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(71) Applicant: **GOLDEN BIOTECHNOLOGY CORPORATION** [US/US]; 101 Hudson Street, Suite 2100, Jersey City, NJ 07302 (US).

(72) Inventors: **LIU, Sheng-Yung**; 15F, No. 27-6, Sec. 2, Jhong-Jheng E. Rd., Danshuei, New Taipei City (TW). **WEN, Wu-Che**; 15F, No. 27-6, Sec. 2, Jhong-Jheng E. Rd., Danshuei, New Taipei City (TW). **CHEN, Chih-Ming**; 15F, No. 27-6, Sec. 2, Jhong-Jheng E. Rd., Danshuei, New Taipei City (TW). **CHENG, Hsiu-Yi**; 15F, No. 27-6, Sec. 2, Jhong-Jheng E. Rd., Danshuei, New Taipei City (TW).

(74) Agent: **LIANG, Chang-Hsing**; Acuity Law Group, P.C., 12707 High Bluff Drive, Suite 200, San Diego, CA 92130-2037 (US).

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(54) **Title**: CYCLOHEXENONE COMPOSITIONS AND PROCESS FOR MAKING THEREOF

(57) **Abstract**: Provided herein are processes of preparing cydohexenone compounds useful for cancer treatments and/or diseases. The present disclosure relates to composition and processes of preparing cyclohexenone compounds. In one aspect, there are provided a process for preparing a compound of formula I, comprising a step of reacting a compound of formula II.

WO 2014/130618 A1

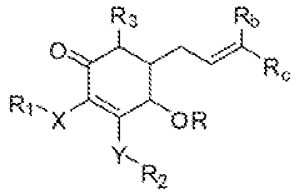
CYCLOHEXENONE COMPOSITIONS AND PROCESS FOR MAKING THEREOF

BACKGROUND OF THE INVENTION

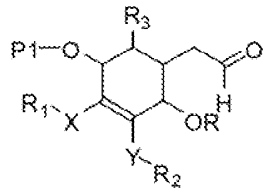
[0001] The present disclosure relates to composition and processes of preparing cyclohexenone compounds.

SUMMARY OF THE INVENTION

[0002] In one aspect, there are provided a process for preparing a compound of formula I:



(I)



comprising a step of reacting a compound of formula II, (II) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base, wherein L is a leaving group, P1 is a hydroxyl protecting group;

each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is an optionally substituted C_1-C_{12}alkyl or $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

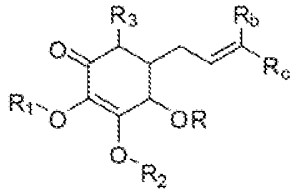
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

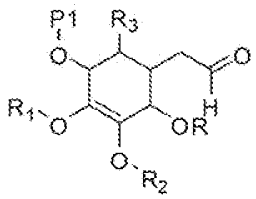
m = 0-11.

[0003] In another aspect, there are provided processes for preparing a compound of formula Ia:



(Ia)

comprising a step of reacting a compound of formula IIa,



(IIa) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base,

wherein L is a leaving group, P1 is a hydroxyl protecting group;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is an optionally substituted C_1-C_{12}alkyl or $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

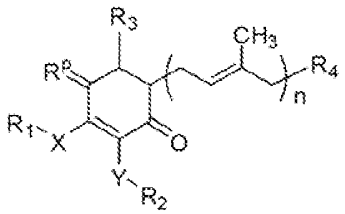
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

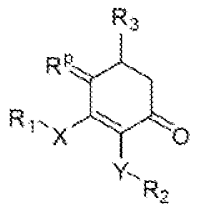
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

m = 0-11.

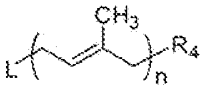
[0004] In another aspect of the present invention, there are provided processes for preparing a compound of formula IV:



(IV)



comprising reacting an enol or enolate compound of formula V, (V) with a



compound of formula (VI), (VI) under suitable conditions, wherein each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R^p is an oxo protecting group;

L is a leaving group;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

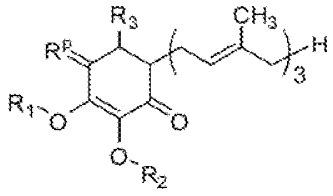
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

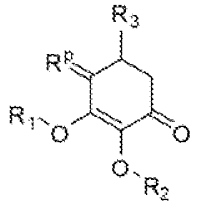
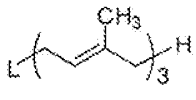
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

and n=1-12.

[0005] In another aspect of the present invention, there are provided processes for preparing a compound of formula IVa:



(IVa)

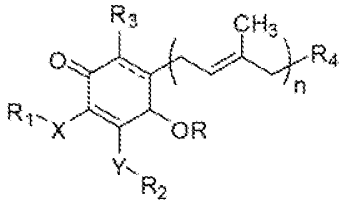
comprising reacting an enol or enolate compound of formula V,  (Va) with a compound of formula (VIa),  (VIa) under suitable conditions, wherein

R^p is an oxo protecting group;

L is a leaving group; and

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl.

[0006] In one aspect, there are provided a compound of formula X:

 (X), or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof, wherein

each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6; the dotted line denotes an optionally present bond; and n=1-12, provided when X and Y are oxygen, each of R_1 and R_2 independently is a substituted C_1-C_{12}alkyl.

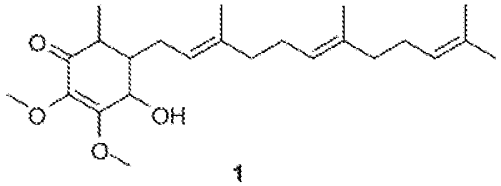
INCORPORATION BY REFERENCE

[0007] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent,

or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0008] Cyclohexenone compounds may be isolated from the extracts of *Antrodia camphorata*. For example, Compounds **1**, and **3-7** are isolated from organic solvent extracts.



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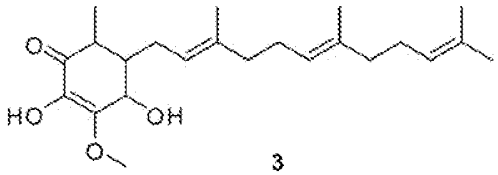

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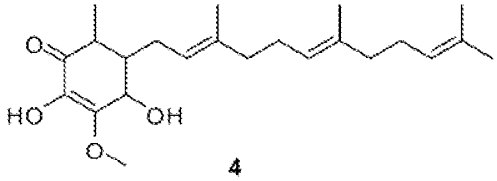

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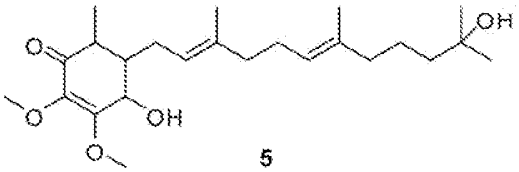

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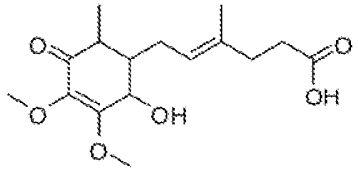

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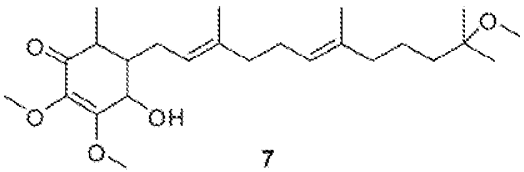

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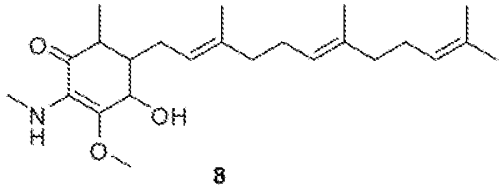
[0009] In some embodiments, certain cyclohexenone compounds can be prepared synthetically. The following are some non-limited examples.



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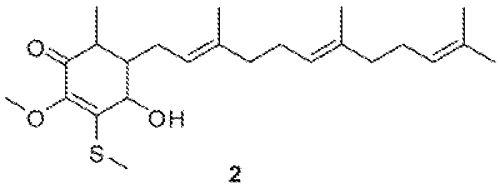

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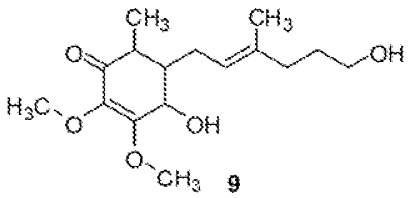

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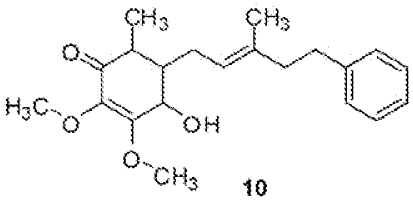

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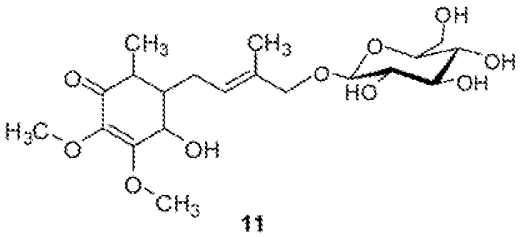

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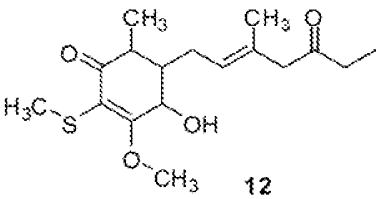

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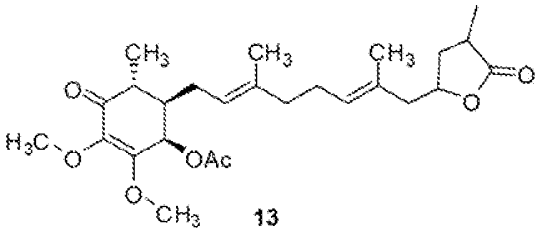

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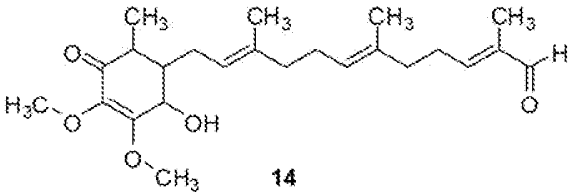

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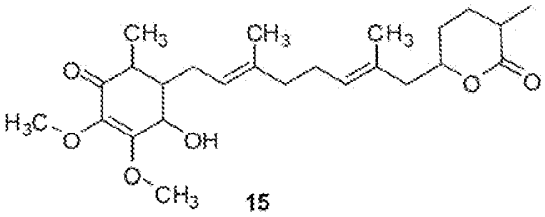

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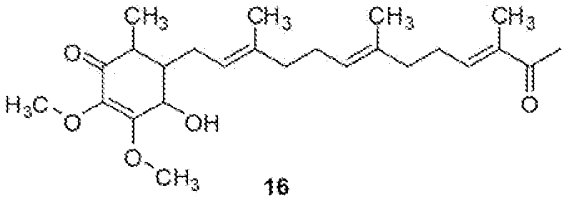

