyl;

in the presence of a copper, nickel or palladium catalyst.

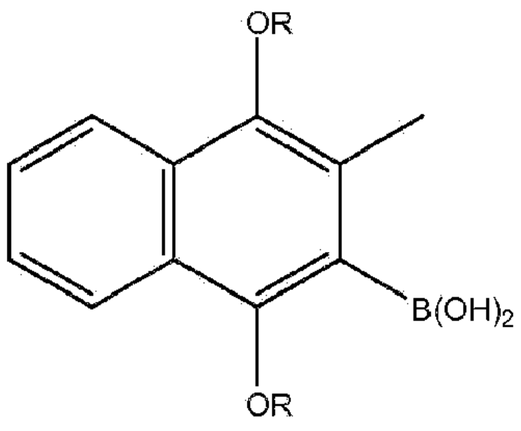
SUZUKI

[0020] A compound of formula (I)



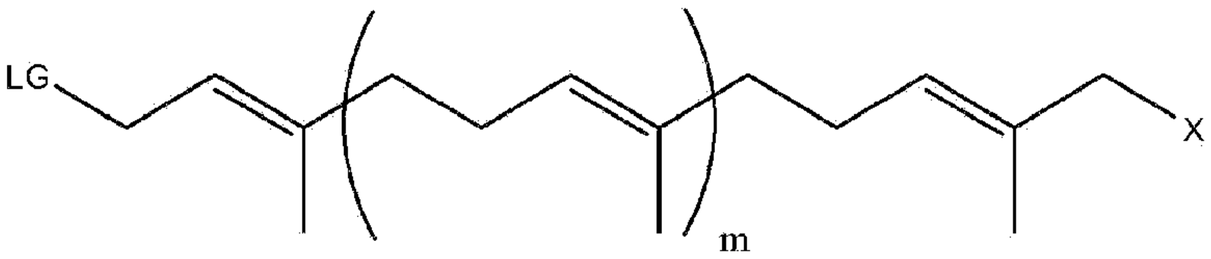
(I)

may be prepared by a process comprising a step in which (i) a compound of formula (IV)



(IV)

where R is an alkyl group; is reacted with a compound of formula (III)

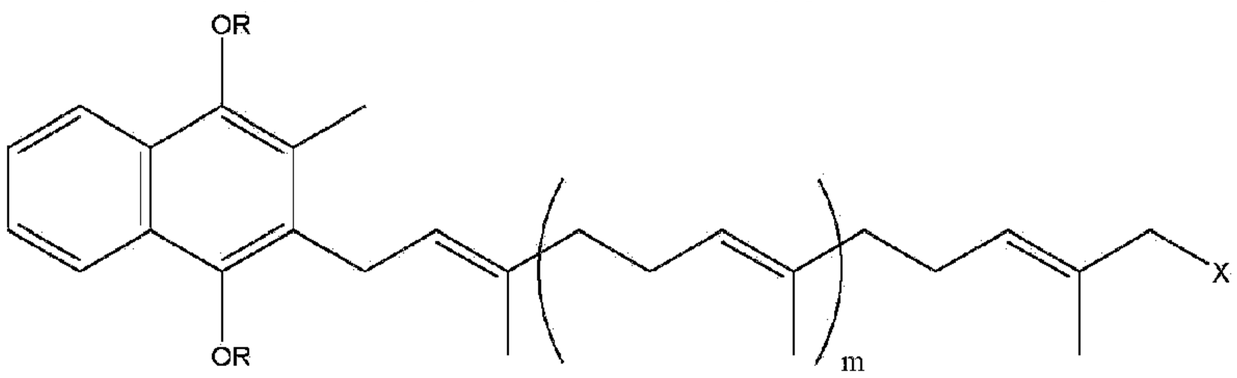


wherein LG is a leaving group, m is an integer of from 0 to 8, n is 0 to 9 and X is hydrogen, halide, hydroxyl, or optionally protected hydroxyl;
in the presence of a Pd (0) catalyst.

Biellmann

[0021] The successful use of either Kumada or Suzuki coupling for preparing the vitamin K2 compounds depends on the availability of a precursor for the all-E polyprenyl side chains. To reach this objective the inventors have employed Biellmann chemistry. This reaction involves the formation of phenythio or phenylsulfonyl substituted compounds and reaction of these sulphur compounds with an electrophile, such as a halide, in the presence of a base. Suitable bases include n-butyl lithium, tert butyl lithium, and non nucleophilic bases such as tertbutoxides. After coupling, the phenythio or phenylsulfonyl groups are removed reductively for example with lithium metal or a metal hydride. The inventors have found that this method is ideal for coupling together two isoprenoid chains to make a new isoprenoid chain of, for example, 7 or more units.

[0022] The reaction of a compound of formula (II) or (IV) with a compound of formula (III) may however be only one step in the formation of a compound of formula (I). The reaction of compounds (II) and (III) or (II) and (IV) yields the compound (I')



(I')

[0023] It will be appreciated that to complete the synthesis of a compound of formula (I) it is necessary to convert the diprotected naphthoquinone (I') back to naphthoquinone. This can be achieved by any convenient oxidation method although typically cerium ammonium nitrate (CAN) can be used.

[0024] The process may therefore incorporate further steps before or after the reaction as described below in order to allow the formation of a compound of formula (I), especially MK-7.

Definitions:

[0025] A polyprenyl side chain is one which derives from the polymerisation of isoprene: 2-methyl-1,3-butadiene.

[0026] Unless otherwise stated, an alkyl group can contain 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, especially methyl or ethyl.

[0027] Halide (Hal) includes fluoro, chloro, bromo and iodo, preferably chloro or bromo. Halides employed as Grignard reagents are preferably bromo.

[0028] The term protecting group covers any known protecting group for the group in question. Hydroxyl protecting groups include acetyl (Ac), benzyl, β-methoxyethoxymethyl ether (MEM),

methoxymethyl ether (MOM), p-methoxybenzyl ether (PMB), methylthiomethyl ether, pivaloyl (Piv), tetrahydropyran (THP), Silyl ether (most popular ones include trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS), and triisopropylsilyl (TIPS) ethers), and methyl ethers. Preferred protecting groups are benzyl or THP.

[0029] The term leaving group is well known in the art and denotes an atom or group of atoms that readily leaves a molecule due to the relative stability of the ion formed. Useful leaving groups include halides, tosylates, mesylates and triflates. Preferred leaving groups are halides.

[0030] In any particular embodiment "n" is 0 to 9, preferably 1 to 8, more preferably 4 to 7, e.g. 6, 7 or 8 isoprenoid units. Values of n which are not compatible with the formation of the claimed intermediate or with the formation of MK-7 from that intermediate are not within the scope of the invention.

[0031] In any particular embodiment "m" is 0 to 8, e.g. 0 to 7, preferably 0 to 5, more preferably 1 to 4, e.g. 2, 3 or 4 isoprenoid units. Values of m which are not compatible with the formation of the claimed intermediate or with the formation of MK-7 from that intermediate are not within the scope of the invention. It will be appreciated that the sum of the various m values of the starting materials will add up to the value of n in the compound of formula (I) taking into account any units formed in the reactions in question. Thus if one isoprene unit is formed by the reactions then n-1 is the total of all m's. Where a reaction process involves multiple reactants in which the variable m is present, it will be appreciated that each m can be different.

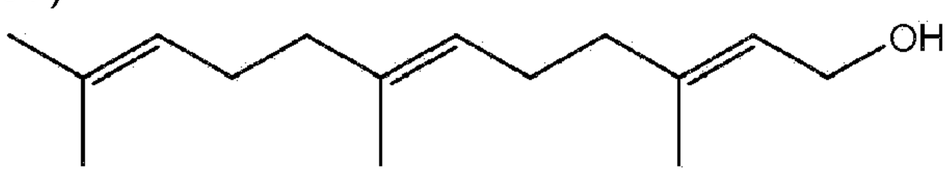
[0032] In compounds of formula (I), X is preferably hydrogen.

Detailed Description of the Invention

[0033] The present disclosure relates to the synthesis of compounds of formula (I), i.e. menaquinone derivatives having varying length of a polyprenyl side chain in their backbone. Whilst the length of the polyprenyl chain in the compound of formula (I) can vary, it is preferred if there are at least 6 isoprenoid units, more preferably at least 7 isoprenoid units in the compound of formula (I). It is preferred therefore if n is at least 3, preferably 4, 5 or 6.

[0034] The compound of formula (III) required to effect the reaction above can contain different numbers of isoprenoid units. The compound of formula (III) is typically not commercially available and itself needs to be synthesised from compounds with a smaller number of isoprenoid units. A particular challenge faced by the synthetic chemist is preparing menaquinone compounds having different numbers of isoprenoid units. In order to manufacture higher menaquinones, i.e. those of 7 isoprenoid units or more, it is normally necessary to have at least one reactant which comprises 4 or more isoprenoid units. Such compounds are still not readily available and therefore need to be synthesised themselves. It will be seen therefore that the synthesis of higher menaquinones is not simple. Starting from commercially available farnesol (A) methods have been devised for extending this molecule

stereoselectively by one isoprenoid unit at a time (see Coates et al Org. Synth. 2007, 84, 43-57)



(A)

[0035] However, where the number of units is high, it may not be practical to add just one unit at a time to compound (A). If 10 units are required, the overall yield of the process might be too low to be of commercial interest. The inventors have therefore sought more ways of forming the menaquinone side chain having multiple isoprenoid units.

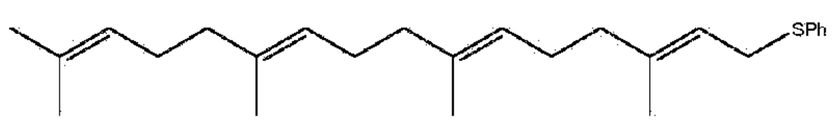
[0036] The inventors have found that Biellmann chemistry provides an ideal way to make even longer vitamin K2 side chain molecules which can then be coupled to a naphthoquinone ring following the chemistry described above. Alternatively this chemistry can be used to increase the size of a side chain already attached to the naphthoquinone ring.

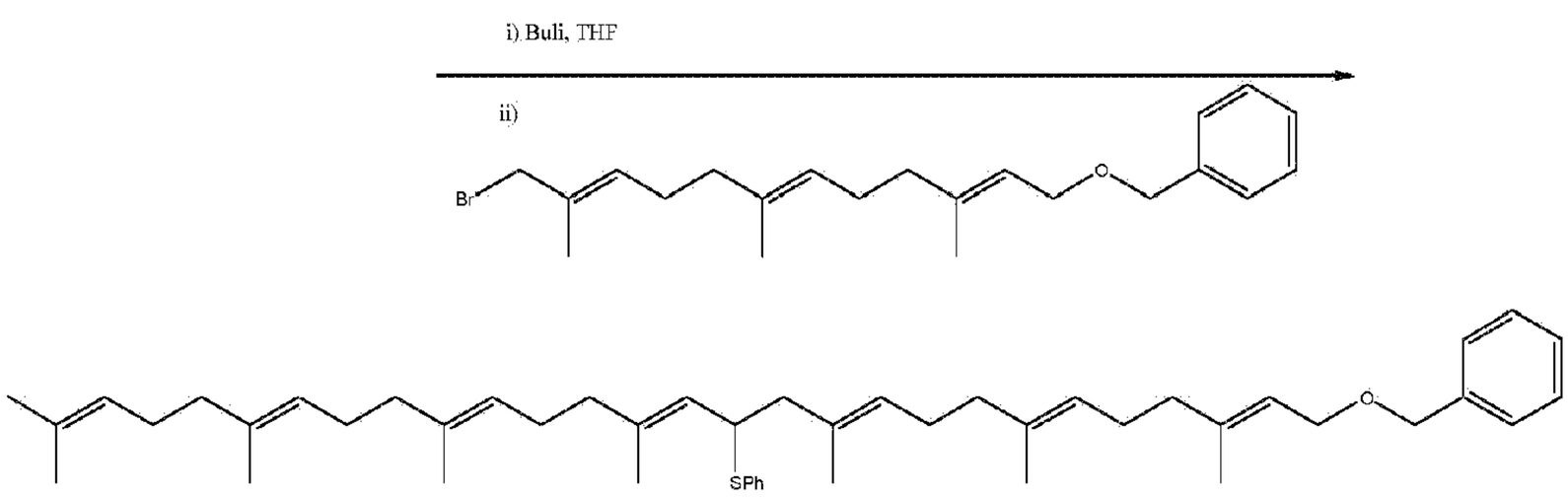
[0037] The most common starting materials for the formation of the isoprenoid side chains are polyprenyl alcohols. It is possible to convert an alcohol into a better leaving group and effect addition of the phenythio or phenylsulfonyl group via a nucleophilic attack of the thiophenyl ion or phenylsulfonyl- ion on the leaving group. For phenylthio group, the inventors have found another method based on the reaction of the alcohol directly with diphenyldisulfide in the presence of a trialkyl phosphine, e.g. PBu_3.

[0038] The resulting phenythio or phenylsulfonyl substituted compounds are readily deprotonated with base forming the corresponding anions which can be reacted with a compound having a suitable leaving group yielding the basis of the isoprenoid carbon chain. Suitable bases include BuLi.

[0039] Scheme 1 examplifies this type of reaction with a bromide and a phenylthio substituted derivative.

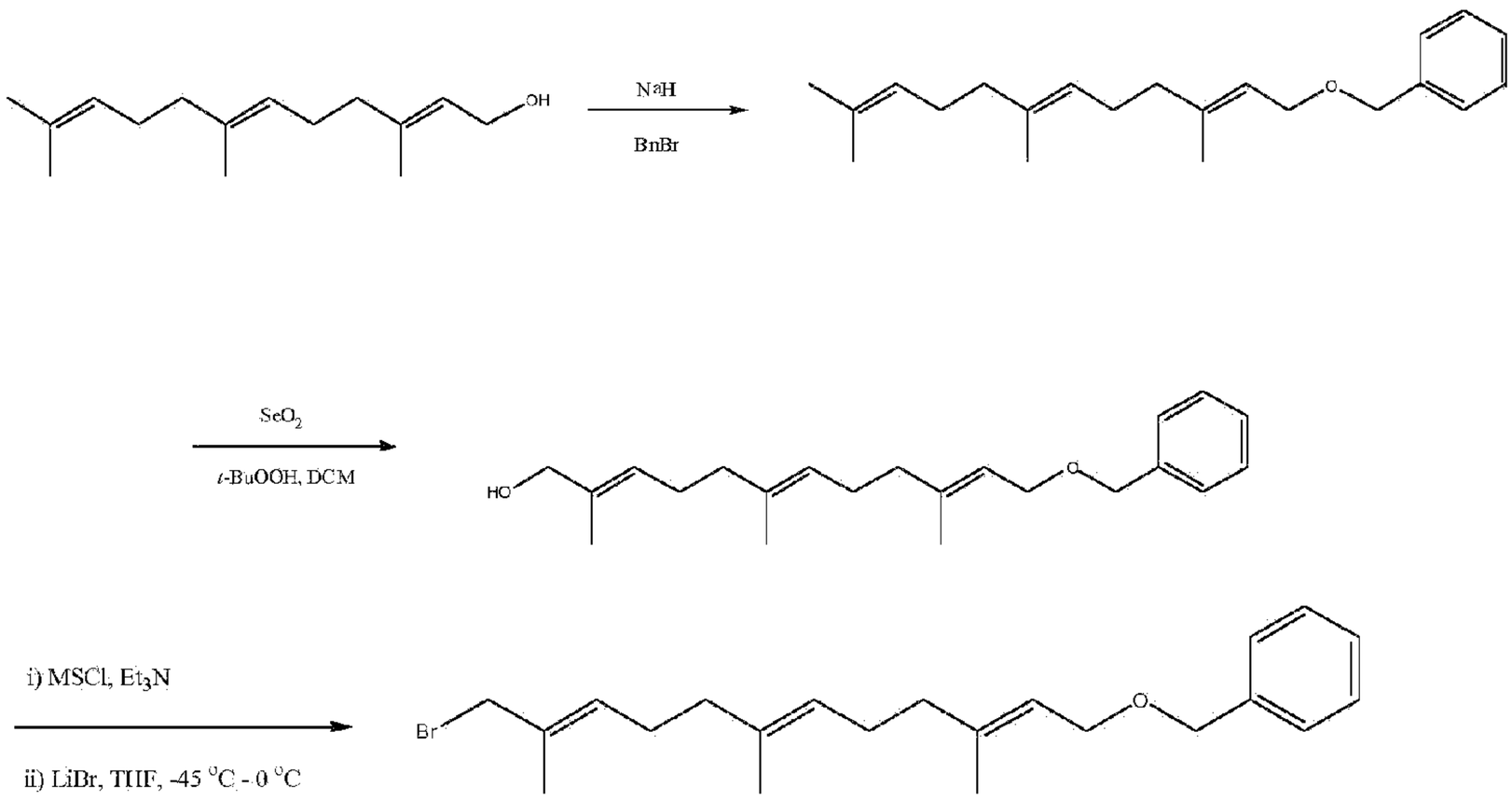
Scheme 1





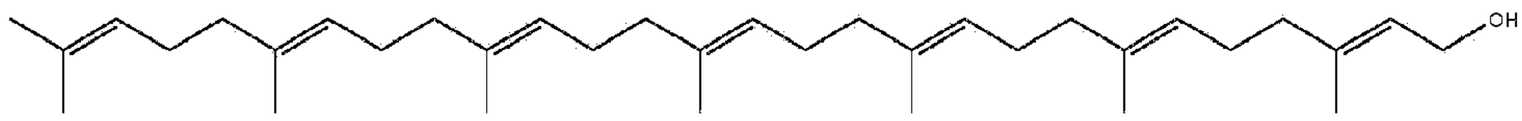
[0040] The bromide reactant in scheme 1 can be conveniently synthesised from farnesol (A). Protection of farnesol with a benzyl group allows the introduction of a terminal OH group using selenium dioxide in t-butylperoxide. This can then be converted to the bromide using known chemistry (scheme 2)

Scheme 2



[0041] Once the coupling has been completed it is preferred that the reduction of the phenythio or phenylsulfonyl group also simultaneously removes any protection present, e.g. the benzyl protecting group leaving an alcohol. Reduction is conveniently effected using lithium metal in an amine solvent such as propylamine or ethylamine or using palladium catalysis with a borohydride, e.g. $PdCl_2$(dppp) and lithium triethyl borohydride. Any other method for reduction of the phenythio or phenylsulfonyl group could also be employed.

[0042] Reduction of the product in scheme 1 yields compound XV

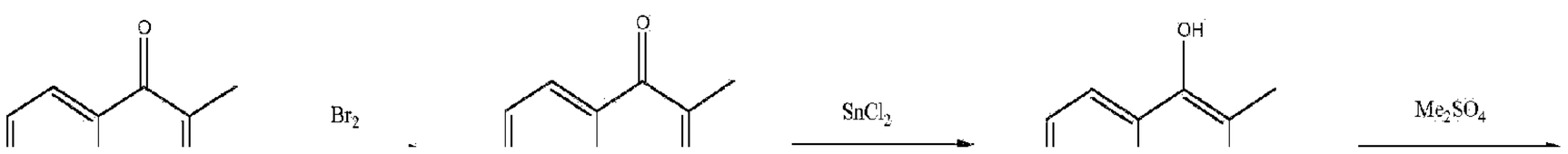


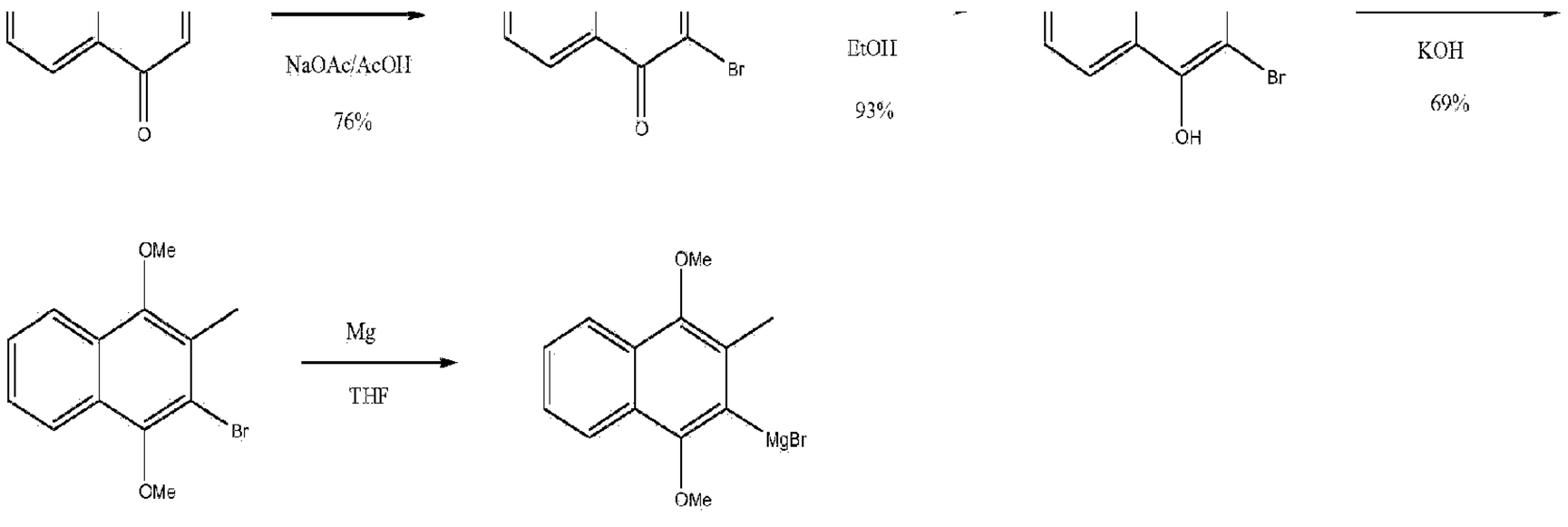
(XV)

which contains 7 isoprenoid units and is therefore a perfect precursor to the side chain of MK-7.

[0043] To complete the synthesis, the naphthoquinone group must be introduced. This compound can be prepared from commercially available 2-methylnaphtoquinone as starting material as outlined in scheme 3. This brominated intermediate is converted to its dimethoxy analogue using tin dichloride in ethanol and subsequent treatment with dimethylsulphate and base. This dimethoxy derivative can then form the corresponding Grignard reagent. This chemistry is well established (Snyder and Rapoport, J Am Chem. Soc 1974, 96, 8046-8054) .

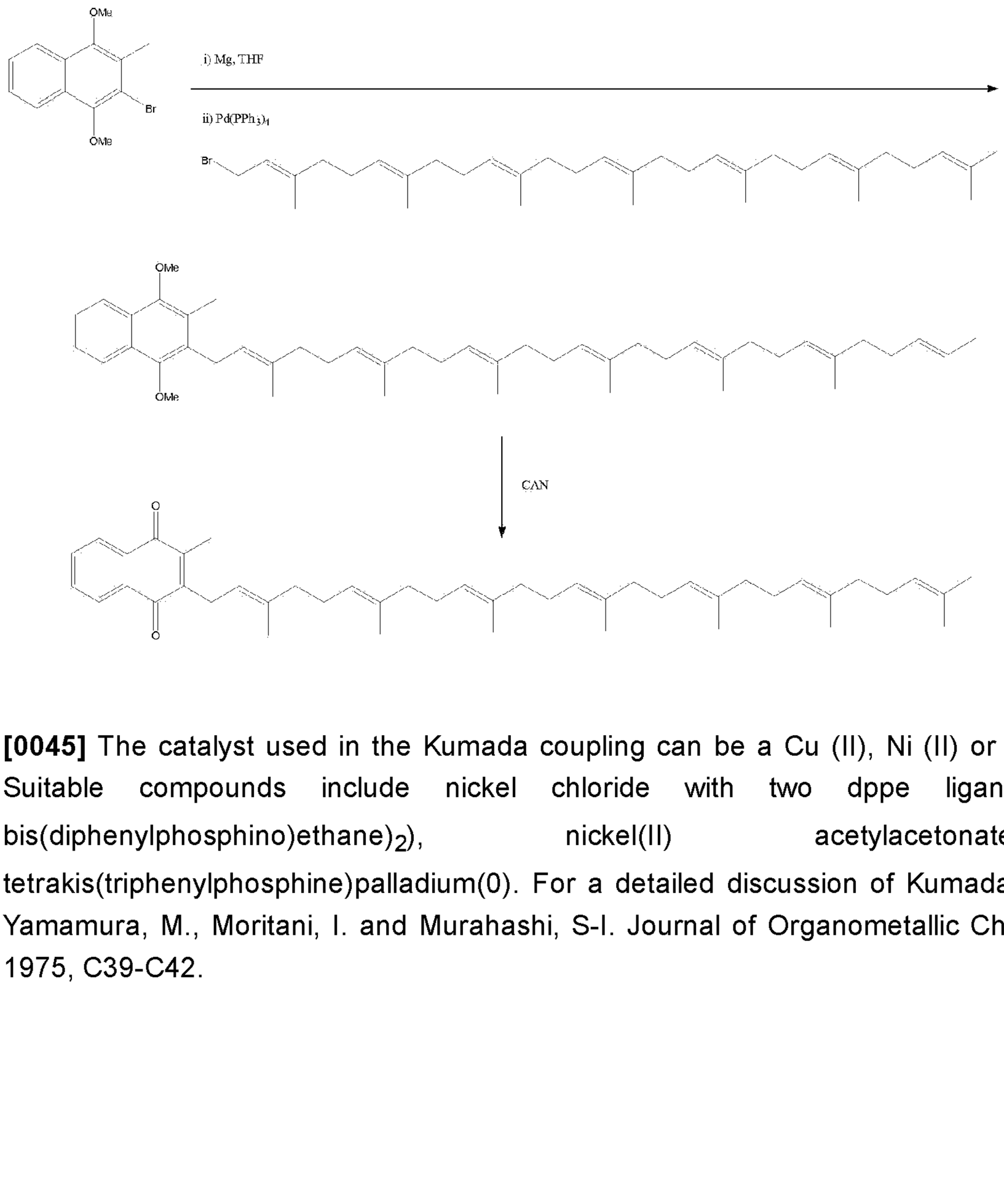
Scheme 3





[0044] The alcohol XV is converted to a halide, but the subsequent coupling to the naphthoquinone derivative using a classical Grignard reaction is not very useful. It is highly preferred if the reaction of the naphthoquinone derivative with the isoprenyl side chain is effected by Kumada coupling chemistry, as described previously. The inventors have found that Kumada chemistry improves yields and again prevents any loss of stereochemistry during the formation of the menaquinone. The coupling proceeds smoothly and the menaquinone MK-7 was obtained after oxidation of the methoxy groups on the naphthoquinone ring by cerium ammonium nitrate (CAN) or other oxidation methods (scheme 4).

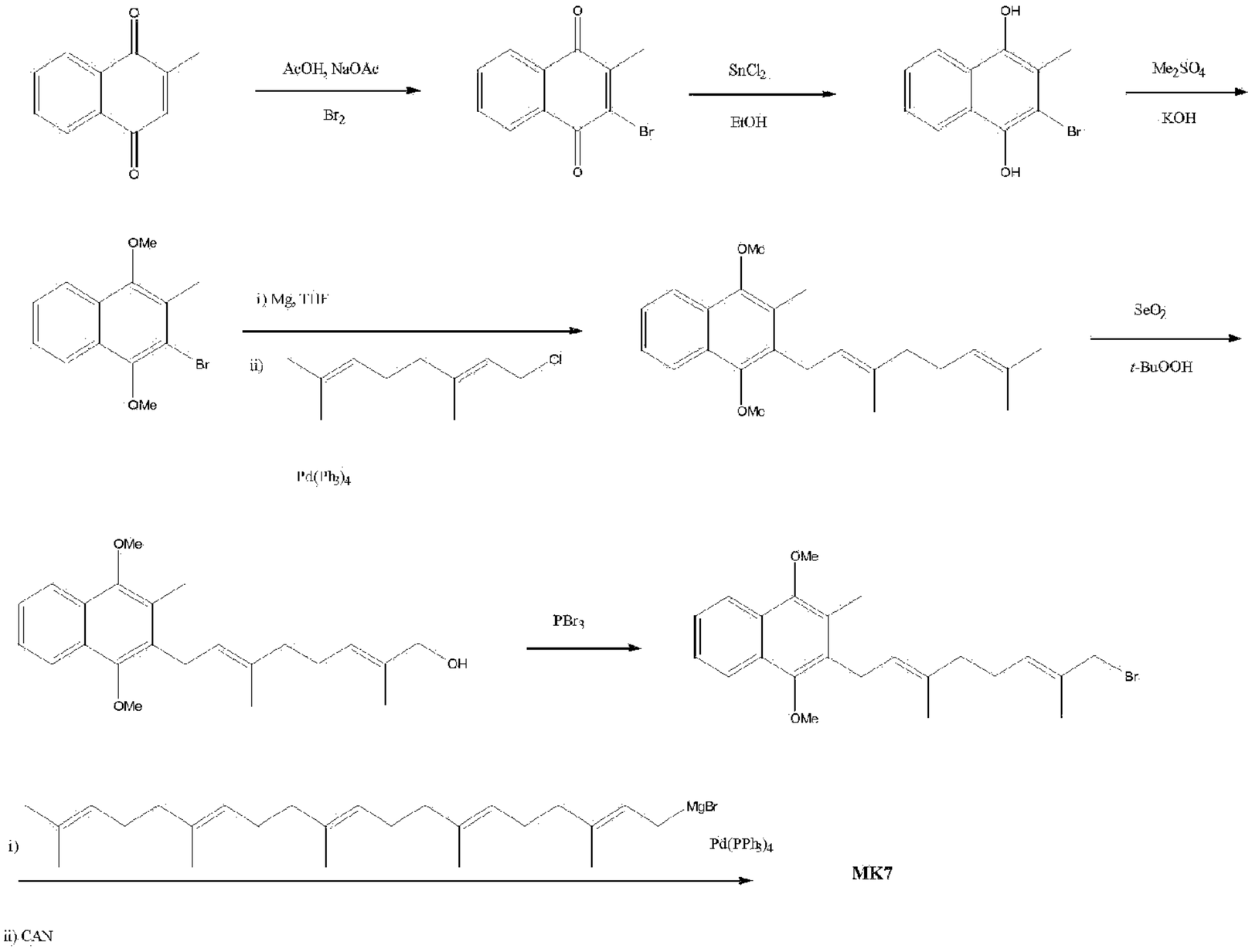
Scheme 4



[0045] The catalyst used in the Kumada coupling can be a Cu (II), Ni (II) or (Pd(0) species. Suitable compounds include nickel chloride with two dppe ligands ($NiCl_2$(1,2-bis(diphenylphosphino)ethane)$_2$), nickel(II) acetylacetonate and tetrakis(triphenylphosphine)palladium(0). For a detailed discussion of Kumada chemistry see Yamamura, M., Moritani, I. and Murahashi, S-I. Journal of Organometallic Chemistry, 91 (2), 1975, C39-C42.

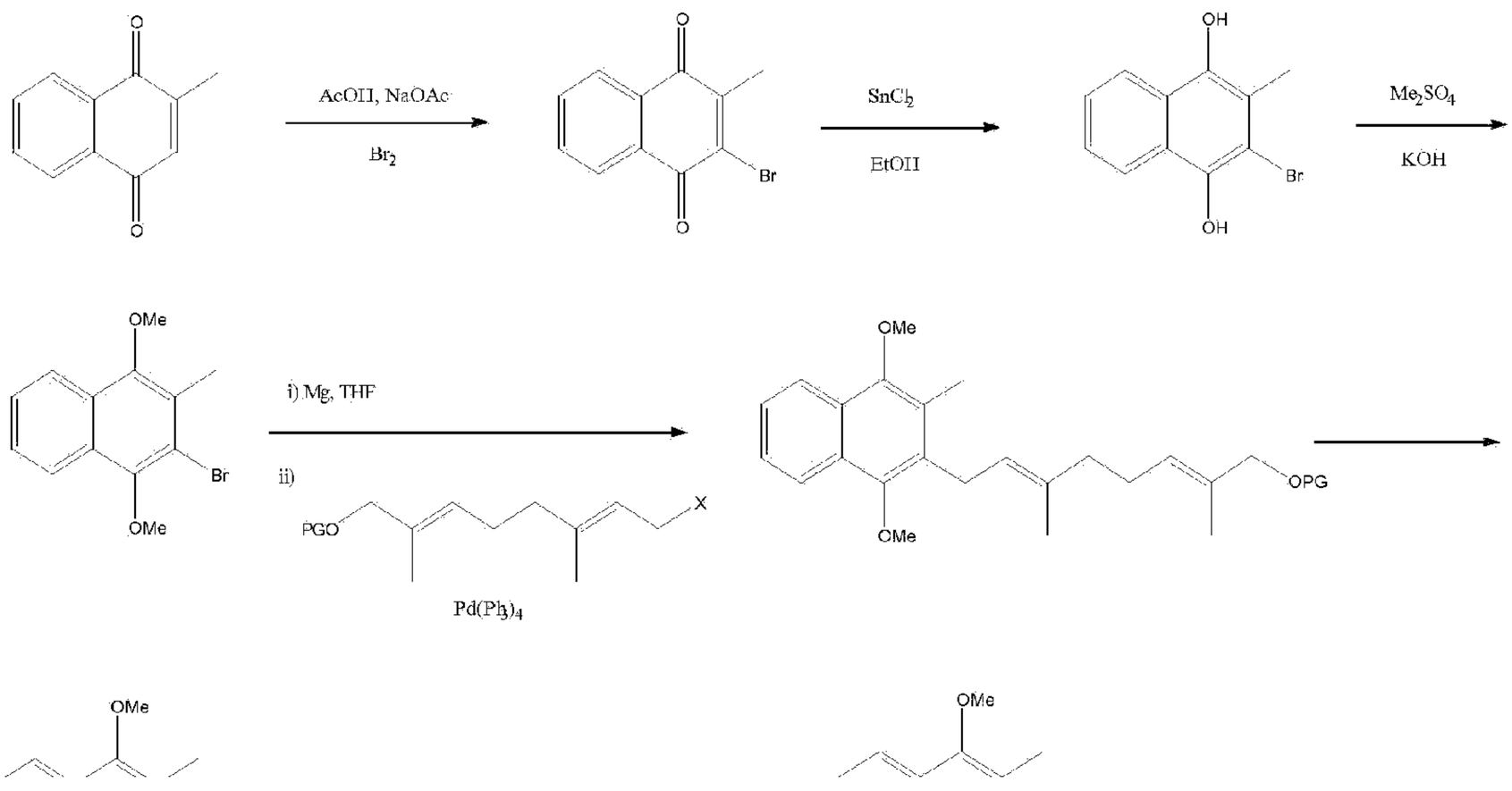
[0046] In another strategy leading to MK-7 the Kumada coupling is actually used twice as outlined in scheme 5. In the first Kumada coupling the Grignard reagent reacts with commercially available geranyl chloride providing the geranyl substituted derivative. Oxidation with SeO_2 affords the alcohol which is transformed into the bromide. The second Kumada coupling between this bromide and the Grignard reagent from pentaisoprenyl compound completed the synthesis of MK-7.

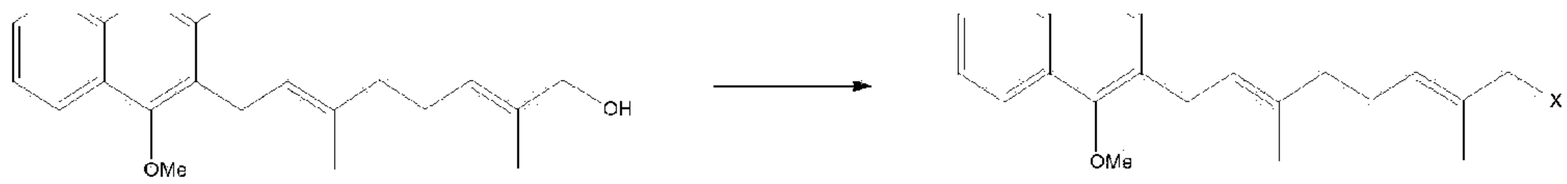
Scheme 5



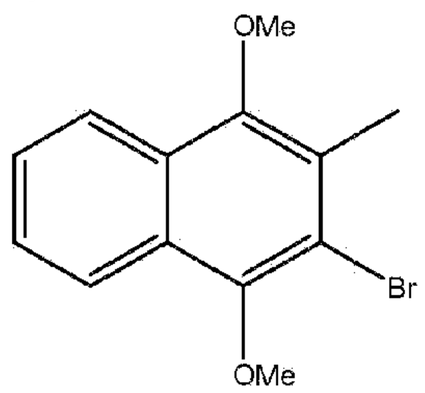
[0047] Scheme 5b is an alternative use of the Kumada coupling strategy using a prohydroxyl reactant during the Kumada coupling stage to readily afford a reactive X group for further reaction.