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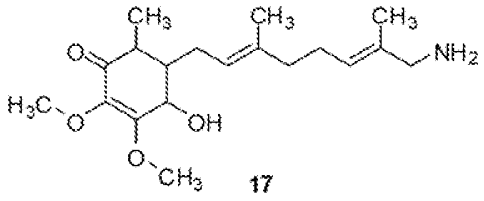

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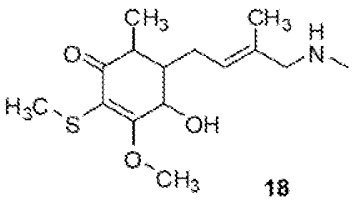

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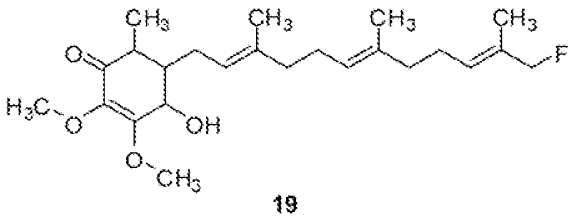

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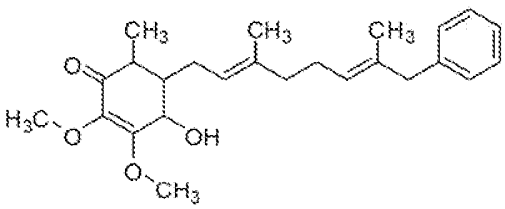

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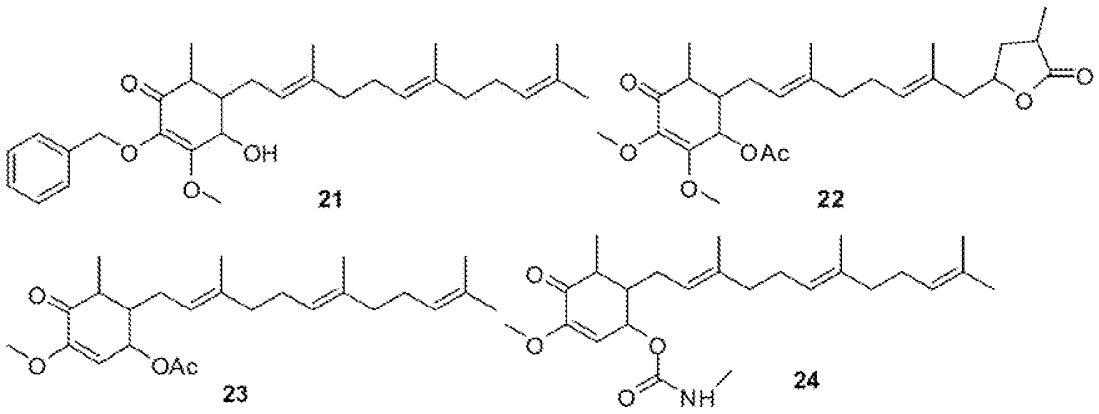
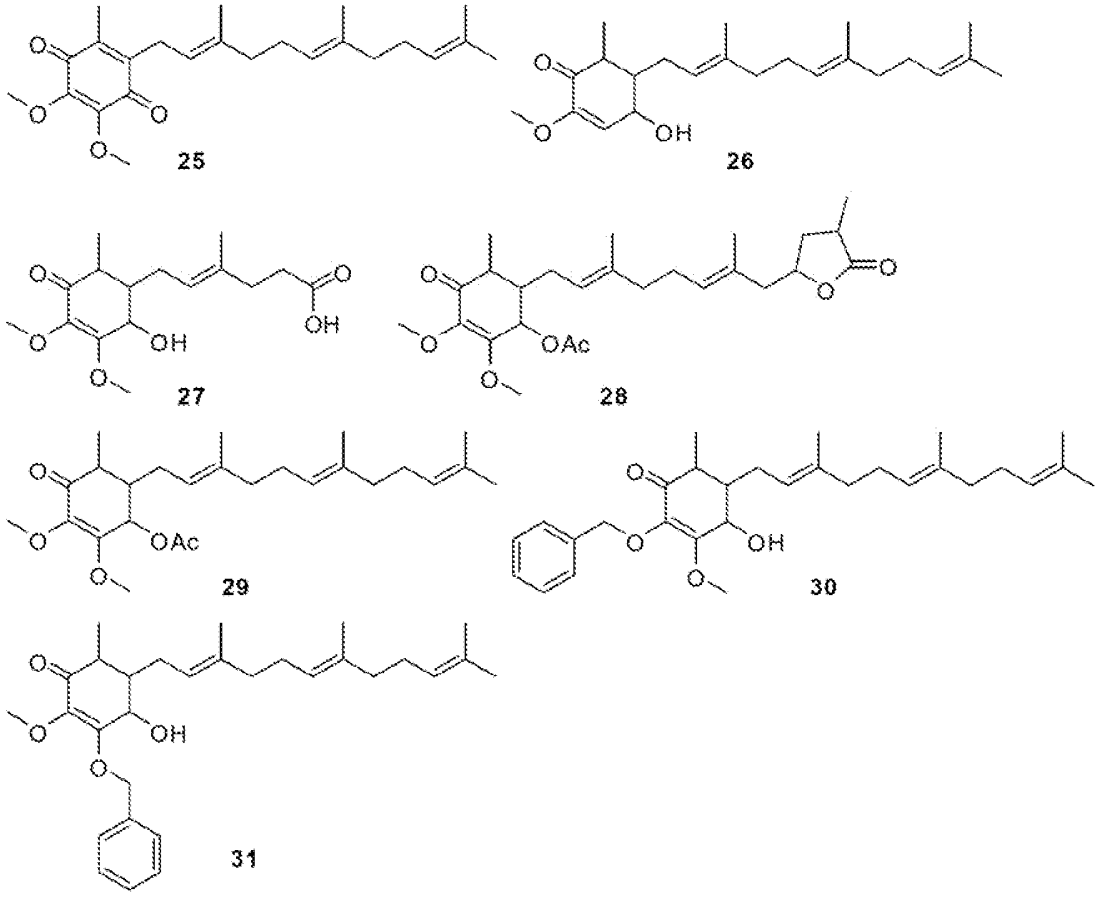
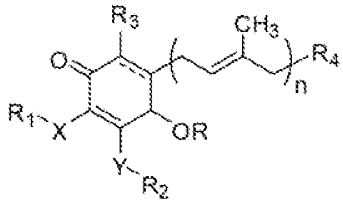


[0010] Many cyclohexenone compounds isolated from the extracts *of Antrodia camphorata* provide certain biological effects. In particular, Compounds **25** to **31** were prepared and tested against Compound **1** to determine their biological properties.



[0011] In some embodiments, there are provided a compound of formula X:



(X), or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof, wherein the dotted line of the ring is either a single or double bond; each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

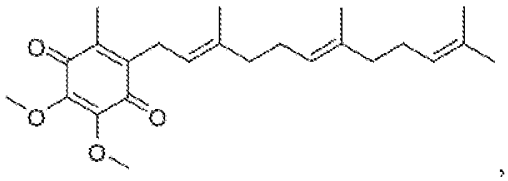
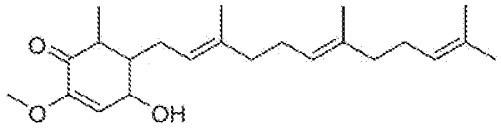
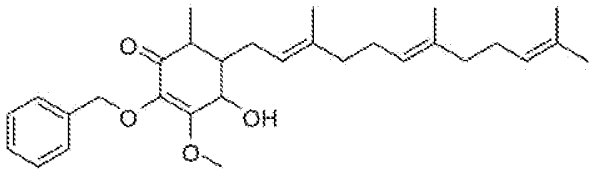
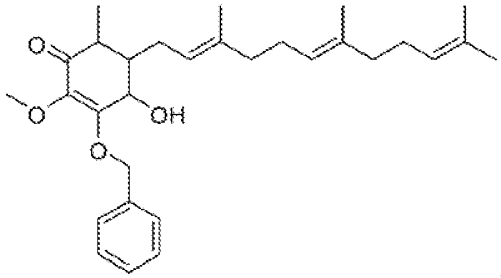
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6; the dotted line denotes an optionally present bond; and n=1-12, provided when X and Y are oxygen, each of R_1 and R_2 independently is a substituted C_1-C_{12}alkyl.

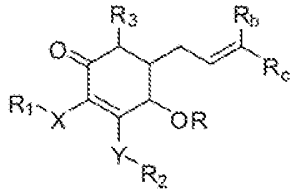
[0012] In certain embodiments, the compound of formula (X) is isolated from the organic solvent extracts of *Antrodia camphorata*. In some embodiments, the organic solvent is selected from alcohols (e.g., methanol, ethanol, propanol, or the like), esters (e.g., methyl acetate, ethyl acetate, or the like), alkanes (e.g., pentane, hexane, heptane, or the like), halogenated alkanes (e.g., chloromethane, chloroethane, chloroform, methylene chloride, and the like), and the like. In certain embodiments, the organic solvent is alcohol. In certain embodiments, the alcohol is ethanol. In some embodiments, the compound of formula (X) is isolated from the aqueous extracts of *Antrodia camphorata*. In some embodiments, the compound of formula (X) is prepared synthetically by the disclosed method herein. In other embodiments, the compound of formula (X) is prepared by other methods readily available in the art such as via synthetic or semi-synthetic methods.