Scheme 5b



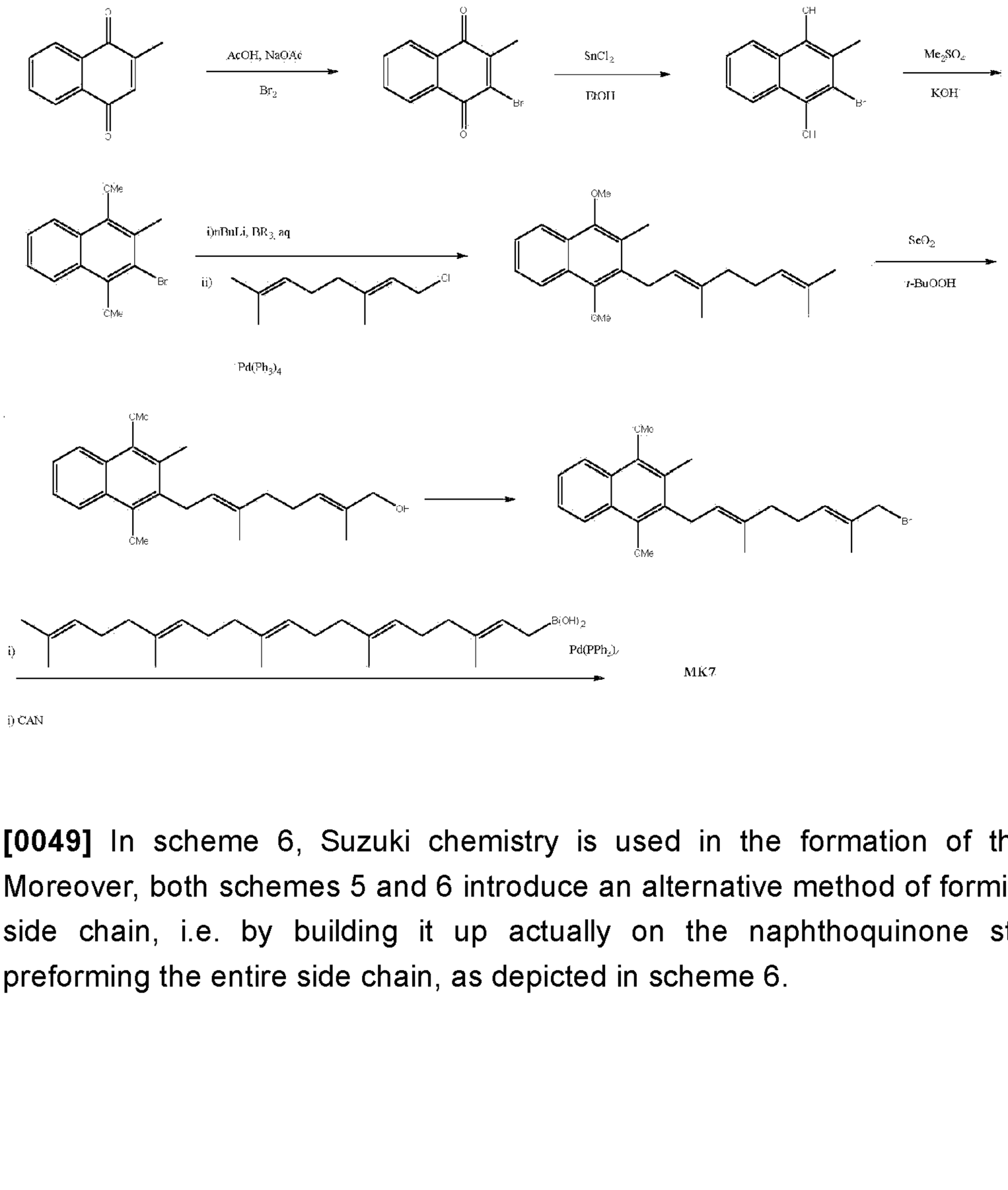


[0048] The inventors also envisage the use of Suzuki coupling chemistry to effect the menaquinone synthesis. The Suzuki reaction involves the reaction of an aryl- or vinyl-boronic acid with an aryl- or vinyl-halide catalyzed by a palladium(0) complex. In the menaquinone synthesis therefore the naphthoquinone bromide



can be converted into a boronic acid using known techniques, e.g. by transmetallation with lithium. Once formed this boronic acid can be coupled with a suitable halide, triflate or tosylate under Suzuki conditions, i.e. using Pd(0) catalysis. The palladium catalyst is preferably 4-coordinate, and usually involves phosphine supporting groups, e.g. tetrakis(triphenylphosphine)palladium(0). Scheme 6 shows the Suzuki coupling in action. For a more detailed discussion of Suzuki chemistry see Suzuki, A. Pure Appl. Chem. 1991, 63, 419-422.

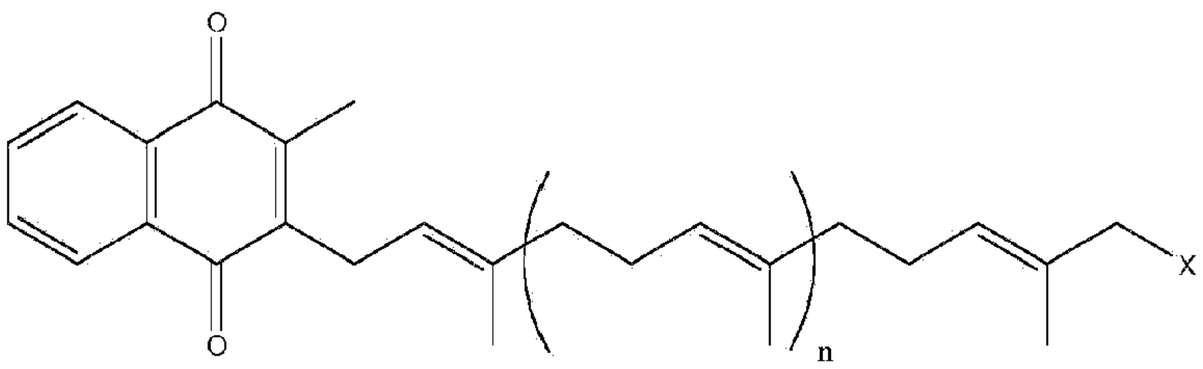
Scheme 6



[0049] In scheme 6, Suzuki chemistry is used in the formation of the MK-7 compound. Moreover, both schemes 5 and 6 introduce an alternative method of forming the menaquinone side chain, i.e. by building it up actually on the naphthoquinone structure rather than preforming the entire side chain, as depicted in scheme 6.

[0050] The Kumada or Suzuki coupling reaction can therefore yield only a relatively short side chain which can then be built up to form a compound of formula (I). To complete the synthesis of a longer chain menaquinone further Kumada, Suzuki or any other chemistry can be used.

[0051] A compound of formula (I)

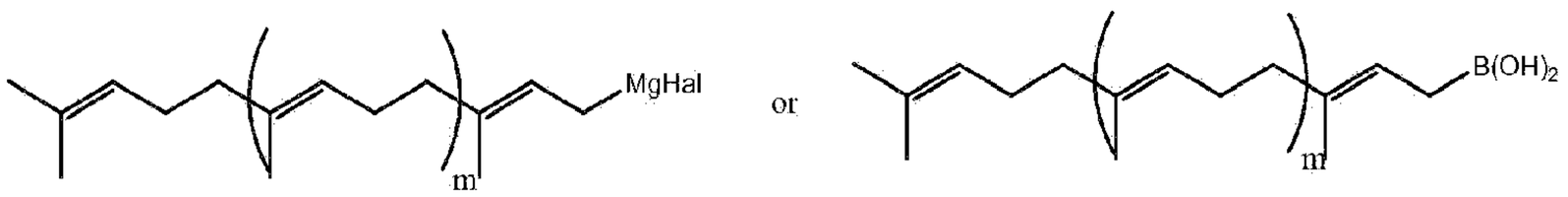


(I)

may be prepared by a process comprising (i) reacting a compound of formula (II) or (IV) with a compound of formula (III) as hereinbefore defined;

(iii) if necessary, converting X into a leaving group;

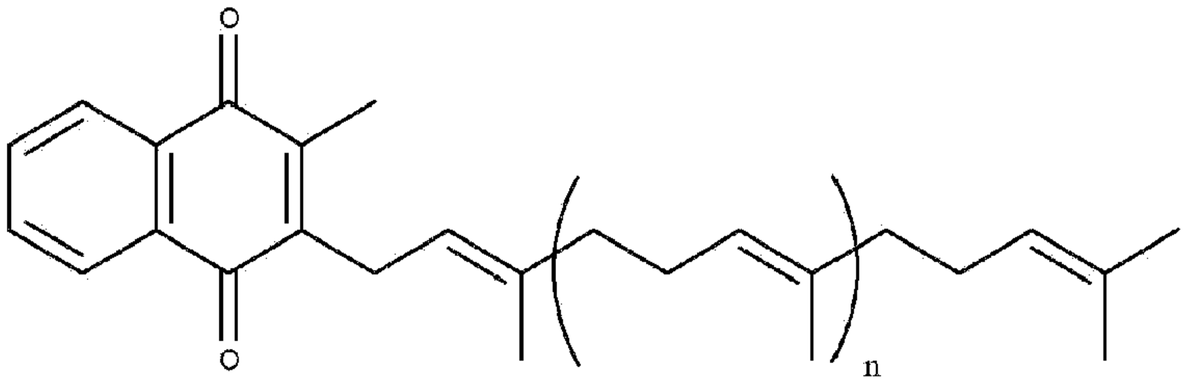
(iv) reacting with a compound



where m is independently as hereinbefore defined;
in the presence of a Ni, Cu or Pd catalyst; and
(v) converting the diprotected naphthoquinone into a naphthoquinone.

[0052] The catalyst used here is chosen depending on the reaction in question, e.g. Pd(0) for a Suzuki coupling, Cu(II), Ni (II) or Pd(0) for Kumada.

[0053] The compound of formula (I)

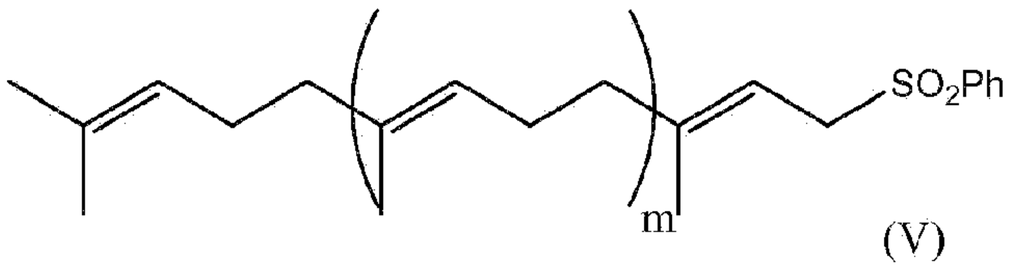


(I)

may be prepared by a process comprising (i) reacting a compound of formula (II) or (IV) with a compound of formula (III) as hereinbefore defined;

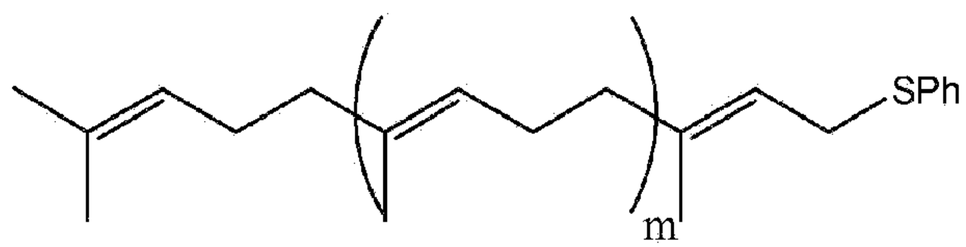
(iii) if necessary, converting X into a leaving group;

(iv) reacting with a compound (V) or (VI)



(V)

or



(VI)

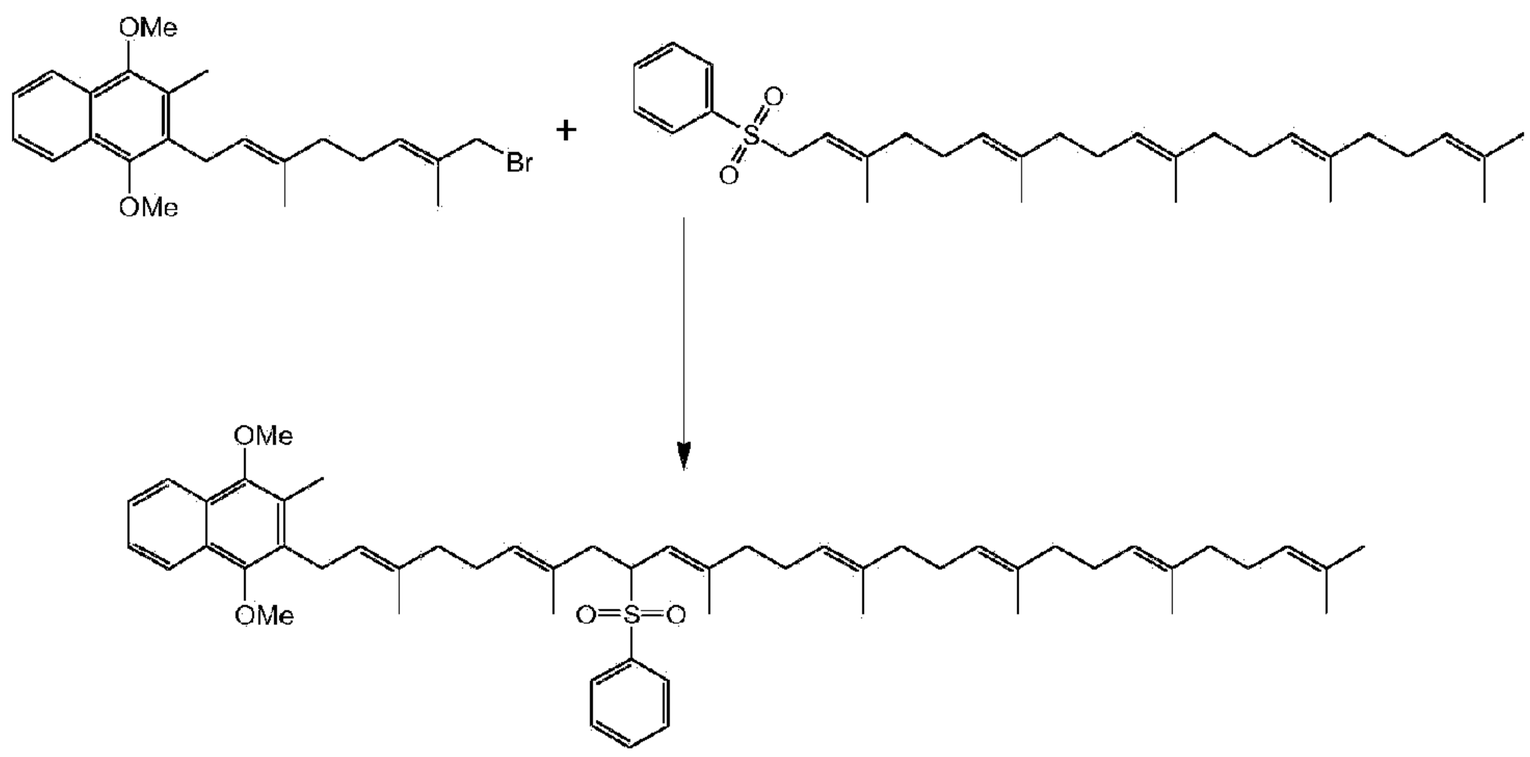
where m is independently as hereinbefore defined
in the presence of a base;

(v) reductively removing the phenythio or phenylsulfonyl groups in the resulting compounds and

(vi) converting by oxidation the diprotected naphthoquinone into a naphthoquinone.

[0054] By varying the number of isoprene units in either molecule coupled using the Biellmann reaction, Suzuki coupling or Kumada coupling all manner of different menaquinone compounds can be produced. It will be appreciated therefore that the values of n in the reactants must be selected to match the number of repeating units desired in the compound of formula (I) bearing in mind, of course, that some isoprenoid units are formed during the reactions themselves. This will be readily achieved by the skilled man.

[0055] Ideally, MK-7 is produced especially where 2 units come from compound (III), 4 units from compound (V) or (VI) (the 7th being formed by the reaction). The preferred process is therefore



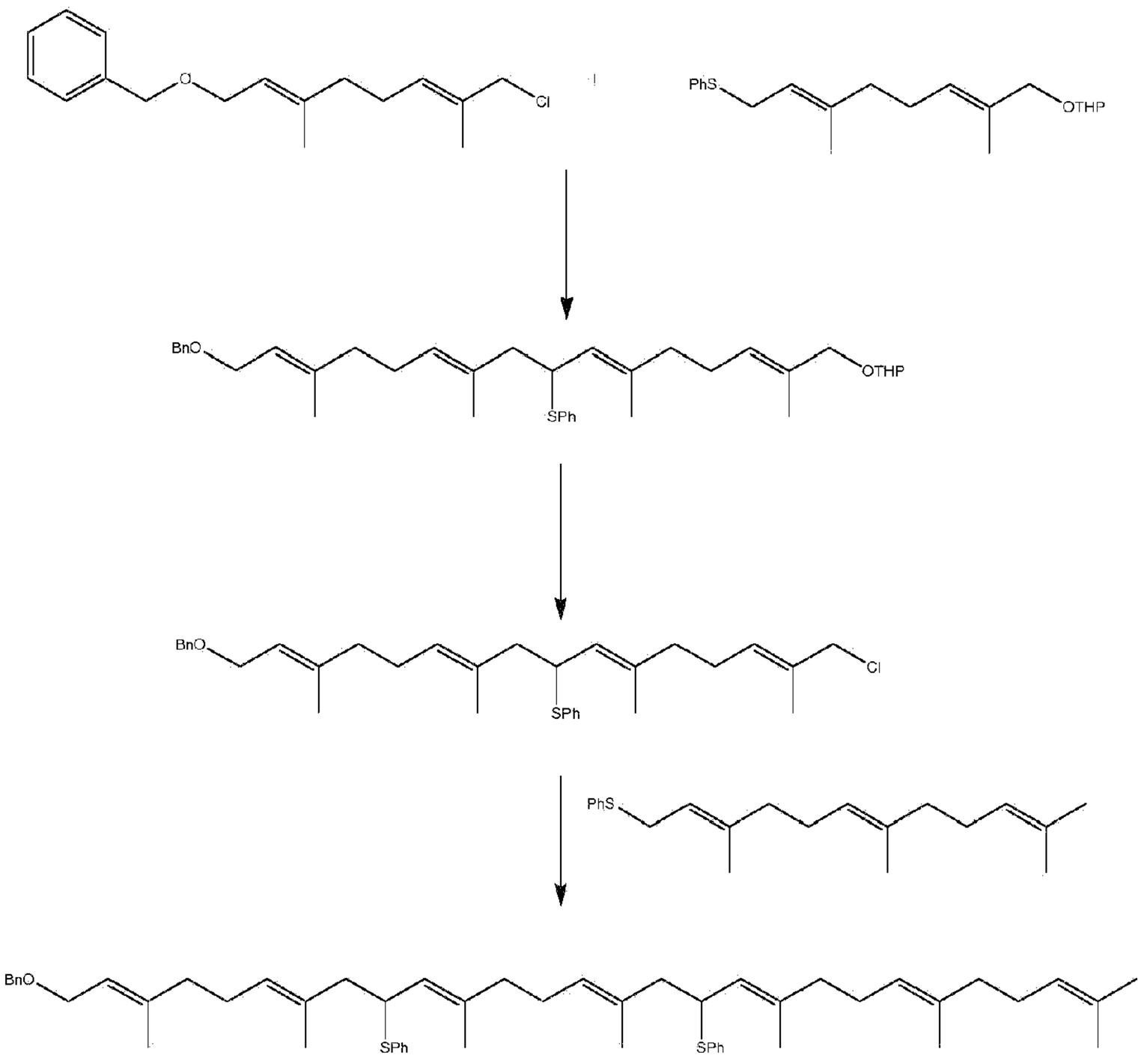
wherein any leaving group may be substituted for Br (e.g. other halogens, tosylate, mesylate etc). A benefit of preparing MK-7 using this "2+5" strategy is that the selenium dioxide reduction step used to form the napthoquinone reactant takes place more readily on a naphthoquinone carrying on 2 isoprenoid units than on a longer chain molecule. This "2+5" method also gives better stereochemistry and has been found to allow the formation of solid, in particular crystalline MK-7.