[0013] In some embodiments, each of X and Y independently is a bond. In some embodiments, R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$. In certain embodiments, R is H, or $C(=O)R_5$. In certain embodiments, R is H, $C(=O)C_3H_8$, $C(=O)C_2H_5$, or $C(=O)CH_3$. In

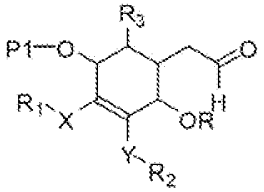
some embodiments, each of R_1, R_2 and R_3 independently is hydrogen, or a substituted C_1-C_{12}alkyl. In some embodiments, each of R_1, R_2 and R_3 independently is hydrogen, or an aryl or heteroaryl substituted C_1-C_{12}alkyl. In certain embodiments, R_1 is methyl, ethyl, propyl, butyl, pentyl or hexyl substituted with phenyl or pyridinyl. In certain embodiments, R_1 is a CH_2-Ph. In certain embodiments, R_1 is H, methyl, ethyl, propyl, butyl, pentyl or hexyl provided one of X and Y is a bond. In certain embodiments, R_2 is methyl, ethyl, propyl, butyl, pentyl or hexyl substituted with phenyl or pyridinyl. In certain embodiments, R_2 is CH_2-Ph. In certain embodiments, R_2 is H, methyl, ethyl, propyl, butyl, pentyl or hexyl provided one of X and Y is a bond. In some embodiments, R_3 is H, methyl, ethyl, propyl, butyl, pentyl or hexyl. In some embodiments, R_4 is H, halogen, NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3, OC_2H_5, $C(=O)CH_3$, $C(=O)C_2H_5$, $C(=O)OCH_3$, $C(=O)OC_2H_5$, $C(=O)NHCH_3$, $C(=O)NHC_2H_5$, $C(=O)NH_2$, $OC(=O)CH_3$, $OC(=O)C_2H_5$, $OC(=O)OCH_3$, $OC(=O)OC_2H_5$, $OC(=O)NHCH_3$, $OC(=O)NHC_2H_5$, or $OC(=O)NH_2$. In some embodiments, R_4 is $C_2H_5C(CH_3)_2OH$, $C_2H_5C(CH_3)_2OCH_3$, CH_2COOH, C_2H_5COOH, CH_2OH, C_2H_5OH, CH_2Ph, C_2H_5Ph, $CH_2CH=C(CH_3)(CHO)$, $CH_2CH=C(CH_3)(C(=O)CH_3)$, 5 or 6-membered lactone, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl, wherein the 5 or 6-membered lactone, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl. In certain embodiments, R_4 is $CH_2CH=C(CH_3)_2$. In certain embodiments, the compound of formula (X) is selected from group consisting of  ,  ,  ,  , and .

[0014] Due to the high cost of obtaining cyclohexnone compounds from *Antrodia camphorata* by purification, and/or to prepare desired analogs for further clinical testing, synthetic processes of preparing cyclohexnone compounds are described herein.

[0015] In accordance with the present invention, there are provided processes for preparing a compound of formula I:



(I)



comprising a step of reacting a compound of formula (II), (II) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base, wherein L is a leaving group, P1 is a hydroxyl protecting group;

each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is hydrogen, C_1-C_{12}alkyl, optionally substituted with $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

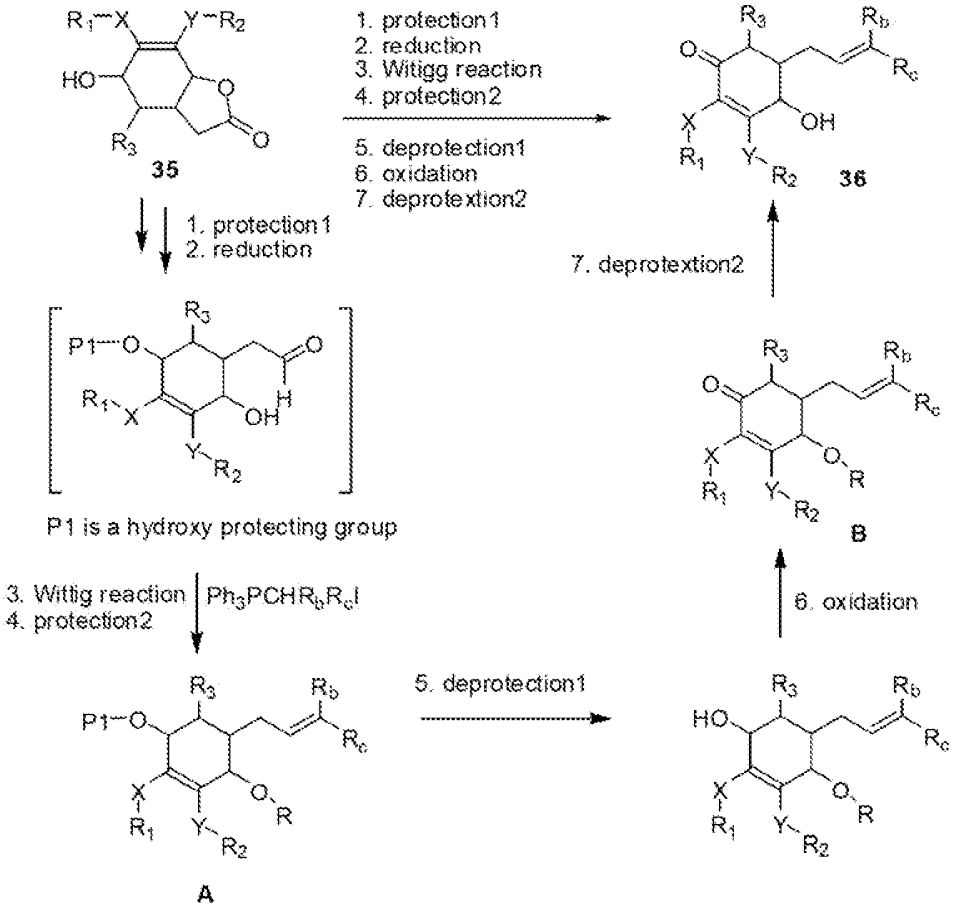
R_4 is hydrogen, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

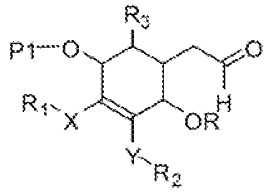
m = 0-11. In certain embodiments, R is a hydroxyl protecting group such as a silyl protecting group, and other suitable protecting groups same of different from P1.

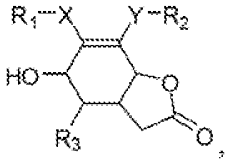
[0016] The reaction between a compound of formula (II) and a compound of formula (III) is known as Wittig reaction. Since aldehydes, in general, are not chemically stable, the compounds of formula (II) in some embodiments, are prepared in situ. Scheme I provides a non-limited exemplary route to prepare a compound of formula (I). Protection of the free hydroxyl group of Compound **35** follows by reduction of the lactone ring to afford the aldehyde compound of formula (II), which then undergo Wittig reaction with $Ph_3PCHR_bR_cI$ to prepare intermediate **A**. After deprotection and oxidation, Compound **B** (which is a compound of formula (I)) is prepared. Compound **36** where R is H can be easily prepared by deprotection reaction.

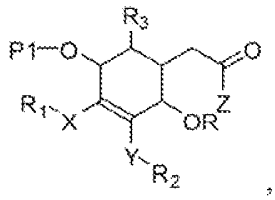
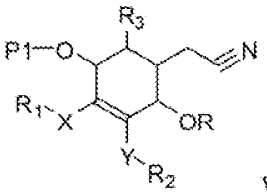


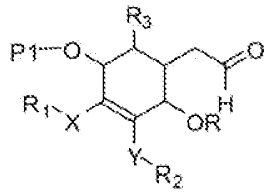
Scheme I. Exemplary synthetic scheme to prepare a compound of formula (I)

[0017] An aldehyde can be prepared from reduction of acylsilanes, carboxylic acids, acid halides, anhydride, esters, lactones, amides, nitriles, or the like. In some instances, an aldehyde can be prepared from oxidation of a free hydroxyl group. A skilled person in the art can readily consider other suitable reaction based on this invention to prepare a compound of

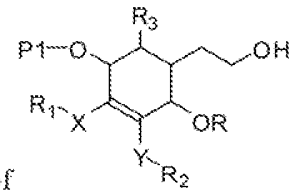
formula (II). In some embodiments, a compound of formula (II),  (II)

is prepared from reduction of a compound having the structure of  ,

 , or  wherein Z is halogen, OR_5 $OC(=O)R_7$, or NR_5R_6.



[0018] In some embodiments, a compound of formula (II), (II) is



prepared from oxidation of a compound having the structure of .

[0019] In some embodiments, R is any suitable hydroxyl protecting group that can survive Wittig reaction conditions. For example, R is $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, $C(=S)NR_5R_6$, or the like.

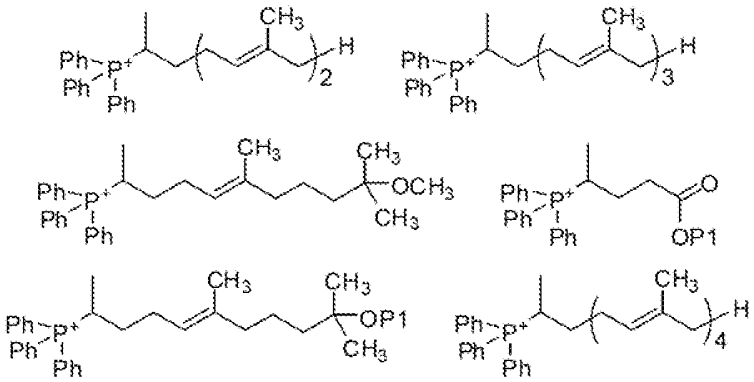
[0020] In some embodiments, said base is a base that can form an ylide from a compound of formula (III), for example, n-butyllithium (n-BuLi), or the like.

[0021] In some embodiments, each of R_1, R_2 and R_3 independently is H, methyl, ethyl, propyl, butyl, pentyl or hexyl optionally substituted with an aryl or heteroaryl. In certain embodiments, each of R_1, R_2 and R_3 independently is H, or methyl.

[0022] The Wittig reaction provided herein is applicable to many isoprene unit precursors. For example, the reaction is applicable where R_b is CH_3 and R_c is CH_2 substituted with $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein is R_4 is hydrogen NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-

C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl; each of R_5 and R_6 is independently H or C_1-C_8alkyl; and R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6.

[0023] For example, without limitation, a skilled artisan may use the following isoprene precursors where P1 is a hydroxy protecting group.

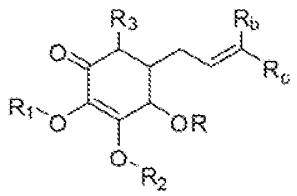


[0024] In some embodiments, there are provided processes of preparing compounds of formula (I) wherein X is oxygen, NR_5 or sulfur. For example, X may be O, S, NH, NCH_3, NC_2H_5, or the like.

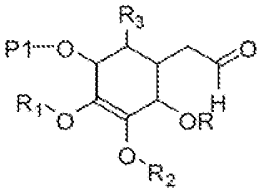
[0025] In other embodiments, there are provided processes of preparing compounds of formula (I) wherein Y is oxygen, NR_5 or sulfur. For example, Y may be O, S, NH, NCH_3, NC_2H_5, or the like.

[0026] In other embodiments, there are provided processes of preparing compounds of formula (I) wherein X is O and Y is O, or X is O and Y is S, or X is S and Y is O, or X is O and Y is NH, or X is NH and Y is O.

[0027] In some embodiments, there are provided processes for preparing a compound of formula (Ia):



(Ia)



comprising a step of reacting a compound of formula IIa, (IIa) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base, wherein wherein L is a leaving group, P1 is a hydroxyl protecting group;

R is H, C(=O)OR_5, C(=O)R_5, C(=O)NR_5R_6, C(=O)SR_5, C(=S)R_5, or C(=S)NR_5R_6;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is hydrogen, C_1-C_{12}alkyl, optionally substituted with $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

R_4 is NR_5R_6, OR_5, OC(=O)R_7, C(=O)OR_5, C(=O)R_5, C(=O)NR_5R_6, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, OC(=O)R_7, C(=O)OR_5, C(=O)R_5, C(=O)NR_5R_6, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

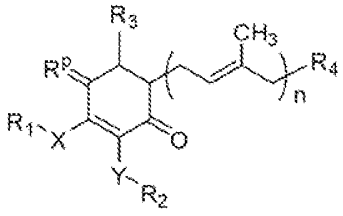
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

m = 0-11.

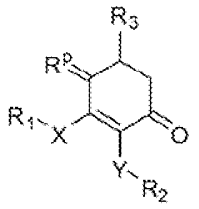
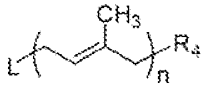
[0028] In some embodiments, there are provided processes of preparing compounds of formula (I) or (Ia) wherein R is H or -C(=O)C_1-C_8alkyl and each of R_1, R_2 and R_3 independently is H, or C_1-C_{12}alkyl.

[0029] In certain embodiments, R is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_1 is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_2 is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_3 is H, methyl, ethyl, propyl, butyl, pentyl, or the like.

[0030] In some embodiments, there are provided processes for preparing a compound of formula IV:



(IV)

comprising reacting an enol or enolate compound of formula V,  (V) with a compound of formula (VI),  (VI) under suitable conditions, wherein each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R^p is an oxo protecting group;

L is a leaving group;

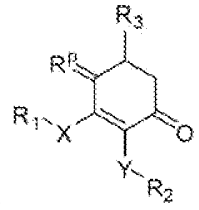
each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

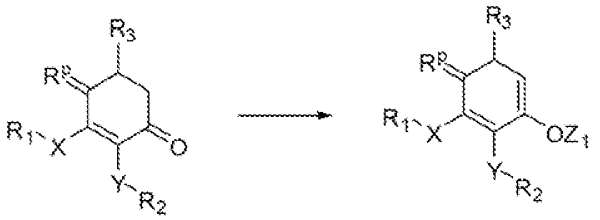
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

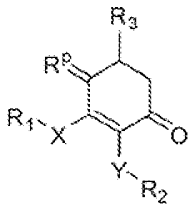
and n=1-12.

[0031] In some embodiments, the enol compound of formula V,  (V) is prepared under suitable conditions (e.g., acid promotion or silyl trapping).



Z_1 = H or silyl protecting group

[0032]



[0033] In some embodiments, the enolate compound of formula V, (V) is prepared by reacting a compound of formula V with a strong base. A skilled artisan will readily find other suitable conditions follows the known procedure to prepare the enol or enolate compound of formula V.

[0034] In certain embodiments, P is an oxo protecting group that can withstand the acidic or basic conditions for generating enol or enolate compound of Formulat V. For example, P is an acyclic or cyclic ketal or an acylic or cyclic thioketal that is stable to aqueous and nonaqueous bases, to nucleophiles including organometallic reagents and to hydride reduction. In some embodiments, P is an acyclic or cyclic thioketal that is stable to aqueous and nonaquieous acids, to nucleophiles including organometallic reagents and to hydride reduction. In certain embodiments, P is 1,3-dithiolane, or the like.

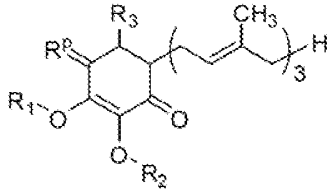
[0035] In some embodiments, L is a leaving group that undergoes either SN1, SN2 or SNi reaction under suitable conditions. For example, L is a halogen such as Cl, Br or I. In some instances, L is hydroxyl derived leaving group such as a tosylate or methlate. Other suitable leaving groups may be used by a skilled artisan follows the readily available known procedure.

[0036] In some embodiments, there are provided processes of preparing compounds of formula (IV), wherein X is oxygen, NR_5 or sulfur. For example, X may be O, S, NH, NCH_5, NC_2H_5, or the like.

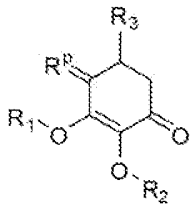
[0037] In other embodiments, there are provided processes of preparing compounds of formula (IV) wherein Y is oxygen, NR_5 or sulfur. For example, Y may be O, S, NH, NCH_5, NC_2H_5, or the like.

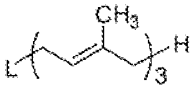
[0038] In other embodiments, there are provided processes of preparing compounds of formula (IV) wherein X is O and Y is O, or X is O and Y is S, or X is S and Y is O, or X is O and Y is NH, or X is NH and Y is O.

[0039] In some embodiments, there are provided processes for preparing a compound of formula IVa:



(IVa)



comprising reacting an enol or enolate compound of formula V, (Va) with a compound of formula (VIa),  (VIa) under suitable conditions, wherein

R^P is an oxo protecting group;

L is a leaving group; and

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl.

[0040] In some embodiments, there are provided processes of preparing compounds of formula (IV) or (IVa) wherein R is H or -C(=O)C_1-C_8alkyl and each of R_1, R_2 and R_3 independently is H, or C_1-C_{12}alkyl.

[0041] In certain embodiments, R is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_1 is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_2 is H, methyl, ethyl, propyl, butyl, pentyl, or the like. In certain embodiments, R_3 is H, methyl, ethyl, propyl, butyl, pentyl, or the like.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

[0042] In certain embodiments, the compounds described herein are modified using various electrophiles or nucleophiles to form new functional groups or substituents. Table 1 entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected, non-limiting examples of covalent linkages and precursor functional groups that are used to prepare the modified compounds. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Table 1: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines

Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

Use of Protecting Groups

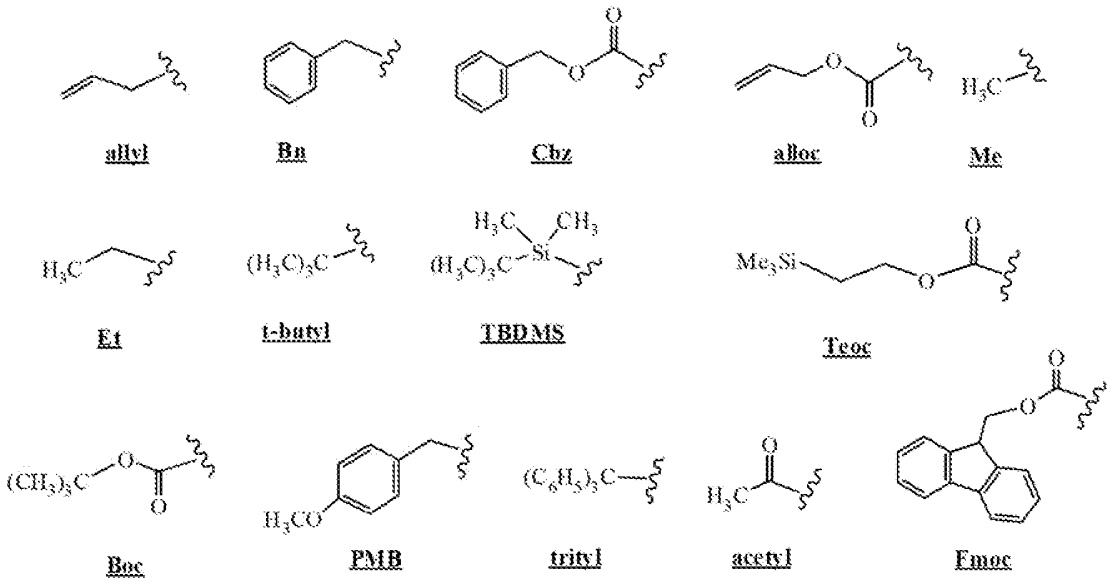
[0043] In the reactions described, it is necessary in certain embodiments to protect reactive functional groups, for example hydroxy, amino, thiol or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting

groups are used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In one embodiment, each protective group is removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. In some embodiments, protective groups are removed by acid, base, and/or hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and are used in certain embodiments to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and/or Fmoc groups, which are base labile. In other embodiments, carboxylic acid and hydroxy reactive moieties are blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[0044] In another embodiment, carboxylic acid and hydroxy reactive moieties are blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids are blocked with base labile groups such as Fmoc. In another embodiment, carboxylic acid reactive moieties are protected by conversion to simple ester compounds as exemplified herein, or they are, in yet another embodiment, blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups are blocked with fluoride labile silyl carbamates.

[0045] Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and are optionally subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid is optionally deprotected with a Pd(0)-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate is attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[0046] Typically blocking/protecting groups are, by way of example only:



[0047] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

[0048] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound provided herein with acids. Pharmaceutically acceptable salts are also obtained by reacting a compound provided herein with a base to form a salt.

[0049] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-

hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein may coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[0050] The term "leaving group" as used herein may be any group which is usually known as a leaving group in organic synthesis, without limitation, for example: halogens such as fluorine, chlorine, bromine and iodine, alkylsulfonyloxy groups such as methanesulfonyloxy, trifluoromethanesulfonyloxy and ethanesulfonyloxy, arylsulfonyloxy groups such as benzenesulfonyloxy and p-toluenesulfonyloxy. Preferred "leaving groups" are halogens such as fluorine, chlorine, bromine and iodine.

[0051] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0052] Unless defined otherwise, all technical and scientific terms used herein have the standard meaning pertaining to the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is

made to a URL or other such identifier or address, it understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[0053] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0054] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. Unless specific definitions are provided, the standard nomenclature employed in connection with, and the standard laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry are employed. In certain instances, standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. In certain embodiments, standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). In some embodiments, reactions and purification techniques are performed e.g., using kits of manufacturer's specifications or as commonly accomplished or as described herein.

[0055] As used throughout this application and the appended claims, the following terms have the following meanings:

[0056] The term "alkyl" as used herein, means a straight, branched chain, or cyclic (in this case, it would also be known as "cycloalkyl") hydrocarbon containing from 1-10 carbon atoms. Illustrative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylhexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[0057] The term "C_1-C_6-alkyl" as used herein, means a straight, branched chain, or cyclic (in this case, it would also be known as "cycloalkyl") hydrocarbon containing from 1-6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-

propyl, iso-propyl, cyclopyl, n-butyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, cyclopentyl, and n-hexyl.

[0058] The term "thioalkyl" as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom. Illustrative examples of thioalkyl include, but are not limited to, methylthio, ethylthio, butylthio, tert-butylthio, and hexylthio.

[0059] The term "halo" or "halogen" as used herein, means a -Cl, -Br, -I or –F.

[0060] As used herein, the term "sulfinyl" refers to a -S(=O)-R, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocycloalkyl (bonded through a ring carbon).

[0061] As used herein, the term "sulfonyl" refers to a -$S(=O)_2$-R, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocycloalkyl (bonded through a ring carbon).