[0056] Tthe inventors have realised that different side chains can be prepared using a double Biellmann coupling (or triple Bielmann etc). Initially, therefore two shorter chain molecules can

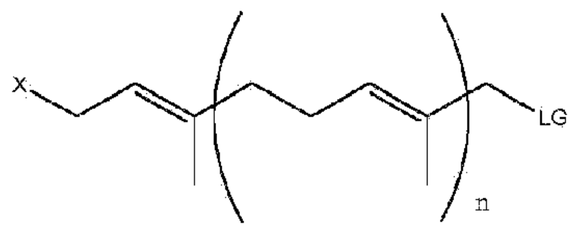
be combined. By using appropriate protection strategies, the coupled species can then be deprotected to reveal an alcohol which can be converted to phenythio or phenylsulfonyl substituted compounds ready for a second Biellmann coupling. In this way, the isoprenoid units needed to form the complete side chain of a long menaquinone can be joined together from shorter starting blocks. Reduction of all phenythio or phenylsulfonyl substituted compounds present can take place as a final step to yield a side chain suitable for coupling to a naphthoquinone related molecule, e.g. using Kumada or Suzuki chemistry. This reaction is highly flexible and allows the formation of side chains for MK-7.

[0057] One such reaction is depicted below in scheme 7

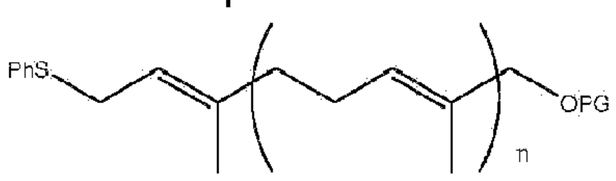
Scheme 7



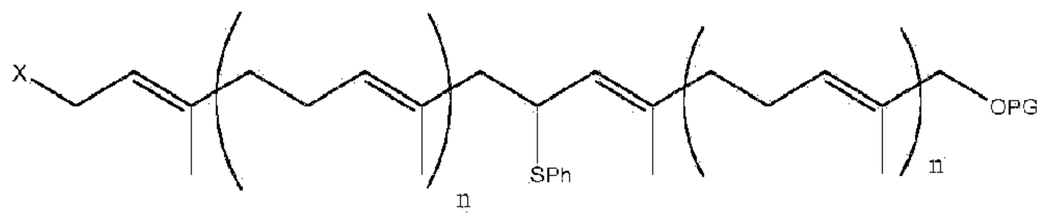
[0058] This "double Biellmann" chemistry may be used to form the polyisoprenoid chain. This may involve a process for the preparation of a compound comprising an isoprenoid repeating unit comprising (i) reacting a compound of formula



with a compound

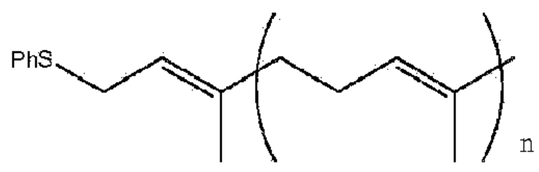


Where PG is a protecting group and n, LG and X are as hereinbefore defined to form

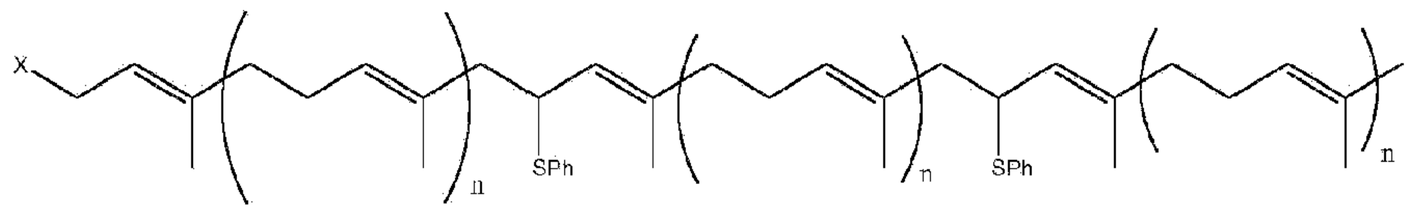


XVI

(ii) converting said OPG group into a leaving group and reacting with a compound



so as to form

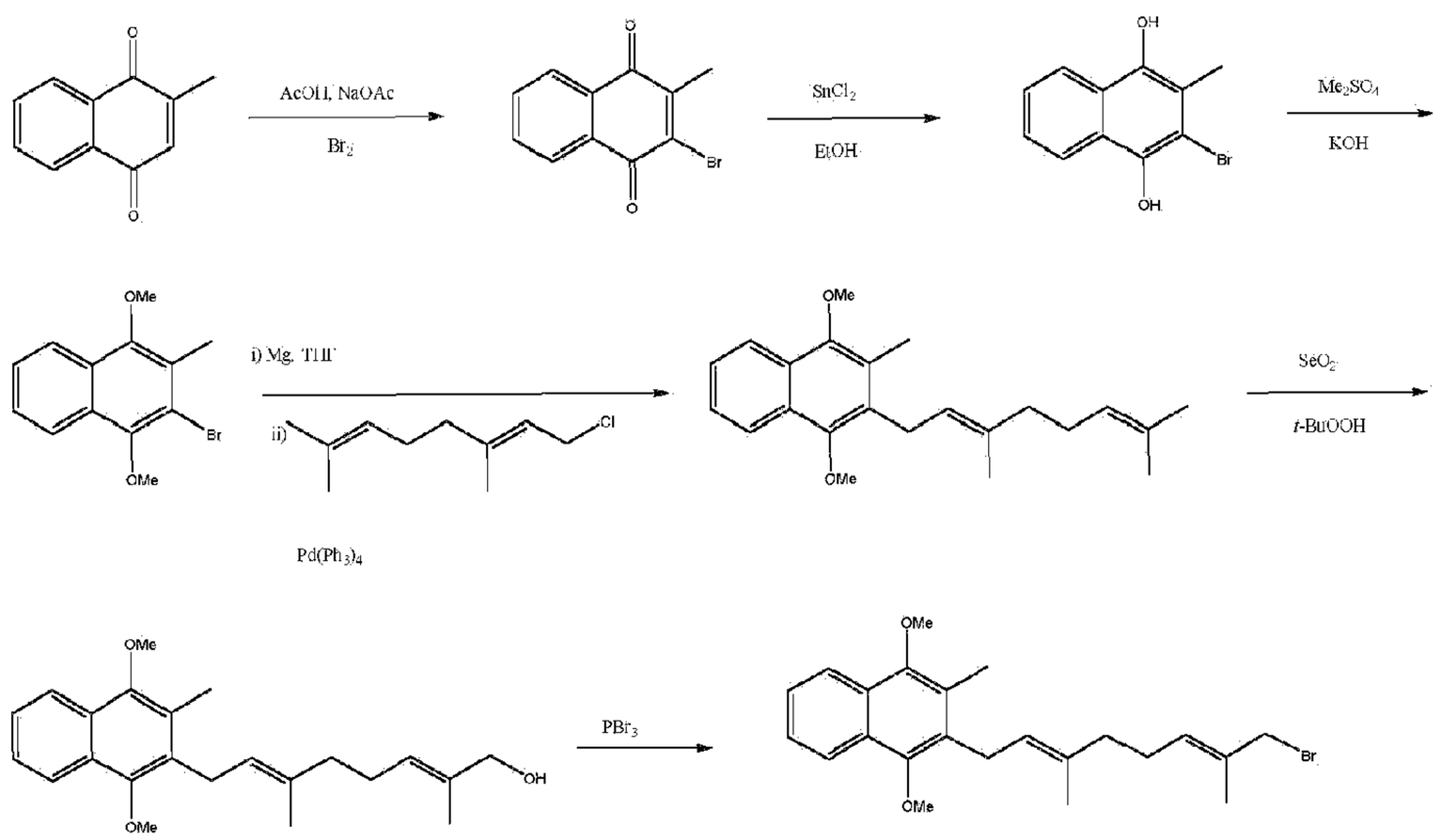


XVII

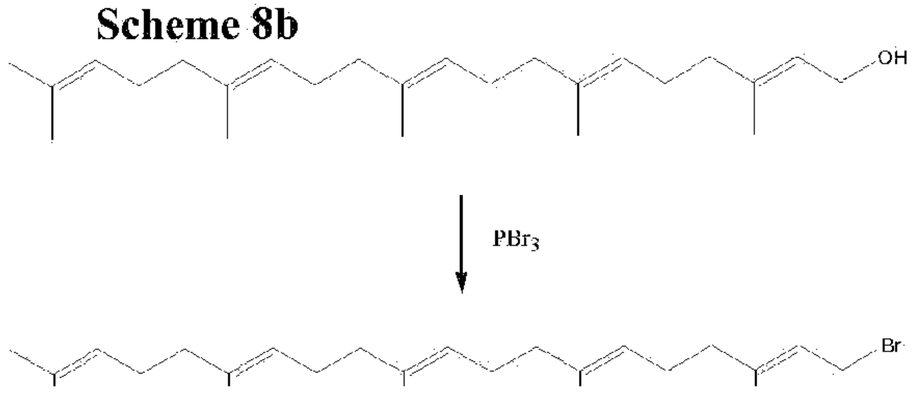
(iii) and optionally reducing said SPh groups to hydride.

[0059] The inventors have also found however, that the Biellmann reaction can be carried out on a molecule in which the protected analogue of the naphthoquinone ring is present. It may be therefore that the phenylthioether required in the Biellmann reaction already carries a protected analogue of naphthoquinone. In scheme 8, after an initial Kumada coupling reaction, the side chain terminus is converted to a hydroxyl using selenium dioxide and this hydroxyl can be converted to a halide and coupled with phenythio or phenylsulfonyl substituted derivatives using chemistry described above.

Scheme 8a



Scheme 8b



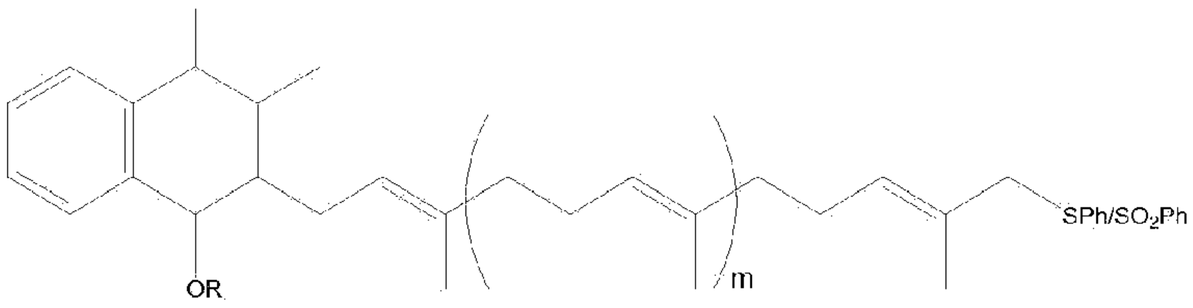
(I)

[0060] Conversion of the hydroxyl into phenythio or phenylsulfonyl group using the chemistry above gives an intermediate which can itself partake in a Biellmann coupling reaction to form a menaquinone molecule upon suitable work up procedures.

[0061] The compound of formula (I) as hereinbefore defined

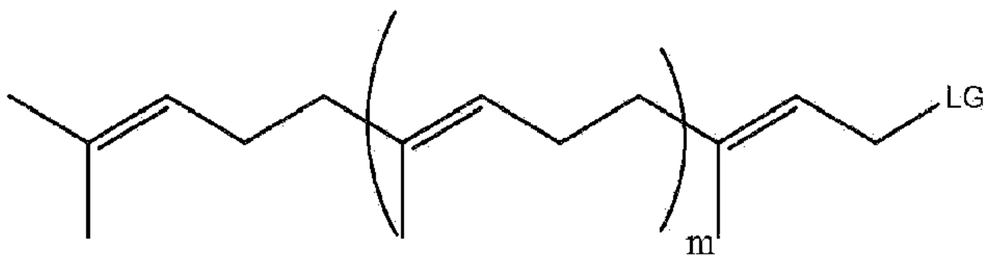
may be prepared by a process comprising (i) reacting a compound of formula (II) or (IV) with a compound of formula (III) in the presence of a copper, nickel or palladium catalyst;

(ii) converting X into a phenythio or phenylsulfonyl group to form compound (VII)



(VII);

(iii) deprotonating (alpha to the sulphur) and reacting with a compound



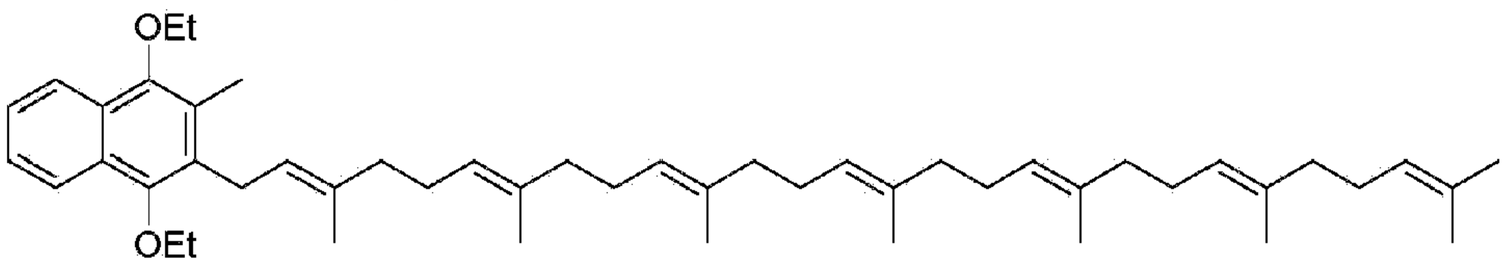
where m is independently as hereinbefore defined;

(iv) reductively removing the phenythio or phenylsulfonyl groups; and

(v) converting by oxidation the diprotected naphthoquinone into a naphthoquinone.

[0062] This reaction can also be carried out using other R groups to protect the naphthoquinone and again it will be appreciated that the sum of the various n values of the starting materials will add up to the value of n in the compound of formula (I) taking into account any units formed in the reactions.

[0063] A key intermediate in the above reaction is new and forms a particular aspect of the invention. The compound is:



[0064] By varying the number of isoprenoid units in either molecule coupled using the Biellmann reaction, Suzuki coupling or Kumada coupling all manner of different menaquinone compounds can be produced.

[0065] The final products of the formula (1) formed by the processes described above are generally known compounds and have well documented therapeutic applications. The formed compounds may therefore be formulated as pharmaceutically acceptable compositions. The compounds of formula (I) have utility in the treatment of osteoporosis, cancer or cardio-vascular disease. The compounds may also be used as vitamin supplements or in any other known application of vitamin K, e.g. for injection into new-born infants to aid blood clotting.

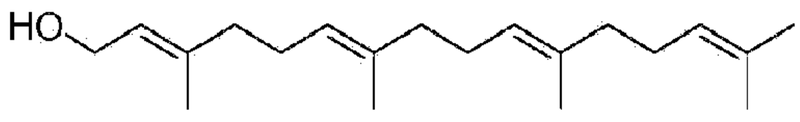
[0066] It is a particular feature of the invention that the MK-7 product achieved is highly pure. It has excellent stereochemical integrity and can be manufactured as solids as opposed to oils. In particular, the MK-7 compound manufactured according to the invention can be crystalline.

[0067] In the schemes above, specific reaction conditions and reagents are disclosed to aid the skilled man in carrying out the reactions described herein. The chemistry could however be carried out under different conditions and using various reagents and the skilled man is aware of this. The reactions disclosed in the schemes are therefore disclosed per se and should not be considered as being limited to the use of the particular reagents mentioned in those schemes. The reactions in the schemes are disclosed irrespective of how each reaction is accomplished as well as in conjunction with the specific reagents mentioned.

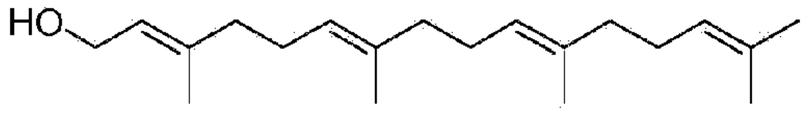
[0068] The invention will now be further described with reference to the following non limiting examples:

Example 1

[0069]



(*E,E,E*)-Geranylgeraniol was prepared according to the literature (Jin, Y., Roberts, F.G and Coates, R.M., Org. Synth. (2007), 84, 43.



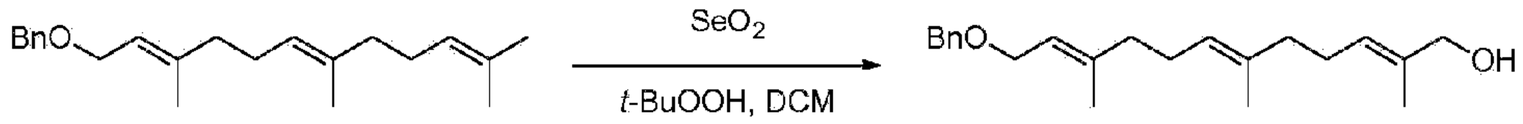
[0070] To a solution of (*E,E,E*)-geranylgeraniol (1.45 g, 5.00 mmol) in 3:1 dry ether/HMPA was added methyllitium (3.3 ml, 1.6 M in ether, 5.2 mmol) at 0 °C under nitrogen followed by *p*-toluenesulfonyl chloride (1.11 g, 5.82 mmol) . After 2 hours at 0 °C lithium thiophenoxide (5.76 mmol, prepared from thiophenol and n-BuLi in THF) was added. The reaction mixture was allowed to reach room temperature and stirred for 2 hours. Water was added and the aqueous phase extracted with heptane (x3). The combined organic extract was washed with $NaHCO_3$ (aq) and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (heptane : EtOAc 95:5) to give 1.42 g (74%) of the product.

Example 2

[0071]



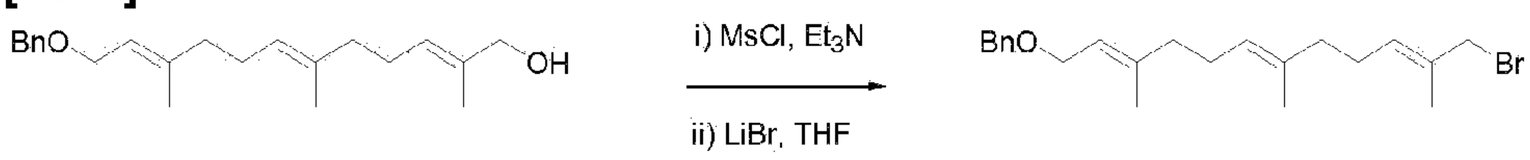
[0072] Benzyloxyfarnesol was prepared as described in the literature (Naruta, Y. J. Org. Chem. (1980), 45, 4097.



[0073] To a solution of benzyloxyfarnesol (50.0 g, 0.16 mol) in DCM (200 ml) was added SeO_2 (1.00 g, 9.01 mmol) and salicylic acid (2.24 g, 16.2 mmol) follwed by *t*-BuOOH (67 ml, 80% in di *t*-butylperoxide:H_2O) at room temperature. The reaction mixture was stirred for 3.5 hours, silicagel added and the reaction mixture concentrated and purified directly by flash chromatography (heptane :EtOAc 7:1-4:1 gradient) to give 21.7 g (41%) as a colorless oil.