[0062] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, nitro, haloalkyl, fluoroalkyl, fluoroalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example an optional substituents may be halide, -CN, -NO_2, or L_sR_s, wherein each L_s is independently selected from a bond, -O-, -C(=O)-, -C(=O)O-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -NHC(=O)-, -C(=O)NH-, $S(=O)_2NH$-, -$NHS(=O)_2$, -OC(=O)NH-, -NHC(=O)O-, or -(C_1-C_6 alkylene)-; and each R_s is selected from H, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. The protecting groups that may form the protective derivatives of the above substituents may be found in sources such as Greene and Wuts, above. In some embodiments, optional substituents are selected from halogen, -CN, -NH_2, -OH, -$N(CH_3)_2$, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, an optional substituents is halogen, -CN, -NH_2, -OH, -$NH(CH_3)$, -$N(CH_3)_2$, alkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, -S-alkyl, or –$S(=O)_2$alkyl. In some embodiments, an optional substituent is selected from halogen, -CN, -NH_2, -OH, -$NH(CH_3)$, -$N(CH_3)_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, substituted groups are substituted with one of the preceding groups. In some embodiments, an optional substituent

on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) includes oxo (=O).

[0063] The term "protected amine" refers to an amine with a removable protecting group which modifies the reactivity of an amine, against undesirable reaction during synthetic procedures and to be later removed. Examples of amine protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc), 9-fluorenylmethyl carbonyl (Fmoc), triphenylmethyl (Tr) and carbobenzyloxy (Cbz). For example, to protect and activate the pyrimidine ring system with the 6-amino moiety in accordance with the present invention, bis-BOC, or bis-FMOC, CBZ, alloc, Teoc, methyl/ethyl-oxycarbonyl, bis-acetyl , or N-succinyl or N-phthaloyl may be used in addition to their mono-N protected analogs.

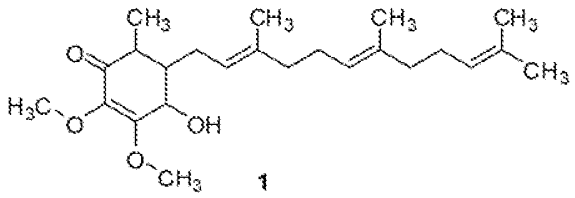
Example

Example 1. Preparation of the exemplary cyclohexenone compounds from *Antrodia camphorata*

[0064] One hundred grams of mycelia, fruiting bodies or mixture of both from *Antrodia camphorata* were placed into a flask. A proper amount of water and alcohol (70-100% alcohol solution) was added into the flask and were stirred at 20-25° C for at least 1 hour. The solution was filtered through a filter and 0.45 μm membrane and the filtrate was collected as the extract.

[0065] The filtrate of *Antrodia camphorata* was subjected to High Performance Liquid chromatography (HPLC) analysis. The separation was performed on a RP18 column, the mobile phase consisted of methanol (A) and 0.3% acetic acid (B), with the gradient conditions of 0-10 min in 95% - 20% B, 10-20 min in 20%-10% B, 20-35 min in 10%-10% B, 35-40 min in 10%-95% B, at the flow rate of 1 ml/min. The column effluent was monitored with a UV-visible detector.

[0066] The fractions collected at 25 to 30 min were collected and concentrated to yield 4-hydroxy-2,3-dimethoxy-6-methyl-5-(3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone (compound **1**), a product of pale yellow brown liquid. The analysis of compound **1** showed the molecular formula of $C_{24}H_{38}O_4$, molecular weight of 390 with melting point of 48 to 52 °C. NMR spectra showed that ^{1}H-NMR ($CDCl_3$) δ (ppm)=1.51, 1.67, 1.71, 1.75, 1.94, 2.03, 2.07, 2.22, 2.25, 3.68, 4.05, 5.07, and 5.14; ^{13}C-NMR ($CDCl_3$) δ (ppm)=12.31, 16.1, 16.12, 17.67, 25.67, 26.44, 26.74, 27.00, 39.71, 39.81, 40.27, 43.34, 59.22, 60.59, 120.97, 123.84, 124.30, 131.32, 135.35, 135.92, 138.05, 160.45, and 197.12.



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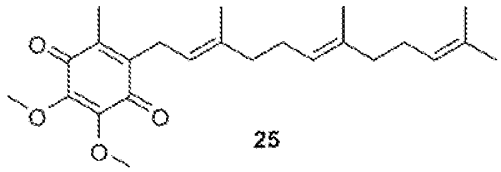
Compound **1**: 4-hydroxy-2,3-dimethoxy-6-methyl-5-(3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone

[0067] Compound **27**, a metabolite of compound **1**, was obtained from urine samples of rats fed with Compound **1** in the animal study. Compound **27** was determined to be 4-hydroxy-2,3-dimethoxy-6-methyl-5-(3-methyl-2-hexenoic acid)cyclohex-2-enone with molecular weight of 312 ($C_{16}H_{24}O_6$). Compound **25** which was determined as 2,3-dimethoxy-5-methyl-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohexa-2,5-diene-1,4-dione (molecular weight of 386.52, $C_{24}H_{34}O_4$), was obtained from the purification process.



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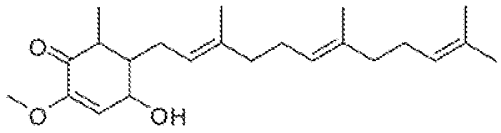
[0068] Compound **26**, 4-hydroxy-2-methoxy-6-methyl-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone, was also prepared by purification process with molecular weight of 350.53 ($C_{23}H_{36}O_3$). Compound **28** was also prepared.



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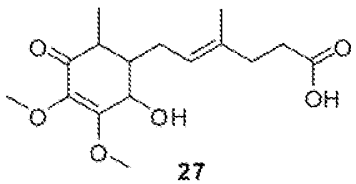
[0069] ^{1}H (500 MHz; CD_3OD) δ 1.16 (3H, d, J = 6.9 Hz), 1.58 (3H, s), 1.60 (3H, s), 1.62 (3H, s), 1.65 (3H, s), 1.77−1.83 (1H, m), 1.93−2.20 (2H, m), 2.00−2.20 (7H, m), 2.23−2.31 (1H, m), 2.63−2.71 (1H, m), 3.59 (3H, s), 4.64 (1H, dd, J = 5.5 and 3.7 Hz), 5.07−5.12 (2H, m), 5.21 (1H, t, J = 7.3 Hz), 5.91 (1H, d, J = 5.7 Hz); ^{13}C (125 MHz; CD_3OD) δ 13.1, 16.2, 17.8, 17.8, 25.9, 27.4, 27.8, 28.2, 40.9, 43.4, 47.5, 48.5, 49.8, 55.3, 65.0, 116.6, 123.3, 125.3, 125.4, 132.1, 136.0, 138.1, 152.0, 198.7.



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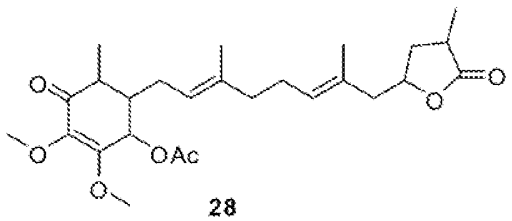
[0070] $[\alpha]^{24}_{D}$ 66.9 (c 0.69, MeOH); ^{1}H (600 MHz; CD_3OD) δ 1.14 (3H, d, *J* = 6.9 Hz), 1.65–1.70 (1H, m), 1.67 (3H, s), 2.24 (2H, t, *J* = 7.4 Hz), 2.32 (2H, t, *J* = 7.4 Hz), 2.43 (2H, t, *J* = 7.4 Hz), 2.44–2.50 (m, 1H), 3.57 (3H, s), 4.04 (3H, s), 4.36 (1H, d, *J* = 3.5 Hz), 5.29 (1H, t, *J* = 7.1 Hz); ^{13}C (150 MHz; CD_3OD) δ 12.8, 16.2, 28.1, 33.8, 35.8, 41.4, 45.6, 58.6, 60.7, 66.8, 123.4, 137.1, 137.2, 164.9, 177.3, 199.4.



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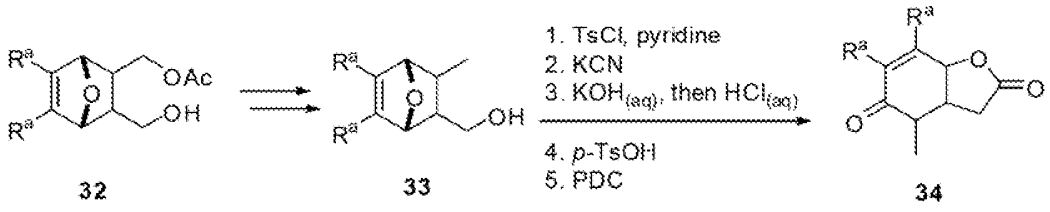
[0071] EI-MS, m/z 486 $[M+Na]^{+}$; ^{1}H (600 MHz; CD_3OD) δ 1.19 (3H, d, *J* = 7.0 Hz), 1.24 (3H, d, *J* = 7.4 Hz), 1.60 (3H, s), 1.69 (3H, s), 1.93–2.00 (2H, m), 2.00–2.04 (1H, m), 2.05–2.08 (2H, m), 2.11 (3H, s), 2.13–2.20 (2H, m), 2.20–2.25 (m, 1H), 2.26–2.31 (2H, m), 2.40 (1H, dd, *J* = 13.8 Hz and 7.0 Hz), 2.50–2.56 (1H, m), 2.73–2.80 (1H, m), 3.63 (3H, s), 4.00 (3H, s), 4.69–4.74 (1H, m), 5.17 (1H, t, *J* = 6.7 Hz), 5.31 (1H, t, *J* = 7.0 Hz), 5.75 (1H, d, *J* = 3.1 Hz); ^{13}C (150 MHz; CD_3OD) δ 13.1, 16.0, 16.2, 16.5, 20.9, 27.1, 28.0, 35.0, 35.6, 40.5, 42.5, 44.2, 45.9, 60.3, 61.1, 70.4, 78.8, 122.5, 129.2, 131.7, 138.3, 138.7, 160.5, 171.4, 182.7, 199.0.

Example 2: Preparation of exemplary cyclohexenone core.

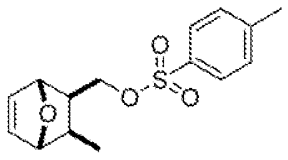


32 **33** **34**

R^a= H, CH_3, OMe, OBn

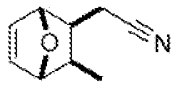
[0072] Compound **33** (R^a = H) was prepared by a known method (e.g, *J. Org. Chem.* **2004**, *69*, 8789-8795) from compound **32**. The exemplary intermediate **34a** (R^a = H) was prepared by the following steps. Other exemplary core intermediates (**34b-d**, R^a = CH_3, OMe, OBn, respectively, or the like) can be prepared accordingly.

Step 1. Preparation of [(1R,2R,3R,4S)-3-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methyl 4-methyl-benzene-1-sulfonate



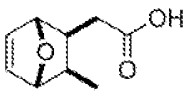
[0073] To a solution of Compound **21** (8.3 g, 59 mmol) in CH_2Cl_2 (210 mL) at ice bath were added Et_3N (21.0 mL, 148 mmol), 4-DMAP (1.0 g, 8.9 mmol), and TsCl (16.9 g, 88.8 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h, washed with H_2O (100 mL × 3) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:3, R_f 0.46) to provide 14.8 g (50.2 mmol, 85%) as a colorless oil. EI-MS, m/z 317 $[M+Na]^+$; $[\alpha]^{24}_D$ −14.8 (c 2.34, $CHCl_3$); ^1H (600 MHz; $CDCl_3$) δ 1.04 (3H, d, J = 7.3 Hz), 1.83−1.90 (1H, m), 1.91−1.97 (1H, m), 2.51 (3H, s), 4.02 (1H, t, J = 9.8 Hz), 4.22 (1H, dd, J = 9.5 and 5.4 Hz), 4.49 (1H, s), 4.75 (1H, s), 6.32 (1H, dd, J = 5.8 Hz and 1.6 Hz), 6.41 (1H, dd, J = 5.8 and 1.6 Hz), 7.43 (2H, d, J = 8.2 Hz), 7.87 (2H, d, J = 8.2 Hz); ^{13}C (150 MHz; $CDCl_3$) δ 14.1, 21.4, 33.6, 39.2, 71.0, 80.0, 84.5, 127.6, 129.7, 132.6, 134.4, 135.9, 144.7.

Step 2. Preparation of 2-[(1R,2S,3R,4S)-3-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl]acetonitrile



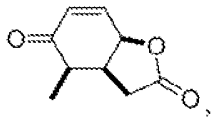
[0074] To a solution of Compound **21** (8.3 g, 59 mmol) in CH_2Cl_2 (210 mL) at ice bath were added Et_3N (21.0 mL, 148 mmol), 4-DMAP (1.0 g, 8.9 mmol), and TsCl (16.9 g, 88.8 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h, washed with H_2O (100 mL × 3) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:3, R_f 0.46) to provide 14.8 g (50.2 mmol, 85%) as a colorless oil. EI-MS, m/z 317 $[M+Na]^+$; $[\alpha]^{24}_D$ −14.8 (c 2.34, $CHCl_3$); ^1H (600 MHz; $CDCl_3$) δ 1.04 (3H, d, J = 7.3 Hz), 1.83−1.90 (1H, m), 1.91−1.97 (1H, m), 2.51 (3H, s), 4.02 (1H, t, J = 9.8 Hz), 4.22 (1H, dd, J = 9.5 and 5.4 Hz), 4.49 (1H, s), 4.75 (1H, s), 6.32 (1H, dd, J = 5.8 Hz and 1.6 Hz), 6.41 (1H, dd, J = 5.8 and 1.6 Hz), 7.43 (2H, d, J = 8.2 Hz), 7.87 (2H, d, J = 8.2 Hz); ^{13}C (150 MHz; $CDCl_3$) δ 14.1, 21.4, 33.6, 39.2, 71.0, 80.0, 84.5, 127.6, 129.7, 132.6, 134.4, 135.9, 144.7.

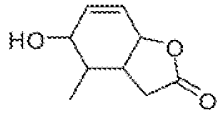
Step 3. Preparation of 2-[(1R,2S,3R,4S)-3-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl]acetic acid



[0075] The nitrile (6.7 g, 45 mmol)prepared in Step 2 was heated to reflux for 4 h in 1N potassium hydroxide solution (480 mL, 480 mmol). After 4 h, the mixture was concentrated. The residue was allowed to cool to ice bath, acidified to pH 1 with conc. $HCl_{(aq)}$, and extracted with EtOAc (300 mL × 3). The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to yield acid (7.4 g, 44 mmol, 98%). TLC R_f 0.63 (EtOAc:hexane,

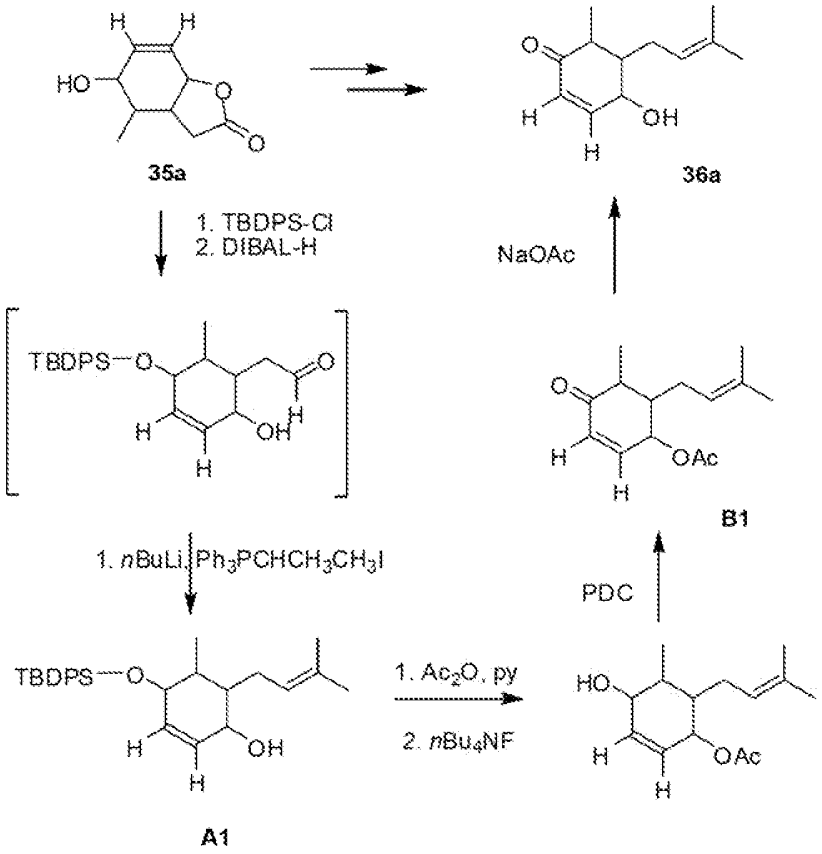
2:1); EI-MS, m/z 191 $[M+Na]^+$; $[\alpha]^{24}_D$ −7.03 (c 1.95, $CHCl_3$); ^1H (600 MHz; $CDCl_3$) δ 1.00 (3H, d, J = 7.3 Hz), 1.77−1.84 (1H, m), 1.98−2.04 (1H, m), 2.39 (1H, dd, J = 16.9 and 10.0 Hz), 2.51 (1H, dd, J = 16.9 and 5.4 Hz), 4.45 (1H, s), 4.65 (1H, s), 6.31 (2H, s); ^{13}C (150 MHz; $CDCl_3$) δ 15.3, 33.5, 34.0, 35.9, 82.8, 84.8, 135.1, 135.6, 179.2.

Step 4. Preparation of (3aS,4R,7aR)-4-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione  **, 34a**

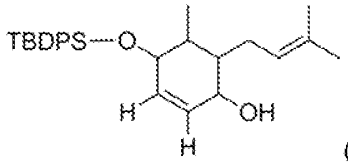
[0076] A solution of acid (500 mg, 2.97 mmol) resulted from Step 3 and *p*-TSA (57 mg, 0.30 mmol) in toluene (20 mL) was heated at 100 °C for 3 h. After 3 h, the mixture was concentrated in vacuo to yield hydroxyl lactone compound **35a** (450 mg); TLC R_f 0.46 (EtOAc:hexane, 2:1); EI-MS, m/z 191 $[M+Na]^+$.  **(35a)**

[0077] To a stirred solution of crude hydroxyl lactone **35a** (450 mg) in CH_2Cl_2 (15 mL) was added PDC (2.0 g, 5.4 mmol). The mixture was stirred at room temperature overnight, diluted with EtOAc (30 mL), and filtered. The residue was concentrated in vacuum and purified by column chromatography on silica gel (EtOAc:hexane, 1:1, TLC R_f 0.38) to provide compound **34a**, 294 mg (1.77 mmol, 60%, 2 steps) as white solids; EI-MS, m/z 189 $[M+Na]^+$; $[\alpha]^{24}_D$ −269.3 (c 2.03, $CHCl_3$); ^1H (600 MHz; $CDCl_3$) δ 1.15 (3H, d, J = 6.9 Hz), 2.17 (1H, dd, J = 17.4 and 12.7 Hz), 2.53 (1H, dd, J = 17.4 and 8.5 Hz), 2.78 (1H, dd, J = 6.7 and 5.5 Hz), 3.26−3.35 (1H, m), 5.32 (1H, dt, J = 7.2 and 1.9 Hz), 6.18 (1H, dd, J = 10.3 and 1.3 Hz), 6.68 (1H, dt, J = 10.3 and 1.9 Hz); ^{13}C (150 MHz; $CDCl_3$) δ 12.9, 29.6, 41.1, 75.2, 131.1, 141.1, 174.4, 197.7.

Example 3: Preparation of an exemplary Compound **36a** from lactone **35a**.



[0078] Compound **36a** was prepared from Compound **35a** under the following steps. The hydroxyl group was first protected with *t*-butyldiphenylsilyl chloride (TBDPS-Cl) (other non-limited exemplary suitable hydroxyl protecting groups that are inert to strong basic conditions can be used as well, e.g., MOM, MEM, THP protecting groups, or the like). The resulted compound was then first reduced by DIBAL-H and then reacted with $Ph_3PCH(CH_3)(CH_3)I$ (Wittig reaction) under the basic condition (*n*-BuLi) to afford the intermediate **A1.** The hydroxyl group of the intermediate **A1** was first protected with Acetate (condition: Ac_2O, pyridine) and then the silyl protecting group TBDPS was removed by n-Bu_4NF. The naked hydroxyl group was then oxidized with PDC to afford Compound **B1**. Deprotection of the acetate group afforded Compound **36a**. A series of Compound **36** can be prepared similarly.