Example 3

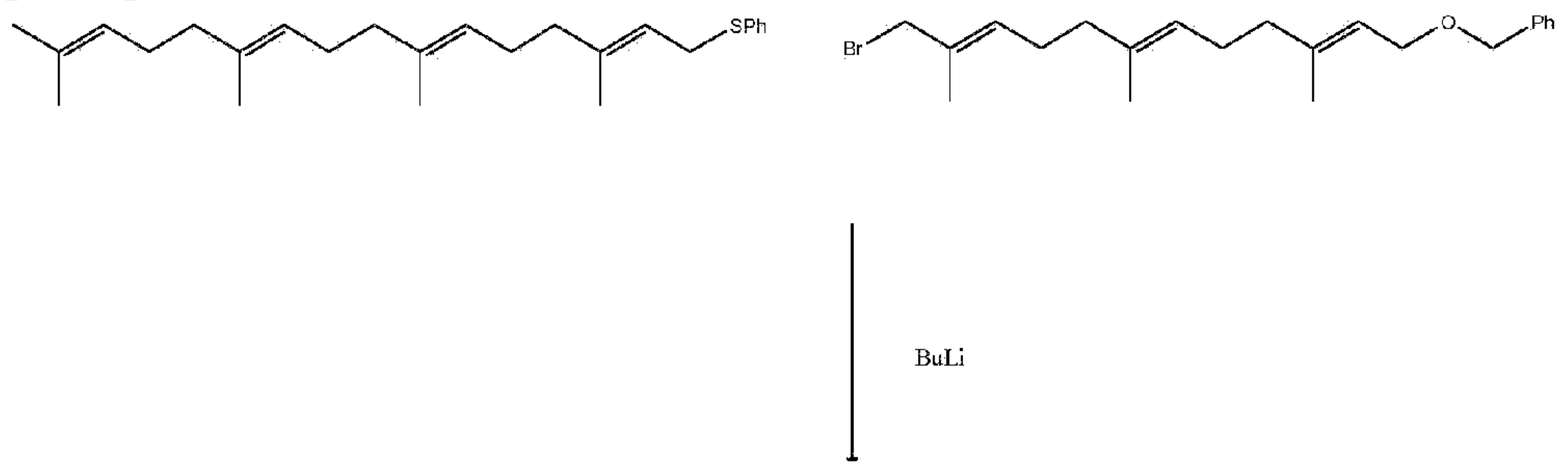
[0074]

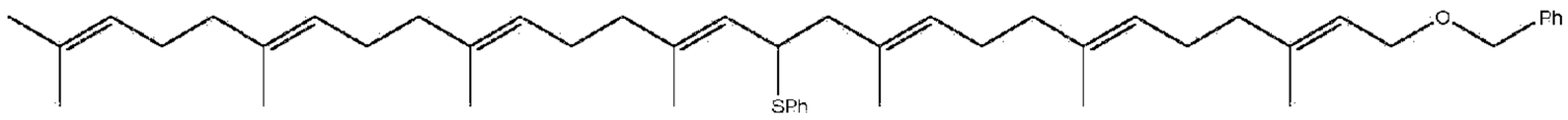


[0075] To a solution of the product from above (21.7 g, 66.0 mmol) in dry THF (220 ml) at -45 °C under argon was added slowly methanesulfonyl chloride (9.75 g, 85.1 mmol), followed by triethylamine (13.3 g, 131 mmol). The thus obtained white suspension was stirred at -45 °C for 45 min. A solution of lithium bromide (22.9 g, 264 mmol) in dry THF (75 ml) was added slowly. The dry ice/acetonitrile bath was replaced by an ice-bath and stirring continued for 1.5 hrs. The reaction mixture was poured into ice-water (600 ml) and the aqueous layer separated and extracted with ether (3x300 ml). The combined organic extracts were washed with ice-cold $NaHCO_3$ (400 ml) and brine (400 ml), dried (Na_2SO_4), filtered and concentrated to give 25.47 g (98%) of the product as a colorless oil used directly in the next step.

Example 4

[0076]

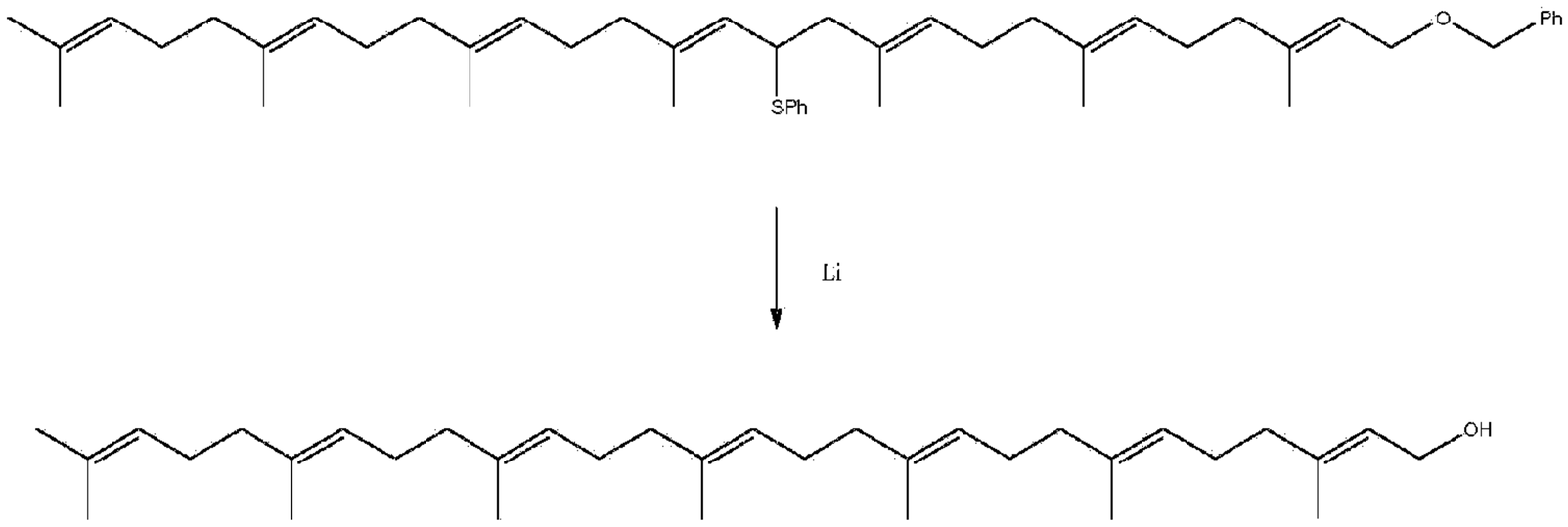




[0077] (*E,E,E*)-geranylgeraniol thiophenyl ether (2.11 g, 5.51 mmol) was dissolved in dry THF (35 ml), cooled to -78 °C and butyllithium added with stirring. The thus obtained bright yellow reaction mixture was stirred at - 78°C for 2.5 hrs under nitrogen. The product from the above reaction (1.78 g, 4.54 mmol) in dry THF (10 ml) was added and stirring continued at -78 °C for another 1.5 hrs. 4 ml 1:1 MeOH/ether was added and the reaction mixture allowed to reach room temperature at which point equal amounts of water and ether were added. The aqueous phase was extracted with ether (x3) and the combined extracts washed with brine, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (heptane : EtOAc gradient) afforded 2.50 g (80%) of the product as a colourless oil.

Example 5

[0078]

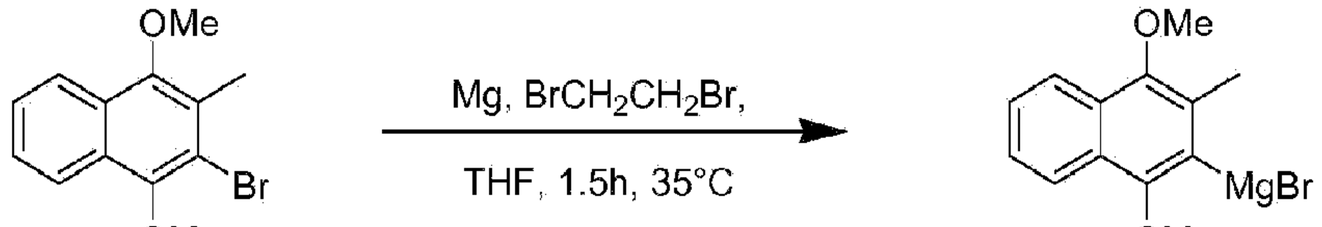


[0079] Under argon a reaction flask was charged with ethylamine (300 ml) at - 78 °C. Lithium (3.30 g, 476 mmol) in small pieces was added and the temperature raised to 0 °C for 45 min. The dark blue solution was cooled to -78 °C and a solution of the product from above (7.50 g, 10.8 mmol) in dry THF (60 ml) was added. After TLC showed complete conversion, 3-hexyne was added until complete dissipation of the blue colour. Methanol was added slowly until the reaction mixture became colourless. The reaction mixture was subsequently poured into ice-water and the aqueous phases extracted with ether (x3). The combined organic extract was washed with water, brine, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (heptane:EtOAc 80:20) afforded 4.20 g (78%) product as a pale yellow oil.

[0080] Heptaprenol was converted to heptaprenyl bromide as described above or by applying PBr_3 in DCM or ether.

Example 6 (not within the scope of the claimed invention)

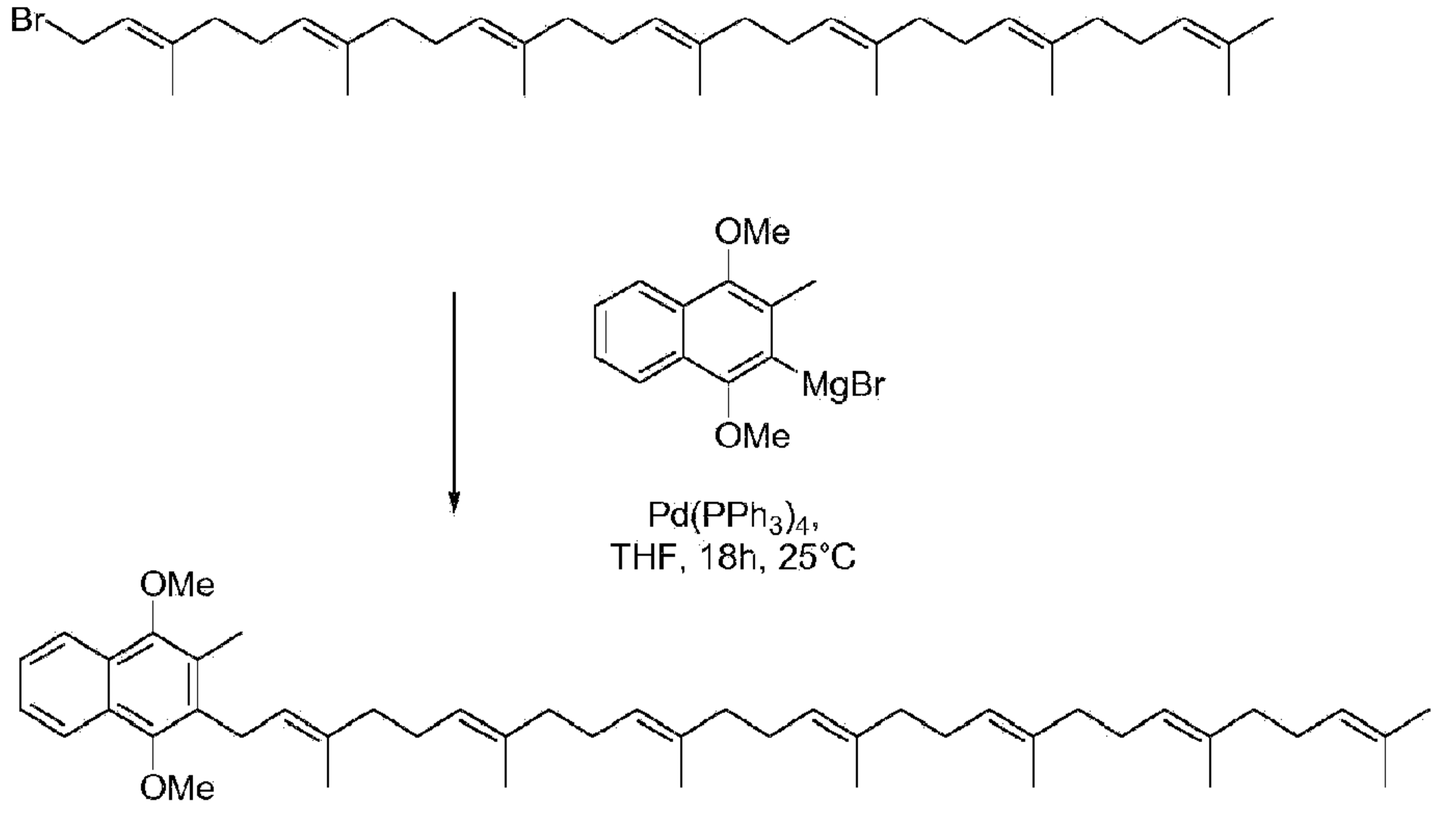
[0081] 2-Bromo-1,4-dimethoxy-3-methyl naphthalene was prepared by a modification of a method described in the literature (Adams, R., Geissman, B. R., Baker, B. R., Teeter, H. M. JACS (1941) 61, 528.)



[0082] 0.37 g (15.3 mmol) magnesium turnings were covered with dry THF and 30 µl 1,2-dibromoethane was added via septum and syringe. The mixture stood for 30 min. 1.43 g (5.08 mmol) 2-bromo-1,4-dimethoxy-3-methyl naphthalene dissolved in 3 ml of dry THF was added drop wise to the magnesium turnings over 30 min. The reaction mixture was cooled with a water bath, when it started to reflux. After that, the mixture was stirred at 35°C for 1.5 hrs in a water bath until TLC showed complete conversion. The Grignard solution was used for the next step.

Example 7 (not within the scope of the claimed invention)

[0083]

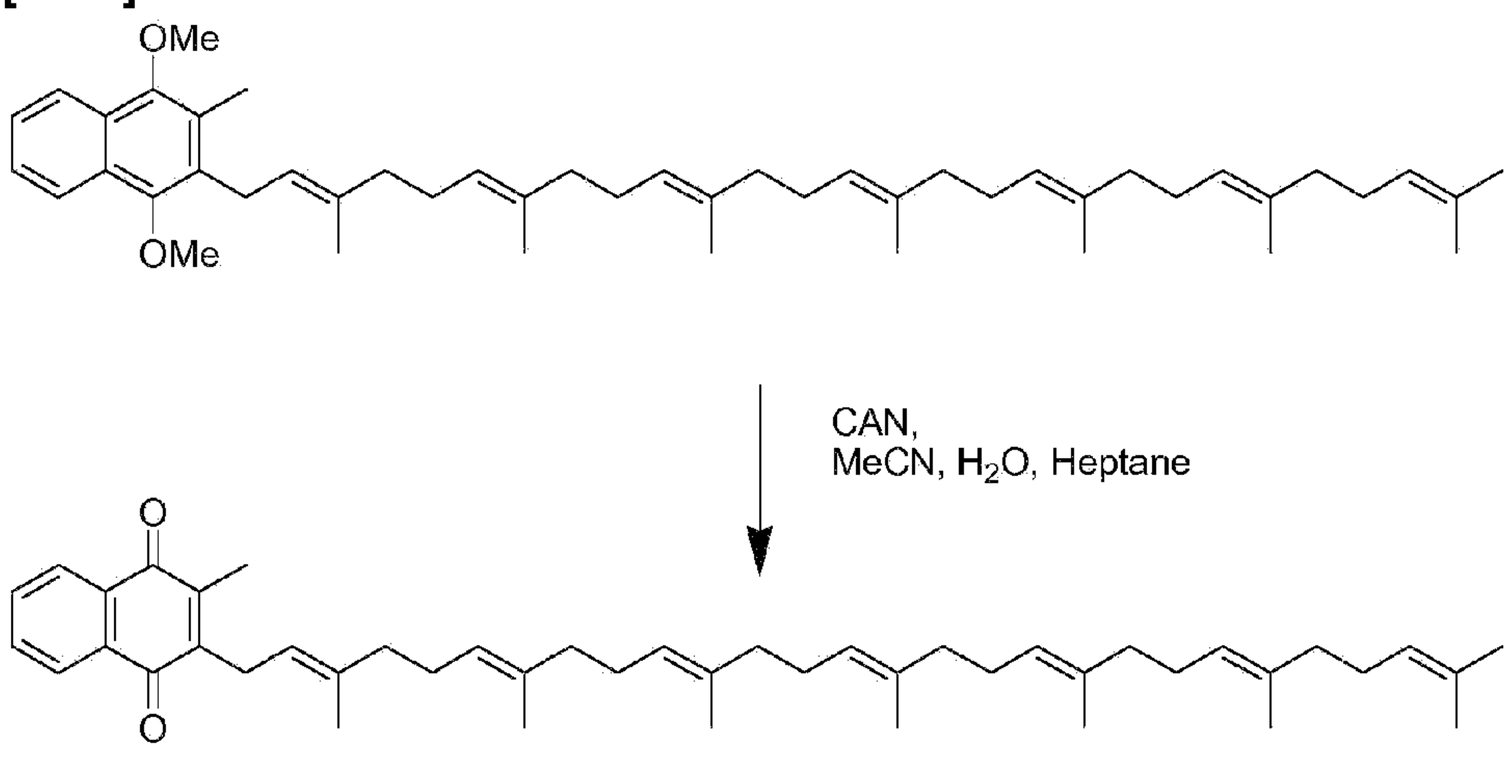


[0084] To heptaprenyl bromide (2.83 g, 5.08 mmol) dissolved in 5 ml of dry THF was added $Pd(Ph_3)_4$ (200 mg). To this yellow suspension, Grignard solution was added portion wise at room temperature after 5 min.. The mixture was stirred over night. The reaction was quenched at room temperature by addition of NH_4Cl, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was filtered through a short plug of silica gel to give

3.45 g of a pale yellow oil used directly in the final step.

Example 8 (not within the scope of the claimed invention)

[0085]

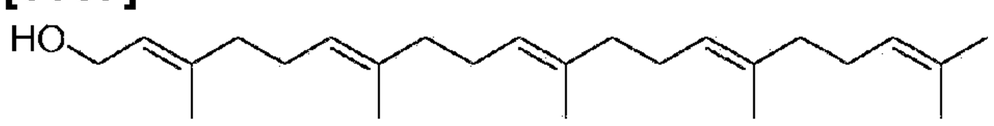


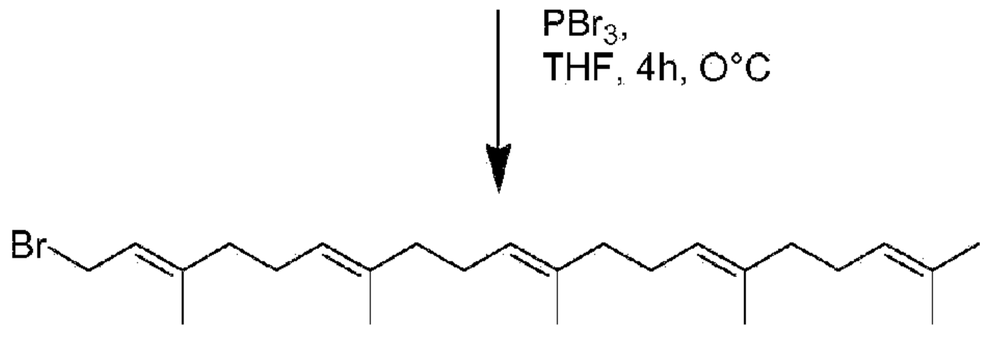
[0086] 2-(3,7,11,15,19,23,27-heptamethyl-octacosa-2,6,10,14,18,22,26-heptaenyl)-1,4-dimethoxy-3-methyl-naphtalene (3.45 g, 5.08 mmol) was suspended in 10 ml of acetonitrile, 10 ml of heptane and 10 ml of H_2O and the suspension was cooled to 0 °C with an ice bath. At 0 °C, CAN (7.00 g, 12.77 mmol) was added portion wise. The orange mixture was stirred at 0 °C for 30 min. and at room temperature for 30 min. The yellow mixture was poured into 100 ml ice water. The layers were separated and the aqueous layer was extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (heptane : EtOAc 99:1-97.5:2.5-95:5) afforded 1.83 g (56%) of the product.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.69-7.63 (m, 2H), 5.08-4.97 (m, 7H), 3.35 (d, ^{3}J=6.9 Hz, 2H) 2.16 (s, 3H), 2.05-1.81 (m, 24H), 1.77 (s, 3H), 1.65 (s, 3H), 1.57 (s, 12H), 1.54 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.34, 184.40, 146.08, 143.27, 137.48, 135.15, 134.84, 133.25, 133.19, 132.13, 132.09, 131.15, 126.24, 126.13, 124.37, 124.23, 124.11, 123.80, 119.05, 39.68, 26.72, 26.65, 26.45, 25.96, 25.65, 17.63, 16.38, 15.97, 12.62

Example 9

[0087]

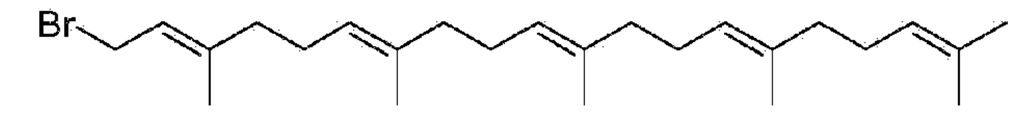


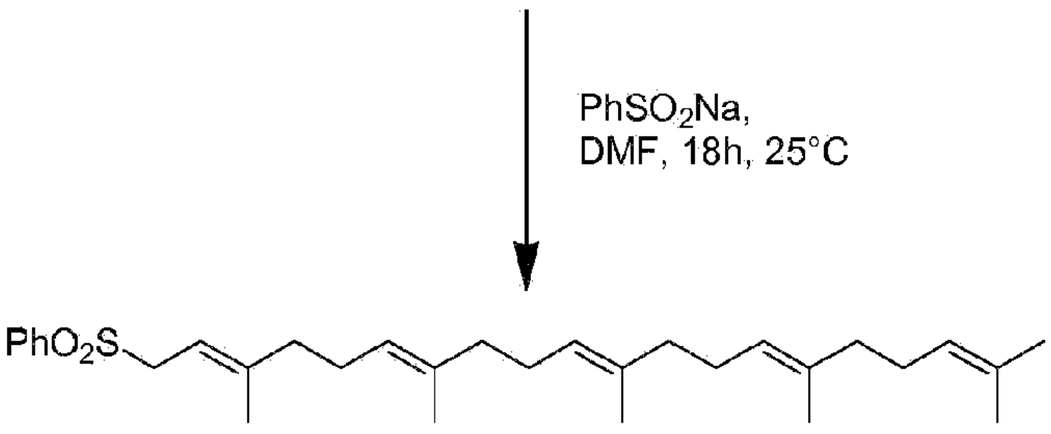


[0088] 10.83 g (30.20 mmol) 3,7,11,15,19-pentamethyl-eicosa-2,6,10,14,18-pentaen-1-ol was dissolved in 60 ml of dry THF. At 0 °C, 1.5 ml (4.32 g, 15.96 mmol) PBr_3 were added drop wise via septum and syringe and the clear, colourless solution was stirred at 0°C for 4 h. The reaction was quenched by addition of ice cold water. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 1-bromo-3,7,11,15,19-pentamethyl-eicosa-2,6,10,14,18-pentaene as a colourless oil (10.89 g, 25.84 mmol, 86%). The crude product was used for the next step without further purification.

Example 10

[0089]





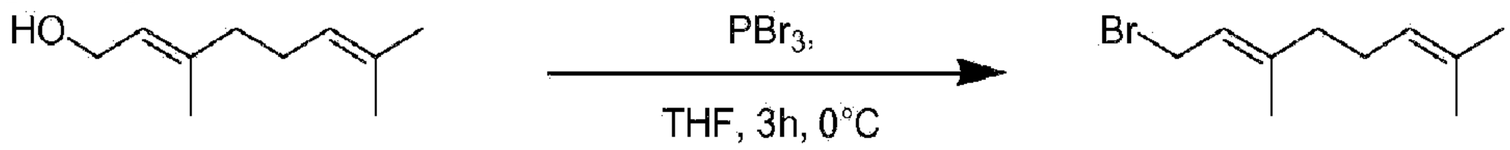
[0090] 10.89 g (25.84 mmol) allylic bromide was dissolved in 200 ml of DMF and 21.30 g (129.75 mmol) benzene sulfinic acid sodium salt was added in one portion at room temperature. The suspension was stirred at room temperature for 18h over night. The mixture was poured into ice water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with ice water and ice cold brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* by rotary evaporation at 40 °C. The residue was purified by dry flash. A gradient heptane : EtOAc (90 : 10) to heptane : EtOAc (70 :30) was used as eluent to afford 6.14 g (12.71 mmol, 50%) of pure (3,7,11,15,19-pentamethyl-eicosa-2,6,10,14,18-pentaene-1-sulfonyl)-benzene (as colourless oil and 2.92 g (6.05 mmol, 24%) of mixed fractions containing mostly (3,7,11,15,19-pentamethyl-eicosa-2,6,10,14,18-pentaene-1-sulfonyl)-benzene as colourless oil.

^1H NMR (200 MHz, $CDCl_3$) δ 7.86-7.81 (m, 2H), 7.60-7.45 (m, 3H), 5.20-5.04 (m, 5H), 3.77 (d,

^{3}J=8.0 Hz, 2H), 2.05-1.87 (m, 16H), 1.65 (s, 3H), 1.56 (s, 12H), 1.27 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.33, 138.60, 135.65, 134.94, 134.80, 133.42, 131.13, 128.85, 128.48, 124.32, 124.15, 124.03, 123.24, 124.37, 110.23, 56.01, 39.63, 31.80, 26.68, 26.57, 26.11, 25.62, 22.61, 17.60, 16.09, 15.93, 14.04.

Example 11

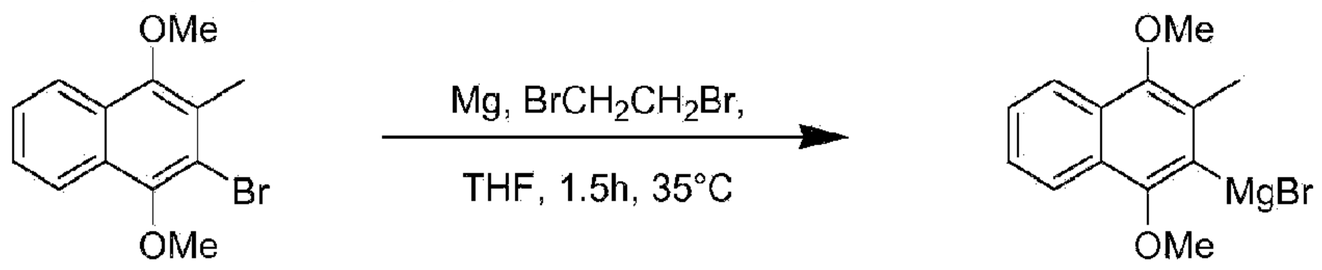
[0091]



[0092] 10.02 g (64.96 mmol) geraniol was dissolved in 120 ml of dry THF. At 0 °C, 3.1 ml (8.93 g, 32.98 mmol) PBr_3 were added drop wise via septum and syringe and the clear, colorless solution was stirred at 0°C for 3 h. The reaction was quenched by addition of ice cold water. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give geranyl bromide as a colourless oil (13.59 g, 62.63 mmol, 96%). The crude product was used for the next step without further purification.

Example 12 (not within the scope of the claimed invention)

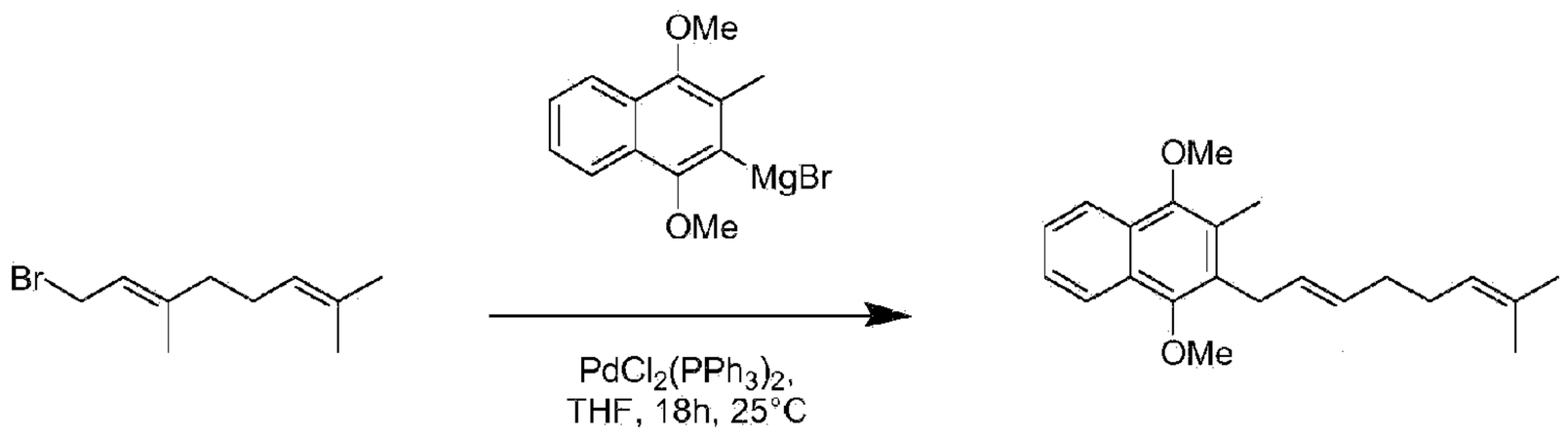
[0093] 2-Bromo-1,4-dimethoxy-3-methyl naphthalene was prepared by a modification of a method described in the literature (Adams, R., Geissman, B. R., Baker, B. R., Teeter, H. M. JACS (1941) 61, 528.)



[0094] 4.68 g (195 mmol) magnesium turnings were covered with dry THF and 0.5 ml (1.09 g, 5.80 mmol) 1,2-dibromo ethane was added via septum and syringe. The mixture stood for 30 min. 18.37 g (65.37 mmol) 2-bromo-1,4-dimethoxy-3-methyl naphthalene dissolved in 30 ml of dry THF was added drop wise to the magnesium turnings over 30 min. The reaction mixture was cooled with a water bath, when it started to reflux. After that, the mixture was stirred at 35°C for 1,5h in a water bath until TLC showed complete conversion. The Grignard solution was used for the next step.

Example 13 (not within the scope of the claimed invention)

[0095]

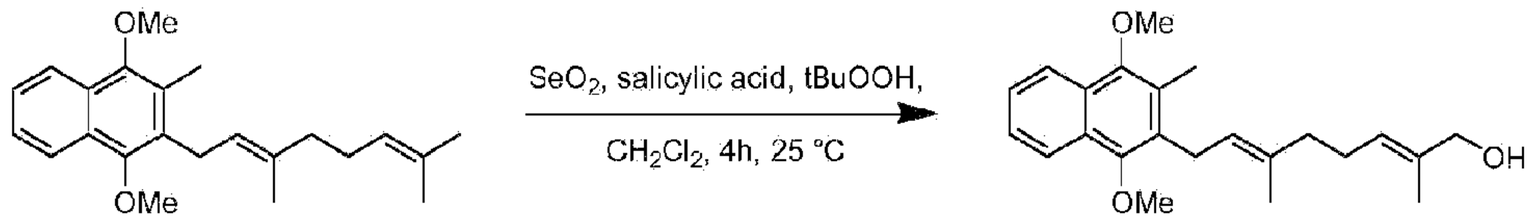


[0096] 13.59 g (62.63 mmol) geranyl bromide dissolved in 100 ml of dry THF was added to 0.91 g (1.297 mmol) $PdCl_2(PPh_3)_2$. To this yellow suspension, Grignard solution was added portion wise at room temperature. The mixture was stirred over night for 18h. The reaction was quenched at room temperature by addition of NH_4Cl, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 23.44 g of a brown oil. The residue was dissolved in little CH_2Cl_2 and was filtered through a plug of SiO_2 (50-60 g) to remove palladium residues. The plug was washed with CH_2Cl_2 until all product was washed out (checked by TLC). The combined fractions were concentrated *in vacuo.* The crude product 2-(3,7-dimethyl-octa-2,6-dienyl)-1,4-dimethoxy-3-methyl-naphtalene was used in the next step without further purification.

^1H NMR (200 MHz, $CDCl_3$) δ 8.07-8.03 (m, 2H), 7.47-7.42 (m, 2H), 5.13-5.07 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.56 (d, ^3J=6.1 Hz, 2H), 2.37 (s, 3H), 2.03 (m, 4H), 1.82 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.07, 149.71, 135.63, 131.37, 130.91, 127.46, 127.24, 126.93, 125.36, 125.23, 124.20, 122.90, 122.25, 122.08, 62.15, 61.28, 39.63, 26.53, 26.31, 25.65, 17.64, 16.32, 12.32

Example 14 (not within the scope of the claimed invention)

[0097]



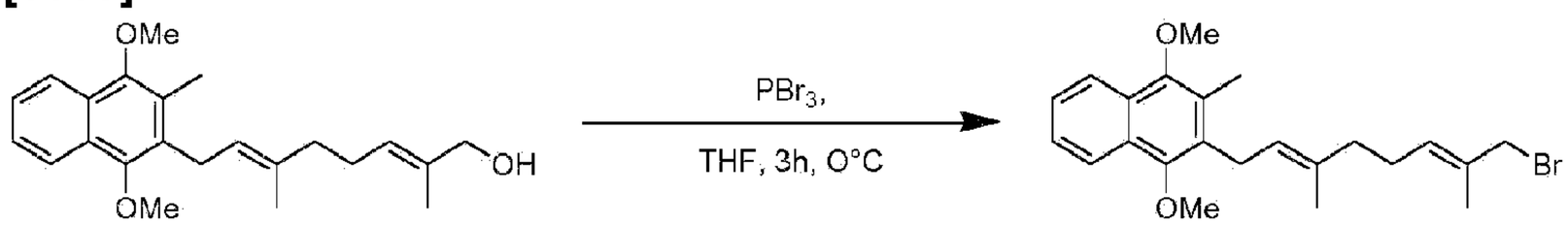
[0098] 0.37 g (3.34 mmol) SeO_2, 0.94 g (6.81 mmol) salicylic acid and 23 ml of *t*-BuOOH (70 wt% in water) were suspended in 85 ml of CH_2Cl_2. The suspension was stirred at room temperature for 40 min and then cooled to 0 °C with an ice bath. At 0 °C, 21.08 g (62.37 mmol) crude 2-(3,7-dimethyl-octa-2,6-dienyl)-1,4-dimethoxy-3-methyl-naphtalene dissolved in 45 ml of CH_2Cl_2 was added in one portion. After stirring at 0 °C for 5h the suspension was diluted

with 150 ml of toluene and the solvent was removed *in vacuo* by rotary evaporation at 40 °C. The residue was taken up in 150 ml of CH_2Cl_2 and the red brown solution was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in *vacuo* by rotary evaporation at 30 °C. The residue was dissolved in 140 ml of dry THF and 7 ml of MeOH, cooled to 0 °C with an ice bath and 2.44 g (64.50 mmol) $NaBH_4$ was added portion wise. The mixture was stirred at 0 °C for 30 min and 50 ml of ice cold saturated NH_4Cl was added portion wise at 0 °C to quench the reaction. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* by rotary evaporation at 30 °C to give a dark brown oil (21.48 g). The residue was purified by dry flash. A gradient heptane : EtOAc (80 : 20) to heptane : EtOAc (60 : 40) was used as eluent to afford 6.43 g (18.17 mmol, 28% over 3 steps from geraniol) of 8-(1,4-dimethoxy-3-methyl-naphtalen-2-yl)-2,6-dimethyl-octa-2,6-dien-1-ol as a oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06-8.01 (m, 2H), 7.48-7.40 (m, 2H), 5.34-5.28 (m, 1H), 5.12-5.05 (m, 1H), 3.92 (m, 2H), 3.86 (s, 3H), 3.54 (d, ^{3}J=5.9 Hz, 2H), 2.36 (s, 3H), 2.14-2.03 (m, 4H), 1.70 (s, 3H), 1.61 (s, 3H).

Example 15 (not within the scope of the claimed invention)

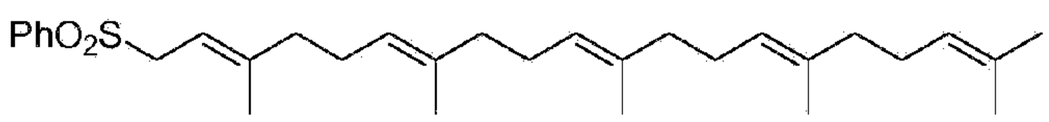
[0099]

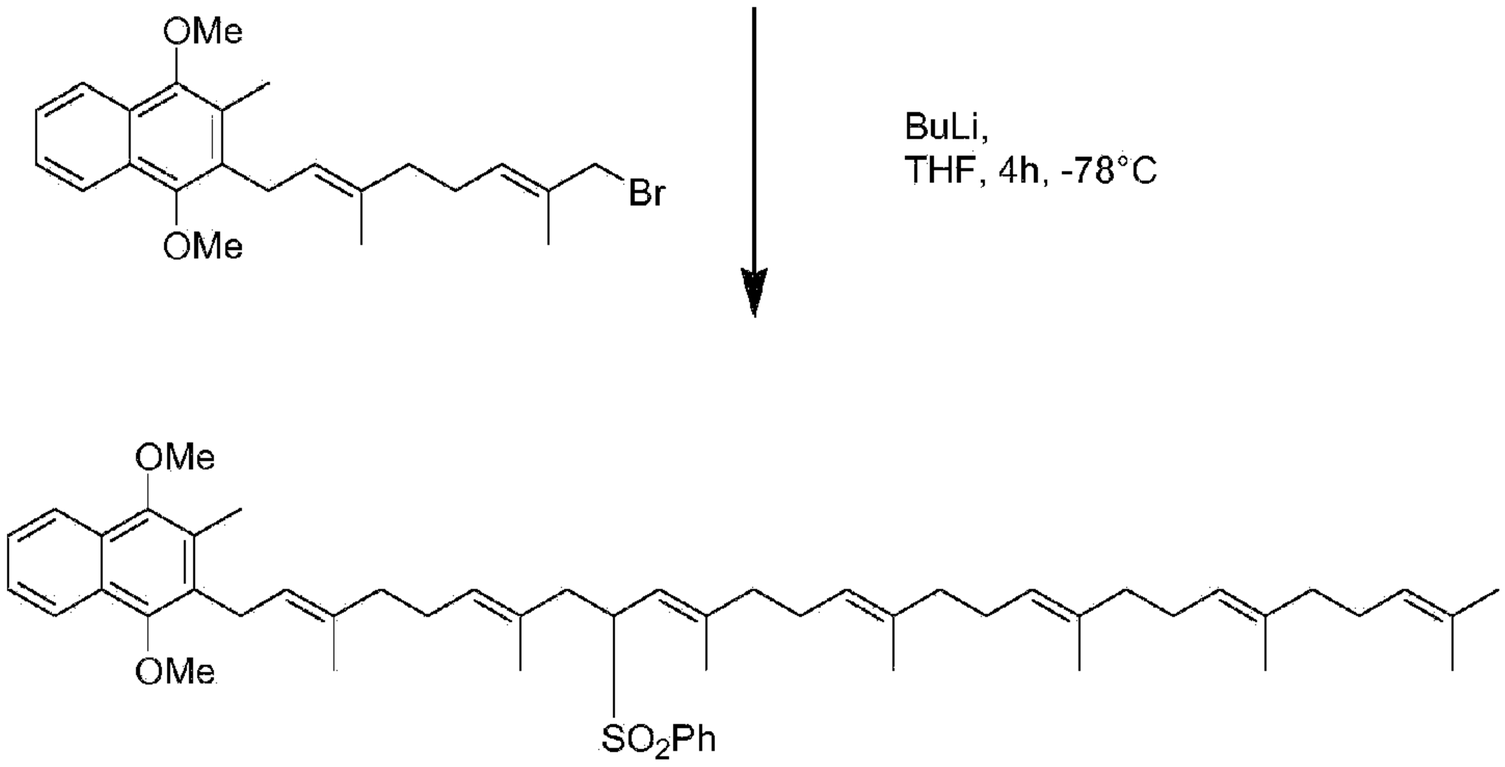


[0100] 6.45 g (18.22 mmol) of 8-(1,4-dimethoxy-3-methyl-naphtalen-2-yl)-2,6-dimethyl-octa-2,6-dien-1-ol was dissolved in 45 ml of dry THF. At 0 °C, 0.9 ml (2.59 g, 9.58 mmol) PBr_3 was added drop wise via septum and syringe and the clear, colourless solution was stirred at 0°C for 3 h. The reaction was quenched by addition of ice cold water. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 2-(8-bromo-3,7-dimethyl-octa-2,6-dienyl)-1,4-dimethoxy-3-methyl-naphtalene as a colorless oil (6.29 g, 15.08 mmol, 83%). The crude product was used for the next step without further purification.