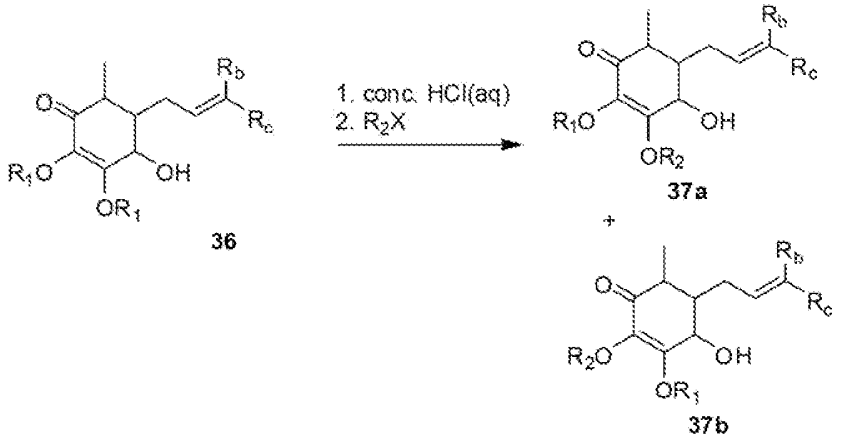
(A1)

[0079] ^1H (600 MHz; CD_3Cl) δ 0.77 (3H, d, *J* = 7.3 Hz), 1.07 (9H, s), 1.65 (3H, s), 1.73 (3H, s), 1.84−1.90 (1H, m), 2.02−2.10 (1H, m), 2.21−2.28 (2H, m), 3.93 (1H, t, *J* = 4.0 Hz), 4.18

(1H, br), 5.20–5.25 (1H, m), 5.66 (1H, dd, J = 9.9 Hz and 4.5 Hz), 5.85 (1H, dd, J = 9.9 Hz and 4.0 Hz), 7.37–7.41 (4H, m), 7.42–7.46 (2H, m), 7.66–7.70 (4H, m).

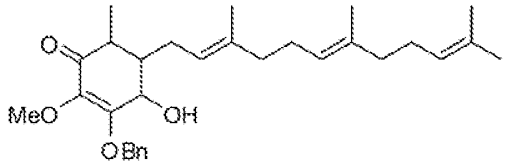
Example 4: Preparation of exemplary Compound **37a** and **37b** from Compound **36**.

[0080] The desired Compounds **37a** and **37b** were prepared by reaction with R_2X (X is a leaving group such as halogen or tosylate) with concentrated HCl in aqueous solution.



[0081] The following compounds were prepared accordingly.

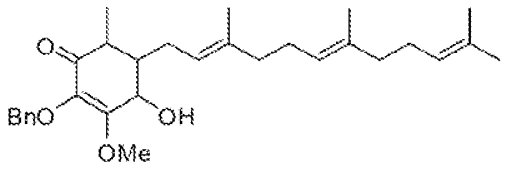
Compound 31: 3-(benzyloxy)-4-hydroxy-2-methoxy-6-methyl-5-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]cyclohex-2-en-1-one



[0082] To (4S,5S,6S)-4-hydroxy-2,3-dimethoxy-6-methyl-5-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]cyclohex-2-en-1-one (10.0 g, 25.6 mmol) in MeOH 50 mL was cooled to 0 °C, conc. $HCl_{(aq)}$ (22.5 mL, 270 mmol) was added. The reaction was stirred at room temperature for 30 min. After 30 min, the mixture was concentrated in vacuo. The residue was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$ (50 mL × 3) and brine (50 mL), dried over Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel (EtOAc:hexane, 1:5, TLC R_f 0.26) to get product 3.0 g (6.4 mmol, 25%); EI-MS, m/z 489 $[M+Na]^+$; $[\alpha]^{24}_D$ +18.6 (c 2.19, $CHCl_3$); ^1H (500 MHz; $CDCl_3$) δ 1.16 (3H, d, J = 7.0 Hz), 1.59 (6H, s), 1.64 (3H, s), 1.67 (3H, s), 1.73–1.75 (1H, m), 1.94–2.00 (2H, m), 2.00–2.09 (7H, m), 2.21–2.24 (2H, m), 2.52–2.56 (1H, m), 3.66 (3H, s), 4.35 (1H, t, J = 3.6 Hz), 5.05–5.10 (2H, m), 5.12 (1H, t, J = 7.0 Hz), 5.28 (1H, d, J = 11.9 Hz), 5.44 (1H, d, J = 11.9 Hz), 7.34–7.39 (5H, m); ^{13}C (125 MHz; $CDCl_3$) δ 12.4, 16.0, 16.1, 17.7, 25.7, 26.5, 26.7,

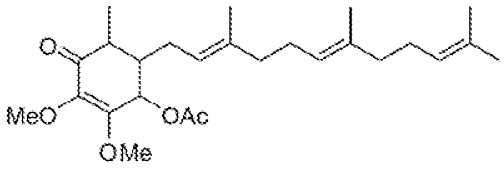
26.9, 39.7, 39.8, 40.4, 43.4, 60.4, 68.1, 73.4, 121.0, 123.9, 124.3, 127.8, 128.4, 128.6, 131.2, 135.2, 136.3, 136.8, 137.9, 159.8, 197.3.

Compound 30: 2-(benzyloxy)-4-hydroxy-3-methoxy-6-methyl-5-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]cyclohex-2-en-1-one



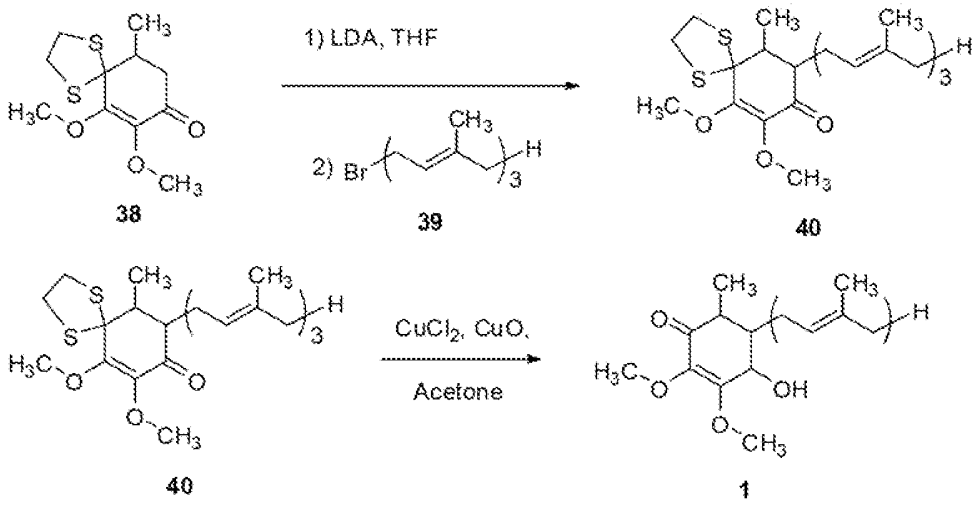
[0083] 6.1 g (13 mmol, 50 %); TLC R_f 0.26 (EtOAc:hexane, 1:5); EI-MS, m/z 489 $[M+Na]^+$; $[\alpha]^{24}_D$ −8.04 (c 2.04, $CHCl_3$); ^1H (600 MHz; $CDCl_3$) δ 1.28 (3H, d, J = 7.3 Hz), 1.49 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 1.65 (s, 3H), 1.67−1.77 (m, 1H), 1.90−1.99 (2H, m), 1.94−1.99 (2H, m), 1.99−2.05 (4H, m), 2.05−2.10 (1H, m), 2.21−2.23 (1H, m), 2.61−2.65 (1H, m), 3.57 (1H, br), 3.67 (3H, s), 4.97−5.00 (1H, m), 5.03−5.06 (2H, m), 5.19 (1H, d, J = 11.9 Hz), 5.46 (1H, d, J = 11.9 Hz), 7.32−7.36 (5H, m); ^{13}C (150 MHz; $CDCl_3$) δ 15.9, 16.0, 17.6, 17.7, 24.0, 25.6, 26.4, 26.7, 35.4, 39.6, 39.7, 44.9, 60.5, 70.8, 73.4, 121.8, 123.9, 124.3, 127.7, 128.4, 128.6, 131.2, 133.7, 135.1, 136.5, 137.9, 165.7, 195.1.

Compound 29: 2,3-dimethoxy-5-methyl-4-oxo-6-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]cyclohex-2-en-1-yl acetate



[0084] To (4S,5S,6S)-4-hydroxy-2,3-dimethoxy-6-methyl-5-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]cyclohex-2-en-1-one (500 mg, 1.38 mmol) in pyridine 5 mL was cooled to 0 °C, acetic anhydride (300 µL, 3.19 mmol) was added. The reaction was stirred at room temperature for 4 h. After 4 h, the mixture was diluted with EtOAc (20 mL), washed with 1N HCl(aq) (10 mL × 2), sat. $NaHCO_3$ (10 mL × 2), brine (20 mL), dried over Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel (EtOAc:hexane, 1:3, TLC R_f 0.56) to get product 404 mg (0.934 mmol, 68%); EI-MS, m/z 433 $[M+H]^+$; ^1H (500 MHz; $CDCl_3$) δ 1.19 (3H, d, J = 7.0 Hz), 1.56 (3H, s), 1.59 (6 H, s), 1.66 (3H, s), 1.83−1.90 (1H, m), 1.92−2.10 (10H, m), 2.08 (3H, s), 2.20−2.38 (1H, m), 2.48−2.56 (1H, m), 3.66 (3H, s), 3.98 (3H, s), 5.06−5.13 (3H, m), 5.74 (1H, d, J = 3.2 Hz).

Example 5: Preparation of exemplary Compound **1** via enolate reaction



[0085] Compound **38** is prepared from 2,3-dimethoxy-5-methylcyclohex-2-ene-1,4-dione. In a reaction flask, compound **38** is slowly added to a solution of LDA in THF at low temperature. After the formation of enolate, compound **39** is added slowly to the reaction mixture under inner gas condition. The reaction is quenched with water at low temperature and purified to afford compound **40**. Deprotection of compound **40** with suitable reagents such as $CuCl_2$, CuO in acetone to afford compound **1.**

Example 6: Determining the cytotoxic effects of exemplary cyclohexenone Compounds **25-31** against Compound **1.**

[0086] Cell viability was measured using Cell Counting Kit-8 (CCK-8, Enzo Life Sciences, Farmingdale, NY). In this assay, WST-8 is reduced by dehydrogenases in cells to produce a yellow-colored product (formazan), which is soluble in culture medium. The amount of formazan generated is directly proportional to the number of living cells. After treatment, CCK-8 solution was added to each well and incubated for 4 h. The concentration of formazan was measured with a spectrophotometer at an absorbance wavelength of 450 nm. Cell viability was expressed as a percentage of the corresponding control.

[0087] To determine whether the cytotoxic effects of Compound **1** correlate with the presence of *Ras* mutations, cell lines derived from human lung cancer (A549 and H838), liver cancer (HepG2 and Hep3B), and leukemia (K562 and THP-1) with wild-type *Ras* (H838, Hep3B, and K562) or mutant *Ras* (A549, HepG2, and THP-1) were used. Cell viability was measured after 48 h of Compound **1** treatment. The cell lines and their IC_{50}s in increasing order were THP-1 (2.22 μM) < A549 (3.24 μM) < H838 (3.32 μM) < Hep3B (3.74 μM) < K562 (5.12 μM) < HepG2 (6.42 μM) (See Table 1).