Example 16 (not within the scope of the claimed invention)

[0101]

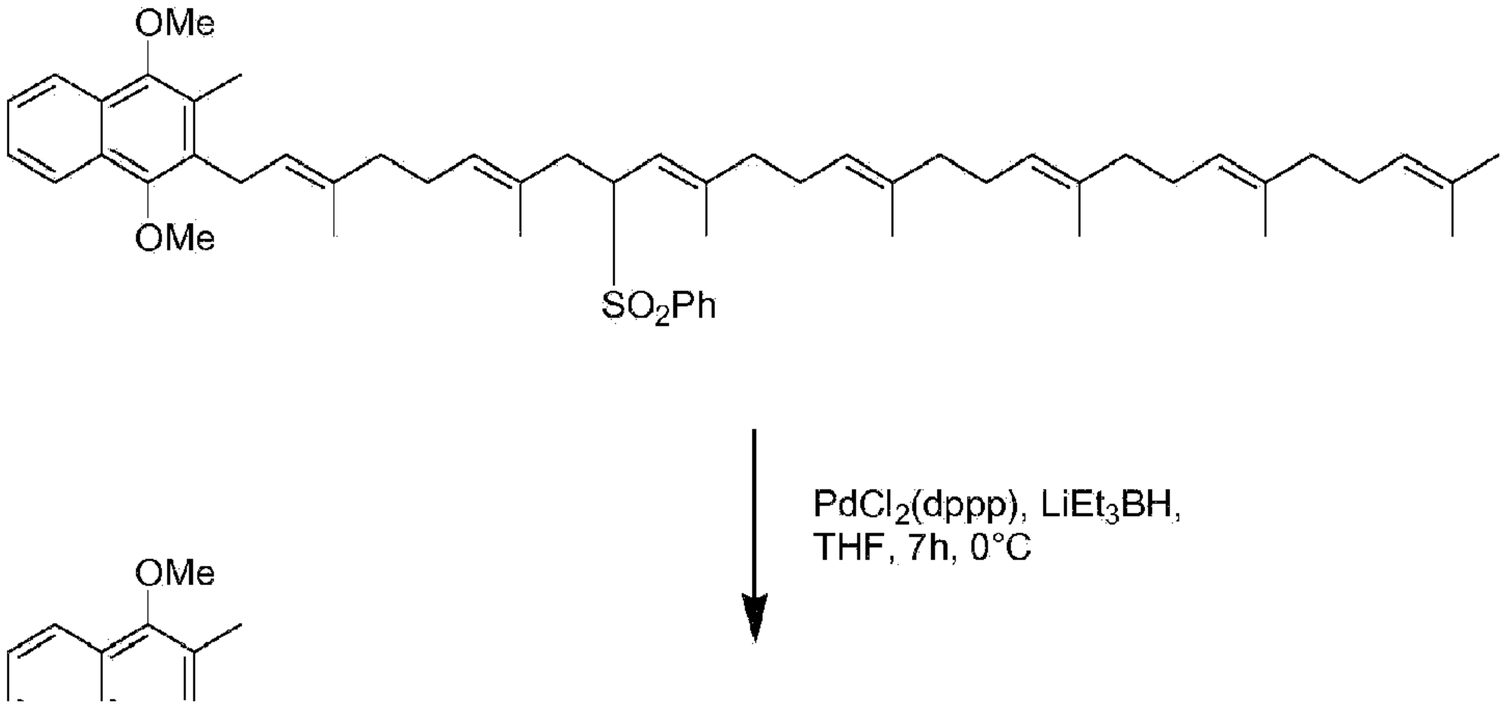


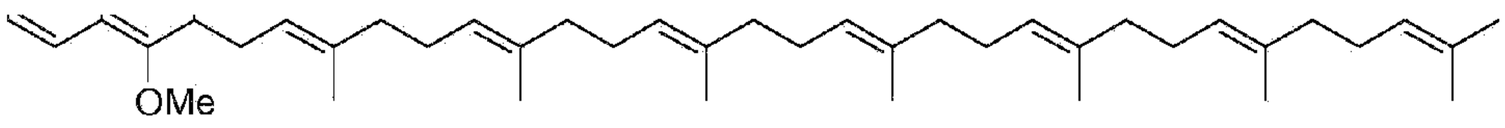


[0102] 9.06 g (18.76 mmol) (3,7,11,15,19-pentamethyl-eicosa-2,6,10,14,18-pentaene-1-sulfonyl)-benzene were dissolved in 80 ml of dry THF and the solution was cooled to -78 °C with CO_2 / MeOH. At -78 °C, 11.80 ml (18.88 mmol) BuLi (1.6 M solution in hexane) was added drop wise via septum and syringe over 10 min. The orange solution was stirred for 2.5 h at -78 °C. 6.07 g (14.56 mmol) 2-(8-bromo-3,7-dimethyl-octa-2,6-dienyl)-1,4-dimethoxy-3-methyl-naphtalene dissolved in 30 ml of dry THF was added via dropping funnel over 10 min. The brown reaction mixture was stirred at -78 °C for 1.5 h. At -78 °C, the reaction was quenched by addition of 50 ml of a Et_2O/MeOH mixture (1:1 v/v). The mixture was allowed to reach room temperature and after that 100 ml of saturated NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* by rotary evaporation at 30 °C to give 16.21 g of 2-(9-benzenesulfonyl-3,7,11,15,19,23,27-heptamethyl-octacosa-2,6,10,14,18,22,26-heptaenyl)-1,4-dimethoxy-3-methyl-naphtalene as a brownish yellow oil, which was used in the next step without further purification.

Example 17 (not within the scope of the claimed invention)

[0103]



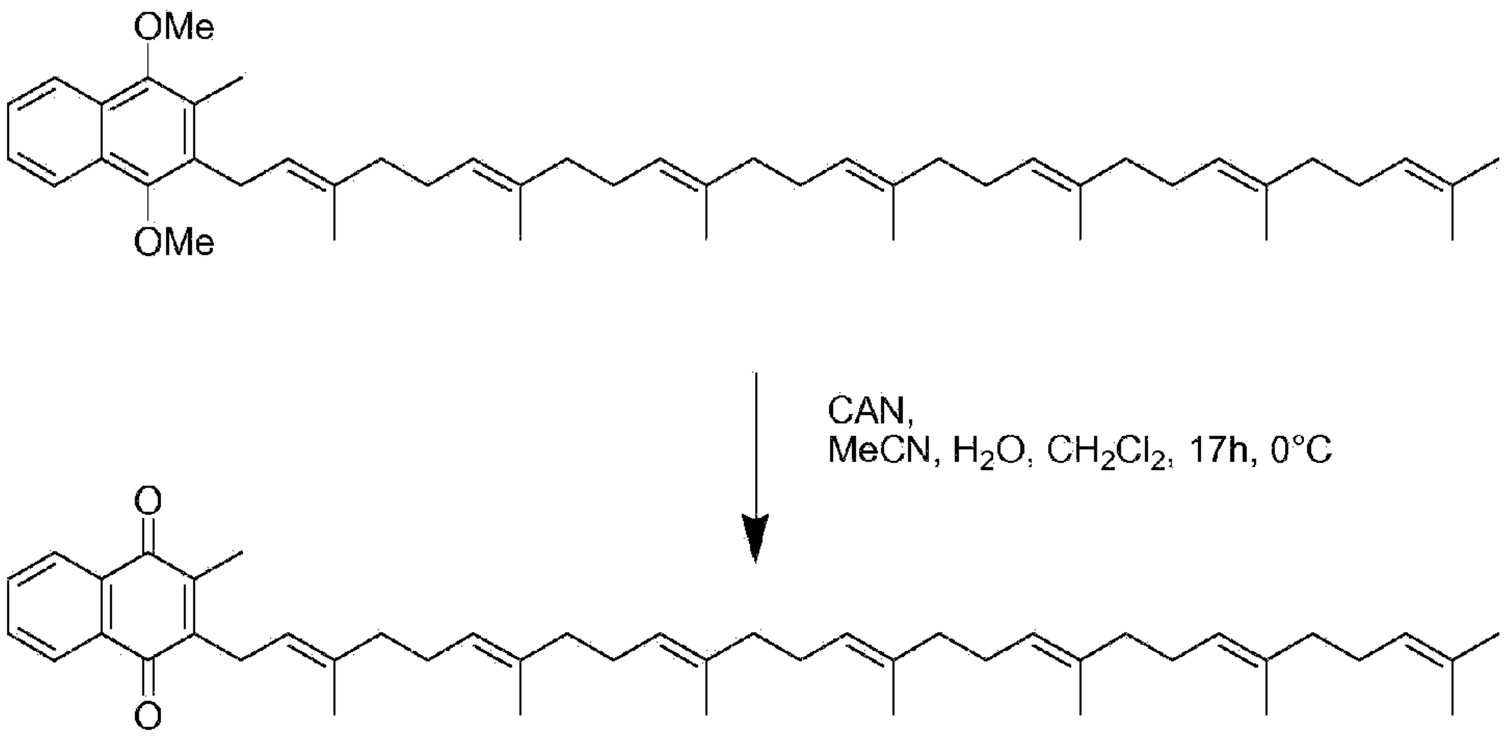


[0104] 16.21 g 2-(9-benzenesulfonyl-3,7,11,15,19,23,27-heptamethyl-octacosa-2,6,10,14,18,22,26-heptaenyl)-1,4-dimethoxy-3-methyl-naphtalene mixture was dissolved in 120 ml of dry THF and 0.57 g (0.96 mmol) $PdCl_2$(dppp) was added in one portion and the suspension was cooled to 0 °C with an ice bath. At 0 °C, 42.00 ml (42.00 mmol) $LiEt_3BH$ (1.0 M solution in THF) were added portion wise via septum and syringe over 20 min. The dark brown solution was stirred at 0 °C for 7 h. At 0 °C, the reaction was quenched by addition 100 ml of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated NH_4Cl solution, dried over Na_2SO_4, filtered and concentrated in *vacuo* by rotary evaporation at 30 °C to give 18.18 g of dark brown oil. It was purified by dry flash with CH_2Cl_2 as eluent to afford 11.01 g of yellow oil, which was used in the next step without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09-8.01 (m, 2H), 7.49-7.41 (m, 2H), 5.11-5.08 (m, 7H), 3.88 (s, 3H), 3.86 (s, 3H), 3.57 (d, ^{3}J=6.3 Hz, 2H) 2.38 (s, 3H), 2.05-1.85 (m, 24H), 1.83 (s, 3H), 1.68 (s, 3H), 1.60 (s, 12H), 1.57 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.07, 149.71, 135.71, 135.08, 134.92, 134.86, 127.46, 127.23, 126.89, 125.35, 125.23, 124.40, 124.25, 124.16, 124.01, 122.80, 122.25, 122.08, 62.14, 61.27, 39.71, 26.75, 26.65, 26.54, 26.31, 25.66, 17.66, 16.39, 15.99, 12.37

Example 18 (not within the scope of the claimed invention)

[0105]



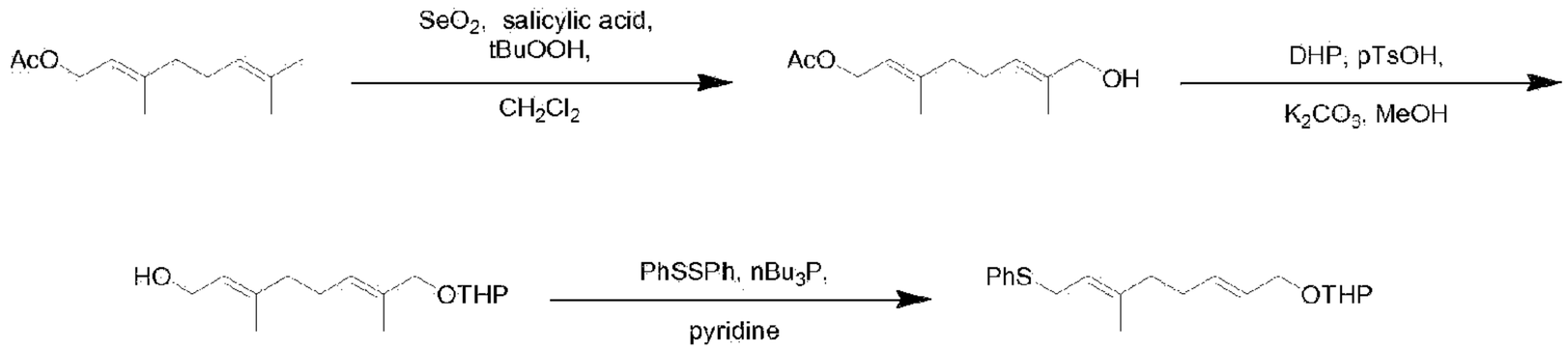
[0106] 2-(3,7,11,15,19,23,27-heptamethyl-octacosa-2,6,10,14,18,22,26-heptaenyl)-1,4-dimethoxy-3-methyl-naphtalene (8.50 g, 12.54 mmol) was suspended in 45 ml of acetonitrile, 45 ml of CH_2Cl_2 and 20 ml of H_2O and the suspension was cooled to 0 °C with an ice bath. At 0

°C, an ice cold solution of 17.26 g (31.48 mmol) CAN in 32 ml of acetonitrile and 32 ml of H_2O was added portion wise via dropping funnel over 20 min. The orange mixture was stirred at 0 °C for 40 min. and at room temperature for 16.5 h over night. The yellow mixture was poured into 100 ml ice water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with ice water, dried over Na_2SO_4, filtered and concentrated in *vacuo* by rotary evaporation at 40 °C to give 8.50 g of yellow oil. It was purified by dry flash. A gradient heptane : EtOAc (100 : 1) to heptane : EtOAc (95 : 5) was used as eluent to afford 4.93 g (7.61 mmol, 42% over 4 steps from 2-(8-bromo-3,7-dimethyl-octa-2,6-dienyl)-1,4-dimethoxy-3-methyl-naphtalene) of brownish yellow oil, which solidified in the fridge and was recrystallized from EtOAc and ethanol to give 3.5 g of MK7 as a bright yellow solid.

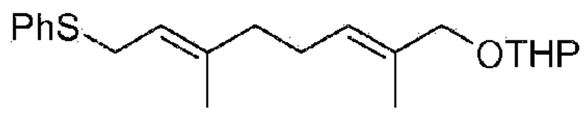
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.69-7.63 (m, 2H), 5.08-4.97 (m, 7H), 3.35 (d, ^{3}J=6.9 Hz, 2H) 2.16 (s, 3H), 2.05-1.81 (m, 24H), 1.77 (s, 3H), 1.65 (s, 3H), 1.57 (s, 12H), 1.54 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.34, 184.40, 146.08, 143.27, 137.48, 135.15, 134.84, 133.25, 133.19, 132.13, 132.09, 131.15, 126.24, 126.13, 124.37, 124.23, 124.11, 123.80, 119.05, 39.68, 26.72, 26.65, 26.45, 25.96, 25.65, 17.63, 16.38, 15.97, 12.62

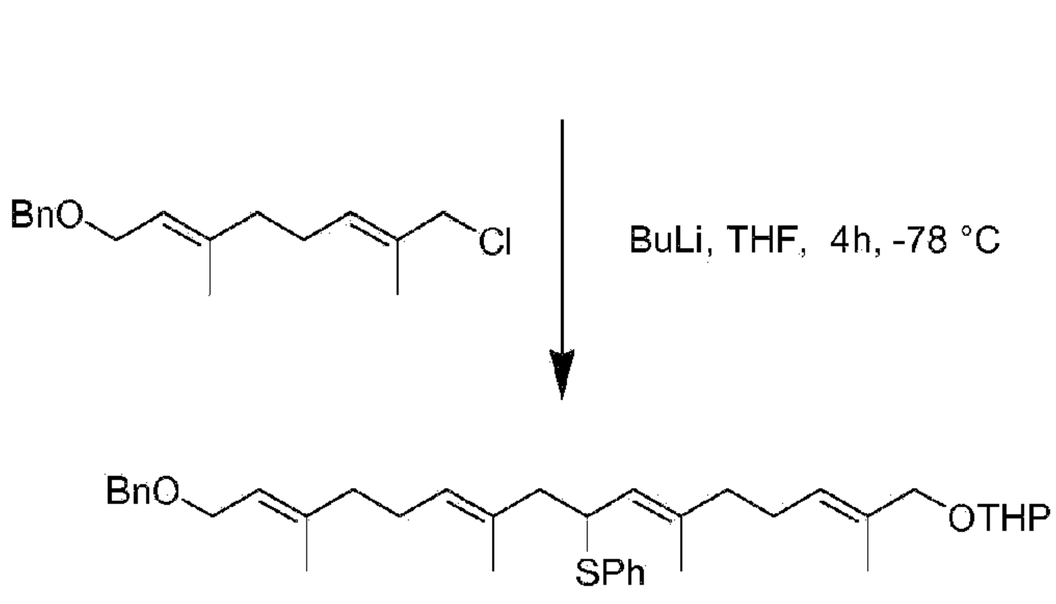
Example 19

[0107] The synthesis of allylic thioether from literature known compounds is outlined in Scheme A.



Scheme **A**: Synthesis of allylic thioether.



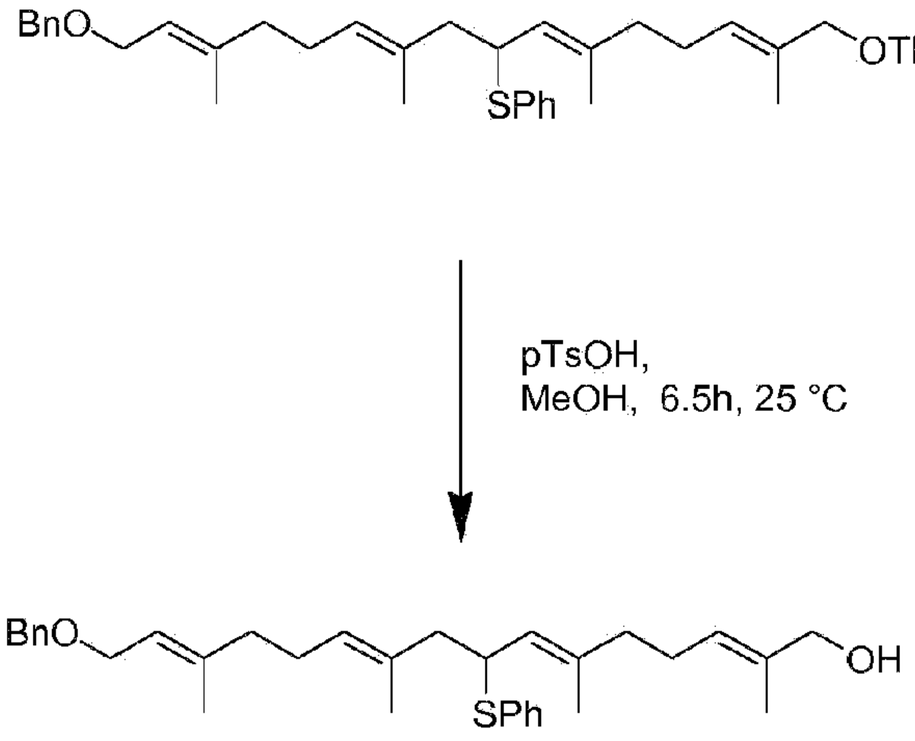


[0108] 1.80 g (5.20 mmol) thioether was dissolved in 30 ml of dry THF. The solution was cooled to -78°C with a CO_2/MeOH cooling bath and at -78°C; 3.30 ml (5.28 mmol) BuLi (1.6 M solution in hexane) was added drop wise via septum and syringe. The clear, yellow orange solution was stirred at -78°C for 2.5 h and then 1.20 g (4.32 mmol) allylic chloride dissolved in 10 ml of dry THF was added drop wise via septum and syringe at -78°C. The clear solution was stirred at -78°C for 1.5 h. At - 78°C, 10 ml of a MeOH/Et_2O mixture (1:1 v/v) was added and the mixture was allowed to reach room temperature and then 35 ml of sat. NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 40 ml). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo by rotary evaporation at 30°C to give 3.15 g of yellow oil. The crude product was further purified by flash column chromatography on SiO_2 using a mixture of heptane:EtOAc (9/1 v/v) as eluent to give a yellow oil (2.09 g, 3.56 mmol, 83%).

^1H NMR (200 MHz, $CDCl_3$) δ 7.42-7.21 (m, 10H), 5.39-5.34 (m, 2H), 5.16-5.14 (m, 1H), 5.01-4.96 (m, 1H), 4.57 (m, 1H), 4.49 (s, 2H), 4.11-3.77 (m, 6H), 3.59-3.41 (m, 1H), 2.35-1.70 (m, 12H), 1.63 (s, 6H), 1.58 (m, 3H), 1.34 (s, 3H)

Example 20

[0109]

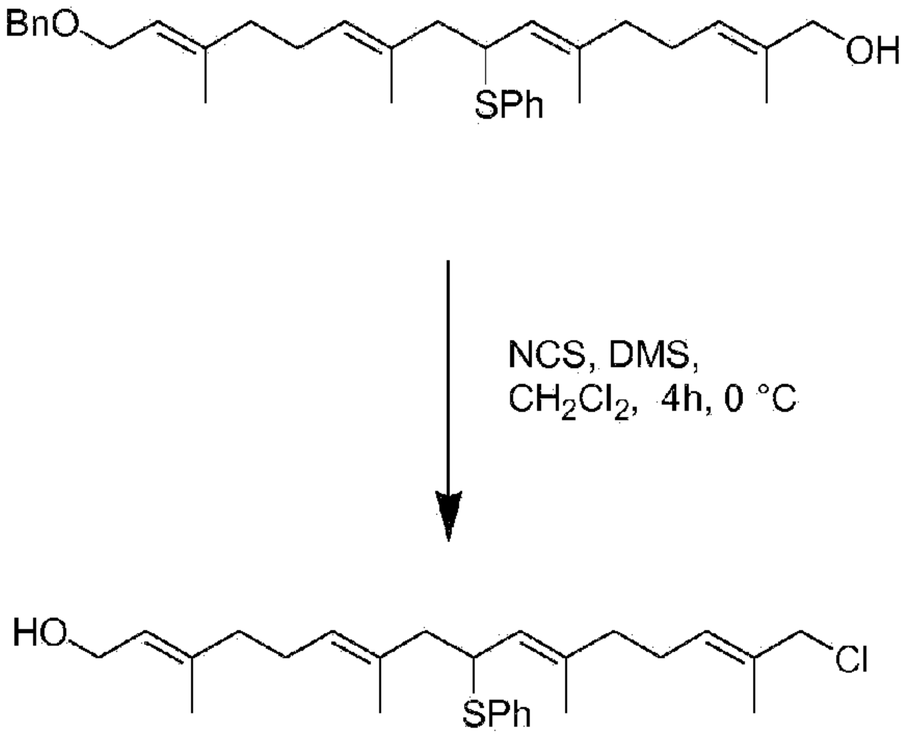


[0110] 2.09 g (3.55 mmol) THP ether was dissolved in 25 ml of dry MeOH. 0.21 g (1.10 mmol) pTsOH monohydrate was added in one portion. The clear mixture was stirred at room temperature for 6.5 h. After that, the reaction mixture was concentrated in vacuo by rotary evaporation at 40°C and the residue was dissolved in 50 ml of CH_2Cl_2 and washed with 50 ml of $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic extracts washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated in vacuo by rotary evaporation at 30°C to give 1.81 g of yellow oil. The crude product was further purified by flash column chromatography on SiO_2 using a mixture of heptane:EtOAc (60/40 v/v) as eluent to give a yellow oil (1.50 g, 2.98 mmol, 84%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.18 (m, 10H), 5.37-5.28 (m, 2H), 5.14-5.13 (m, 1H), 5.00-4.94 (m, 1H), 4.48 (s, 2H), 4.06-3.92 (m, 5H), 2.34-1.90 (m, 10H), 1.62 (s, 6H), 1.56 (m, 3H), 1.36 (s, 3H)

Example 21

[0111]

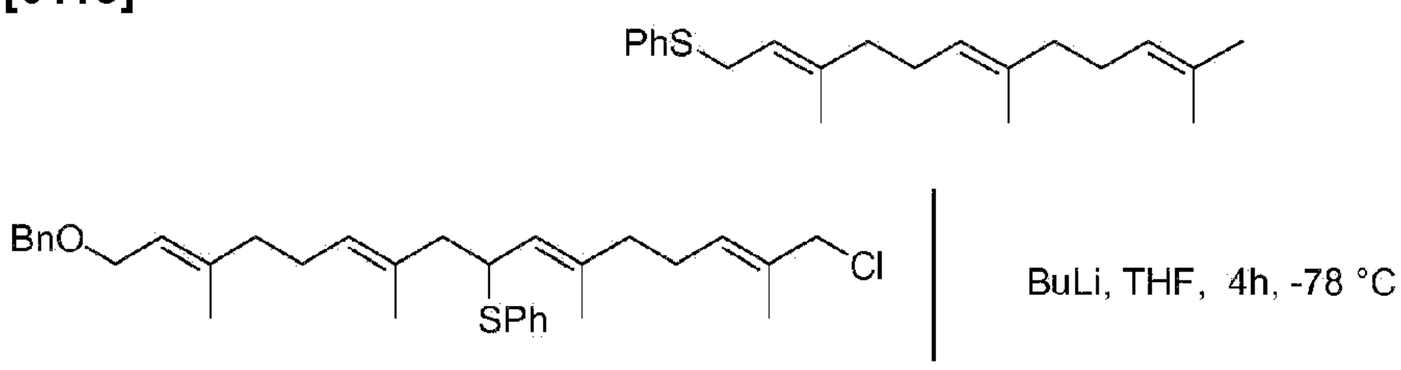


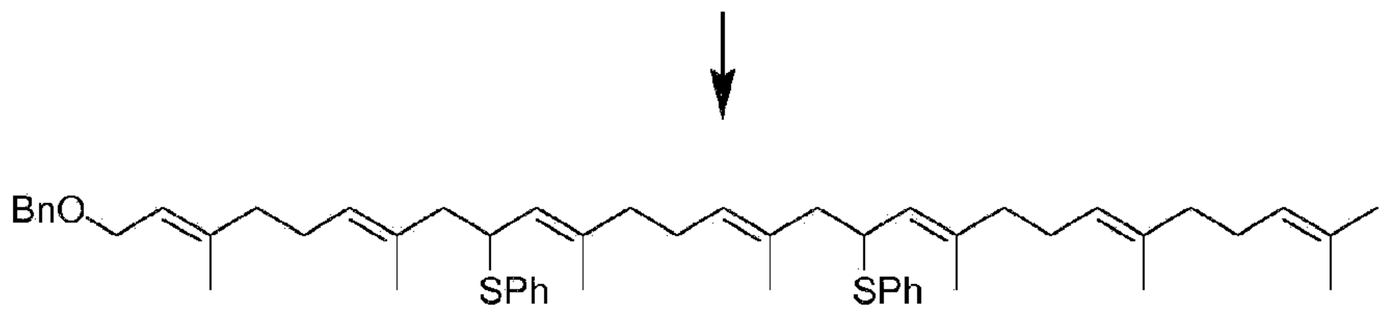
[0112] 0.74 g (5.54 mmol) NCS were suspended in 20 ml of dry CH_2Cl_2. At 0°C, 0.55 ml (0.47 g, 7.41 mmol) DMS was added neat via syringe. The colourless suspension was stirred for 15 min. and then 1.5 g (2.98 mmol) allylic alcohol was added. The mixture was stirred at 0°C for 4 h. The mixture was poured into 50 ml of ice cold brine. The layers were separated and the aqueous layer was extracted with heptane (2 x 50 ml). The combined organic extracts were diluted with 100 ml of heptane washed with brine (2 x 100 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* by rotary evaporation at 40 °C to give the product as a bright yellow oil (1.51 g, 2.89 mmol, 97%). The crude product was used in the next step without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76-7.20 (m, 10H), 5.42-5.35 (m, 2H), 5.18-5.10 (m, 1H), 5.00-4.95 (m, 1H), 4.48 (s, 2H), 4.02-3.94 (m, 5H), 2.55-1.95 (m, 10H), 1.76-1.57 (m, 12H).
$CDCl_3$ solvent peak: δ 7.24.

Example 22

[0113]



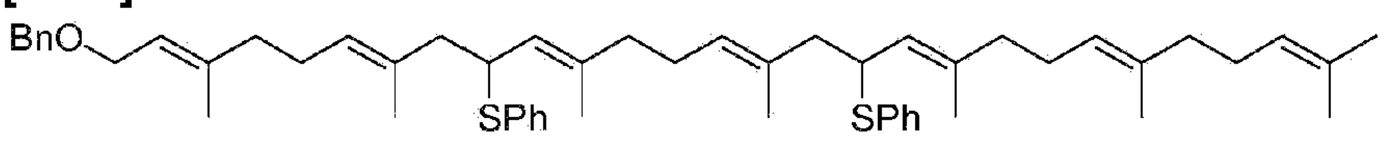


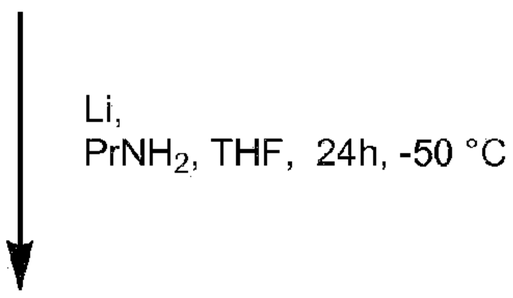
[0114] 1.18 g (3.76 mmol) farnesol thiophenylether was dissolved in 20 ml of dry THF. The solution was cooled to -78°C with a CO_2/MeOH cooling bath and at -78°C; 2.30 ml (3.68 mmol) BuLi (1.6 M solution in hexane) was added drop wise via septum and syringe. The clear, yellow orange solution was stirred at -78°C for 2.5 h and then 1.51 g (2.89 mmol) allylic chloride dissolved in 7 ml of dry THF was added drop wise via septum and syringe at -78°C. The clear solution was stirred at - 78°C for 1.5 h. At -78°C, 18 ml of a MeOH/Et_2O mixture (1:1 v/v) was added and the mixture was allowed to reach room temperature and then 30 ml of sat. NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 ml). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo by rotary evaporation at 30°C to give 2.64 g of yellow oil. The crude product was further purified by flash column chromatography on SiO_2 using a mixture of heptane:EtOAc (9/1 v/v) as eluent to give a yellow oil (1.55 g, 1.93 mmol, 67%).

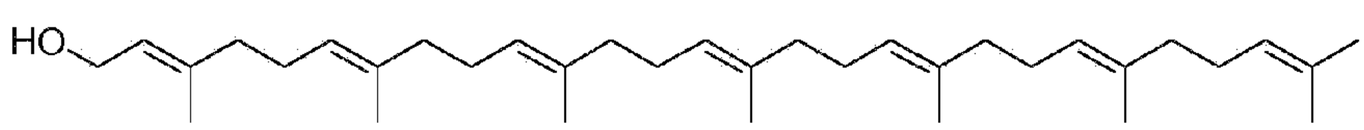
^1H NMR (200 MHz, $CDCl_3$) δ 7.55-7.20 (m, 15H), 5.42-5.35 (m, 1H), 5.14-4.95 (m, 6H), 4.48 (s, 2H), 4.02-3.92 (m, 4H), 2.44-1.76 (m, 20H), 1.71-1.52 (m, 18H), 1.34-1.25 (m, 6H).
$CDCl_3$ solvent peak: δ 7.24.

Example 23

[0115]







[0116] At -50°C, 0.16 g of Li-wire was added to 10 ml of propylamine and 1.57 g (1.96 mmol) dissolved in 16 ml of propylamine was added portion wise. The mixture was stirred at -50°C for 24 h. Excess Li was removed and the blue color was dissipated by addition of 3-hexyne. To the resulting yellowish suspension, MeOH was added at -50°C until a colourless suspension was

obtained. The resulting salts were dissolved in water. The volatiles were removed by rotary evaporation and the residue was extracted with diethyl ether (3 x 30 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo by rotary evaporation at 30°C.The crude product was further purified by flash column chromatography on SiO_2 using a mixture of heptane:EtOAc (9/1 v/v) as eluent.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

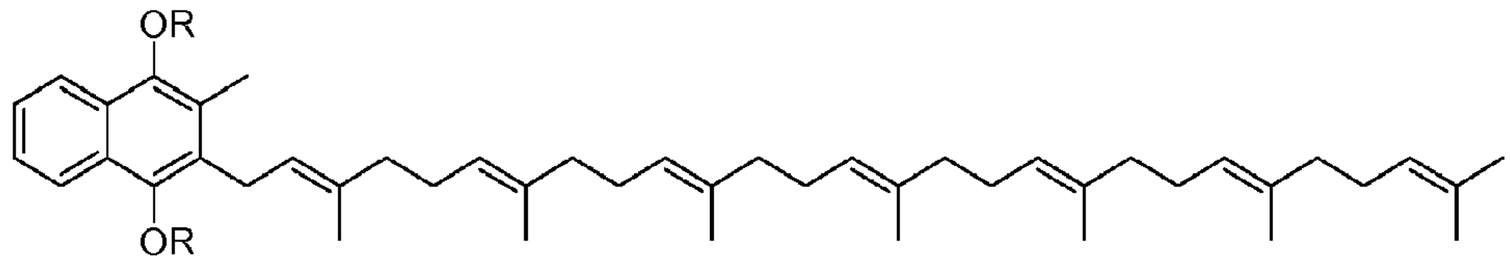
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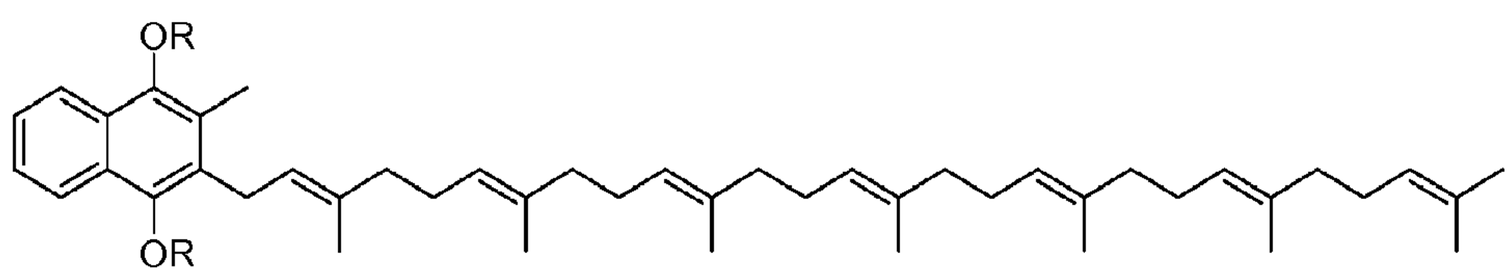
Patentkrav

1. Forbindelsen



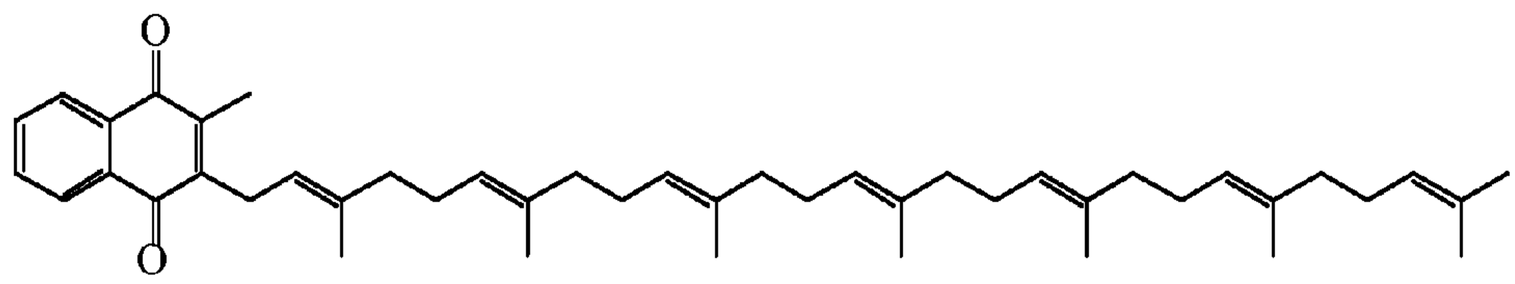
hvor R er ethyl.

2. Fremgangsmåde til fremstillingen af MK-7 omfattende at omdanne en forbindelse



hvor R er en ethyl-gruppe;

til MK-7:



.

3. Fremgangsmåde ifølge krav 2, hvor omdannelse opnås under anvendelse af ceriumammoniumnitrat.