[0088] Next, the IC_{50} values for Compound **1** analogs (Compounds **29, 30** and **31**), a metabolite (Compound **27**), and analogues isolated from filamentous *A. camphorata* (Compounds **25, 26, 28**) were determined in H838 cells. The results indicated that the 2'-hydroxy group and the farnesyl group of Compound **1** were important for its cytotoxic effects. Further, Compound **31** was even more cytotoxic than Compound **1**. (Table 1)

[0089] Table 1. IC_{50} values of exemplary compounds of formula X determined by CCK-8 cell viability assay.

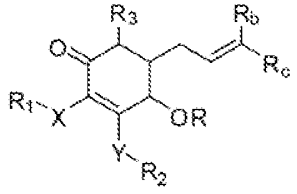
Compound	A549	H838	Hep3B	HepG2	K562	THP-1
1	3.24±0.35	2.96±0.05	3.74±0.35	6.42±0.08	5.12±0.83	2.22±0.03
25	-	22.56±6.45	-	-	-	-
26	-	11.34±4.17	-	-	-	-
27	-	>100	-	-	-	-
28	-	>100	-	-	-	-
29	-	>100	-	-	-	-
30	22.61±2.24	25.56±6.54	9.06±3.03	27.03±6.06	-	-
31	6.68±0.75	3.41±1.43	7.46±7.06	8.98±0.97	-	-

Values were presented as means ± S.E.M.

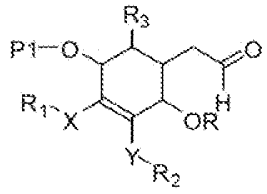
[0090] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula I:



(I)



comprising a step of reacting a compound of formula II, (II) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base, wherein

L is a leaving group, P1 is a hydroxyl protecting group;

each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is an optionally substituted C_1-C_{12}alkyl or $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

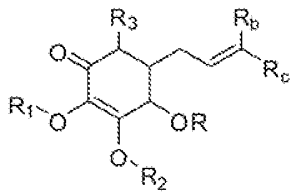
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

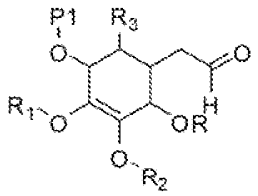
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

m = 0-11.

2. A process for preparing a compound of formula Ia:



(Ia)



comprising a step of reacting a compound of formula IIa, (IIa) with a compound of formula (III), $Ph_3PCHR_bR_cL$ (III) in the presence of a base,

wherein L is a leaving group, P1 is a hydroxyl protecting group;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

each of R_b and R_c independently is an optionally substituted C_1-C_{12}alkyl or $(CH_2CH=C(CH_3)(CH_2))_m$-R_4, wherein

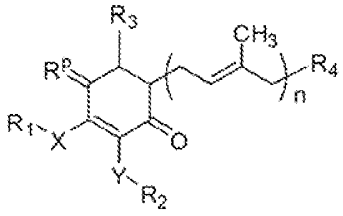
R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

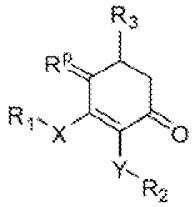
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

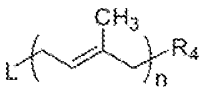
m = 0-11.

3. A process for preparing a compound of formula IV:



(IV)



comprising reacting an enol or enolate compound of formula V, (V) with a compound of formula (VI),  (VI) under suitable conditions, wherein

each of X and Y independently is oxygen, NR_5 or sulfur;

R^P is an oxo protecting group;

L is a leaving group;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

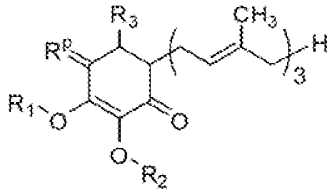
R_4 is NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

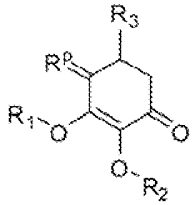
R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6; and

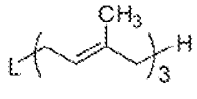
n=1-12 .

4. A process for preparing a compound of formula IVa:



(IVa)



comprising reacting an enol or enolate compound of formula V, (Va) with a compound of formula (VIa),  (VIa) under suitable conditions, wherein

R^P is an oxo protecting group;

L is a leaving group; and

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl.

5. The process according to any one of claims 1-4, wherein each of R_1, R_2 and R_3 independently is H, methyl, ethyl, propyl, butyl, pentyl or hexyl.

6. The process according to claim 1 or claim 2, wherein said base is a lithium salt.

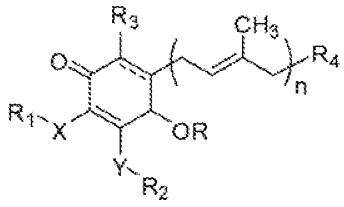
7. The process according to claim 6, wherein said lithium salt is n-butyllithium.

8. The process according to claim 3 or 4, wherein said enolate compound is prepared under basic conditions.

9. The process according to claim 3 or 4, wherein said enol compound is prepared under acidic conditions.

10. The process according to claim 3 or 4, wherein R^F is an acyclic or cyclic acetal, acyclic or cylic ketal, dithio acetal, dithio ketal, cyclic dithio acetal, cyclic dithio ketal, substituted hydrazone, oxime, oxime derivative, or oxazolidine.

11. A compound of formula X:



(X), or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof, wherein

each of X and Y independently is a bond, oxygen, NR_5 or sulfur;

R is H, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, $C(=O)SR_5$, $C(=S)R_5$, or $C(=S)NR_5R_6$;

each of R_1, R_2 and R_3 independently is H, or an optionally substituted C_1-C_{12}alkyl;

R_4 is H, NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

each of R_5 and R_6 is independently H or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6; the dotted line denotes an optionally present bond; and n=1-12, provided when X and Y are oxygen, each of R_1 and R_2 independently is a substituted C_1-C_{12}alkyl.

12. The compound of claim 11, wherein R is a hydrogen, $C(=O)C_3H_8$, $C(=O)C_2H_5$, or $C(=O)CH_3$

13. The compound of claim 11, wherein each of R_1, R_2 and R_3 independently is hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl optionally substituted with a aryl or heteroaryl.

14. The compound of claim 13, wherein R_1 is methyl substituted with phenyl.

15. The compound of claim 13, wherein R_2 is methyl substituted with phenyl.

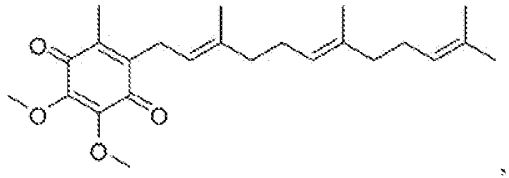
16. The compound of claim 11, wherein R_4 is halogen, NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3, OC_2H_5, $C(=O)CH_3$, $C(=O)C_2H_5$, $C(=O)OCH_3$, $C(=O)OC_2H_5$, $C(=O)NHCH_3$, $C(=O)NHC_2H_5$, $C(=O)NH_2$, $OC(=O)CH_3$, $OC(=O)C_2H_5$, $OC(=O)OCH_3$, $OC(=O)OC_2H_5$, $OC(=O)NHCH_3$, $OC(=O)NHC_2H_5$, or $OC(=O)NH_2$.

17. The compound of claim 11, wherein R_4 is $C_2H_5C(CH_3)_2OH$, $C_2H_5C(CH_3)_2OCH_3$, CH_2COOH, C_2H_5COOH, CH_2OH, C_2H_5OH, CH_2Ph, C_2H_5Ph, $CH_2CH=C(CH_3)(CHO)$, $CH_2CH=C(CH_3)(C(=O)CH_3)$, 5 or 6-membered lactone, aryl, or glucosyl, wherein 5 or 6-membered lactone, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl.

18. The compound of claim 17, wherein R_4 is C_1-C_8alkyl optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl.

19. The compound of claim 18, wherein R_4 is $CH_2CH=C(CH_3)_2$.

20. The compound of claim 11, wherein said compound is selected from group consisting of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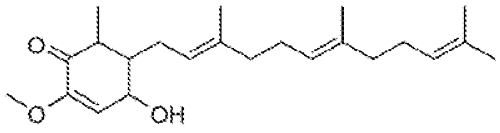
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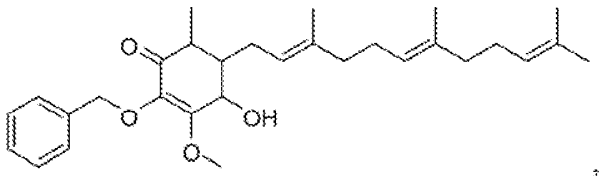
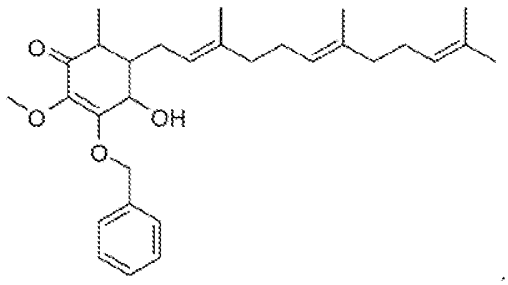

, and

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/017284

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 45/61 (2014.01)
USPC - 568/365
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)
IPC(8) - C07C 45/61 (2014.01)
USPC - 568/343, 349, 364, 365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C07C 45/61 (2014.02)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0005825 A1 (LIU et al) 03 January 2013 (03.01.2013) entire document	1-10
A	US 2010/0210869 A1 (WU et al) 19 August 2010 (19.08.2010) entire document	1-10
A	US 2012/0309732 A1 (CHEN et al) 06 December 2012 (06.12.2012) entire document	1-10
A	EP 2 233 463 A1 (LIU et al) 29 September 2010 (29.09.2010) entire document	1-10

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2014	14 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/017284

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/017284

<Continued from Box III: Observations where unity of invention is lacking>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-10 are drawn to processes for preparing a compound of formula I, Ia, IV, and IVa.

Group II: claims 11-20 are drawn to a compound of formula X or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof.

The inventions listed in Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, processes for preparing a compound, are not present in Group II; and the special technical features of Group II, compounds of formula X, are not present in Group I.

The Groups I and II share the technical features of a compound having the cyclohexanone core structure of formulas I, Ia, IV, IVa, and X, or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2013/0005825 to Liu et al. teach a compound of formula X: or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof: wherein each of X and Y independently is oxygen; R is H; each of R1, R2 and R3 independently is C1alkyl; R4 is H; and n is 3 (see Para. [0013], preferred compound of the general formula (1) is 4-hydroxy-2,3-dimethoxy-6-methyl-5-(3,7,11-trimethyldodeca-2,6,10-trienyl)-cyclohex-2-enone as shown in formula (2)...).

The inventions listed in Groups I and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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(71)申请人 国鼎生物科技股份有限公司
地址 美国新泽西州

(72)发明人 刘胜勇 温武哲 陈志铭 郑秀宜

(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
代理人 高瑜 郑霞

(51)Int.Cl.
C07C 45/61(2006.01)

权利要求书4页 说明书27页

(54)发明名称

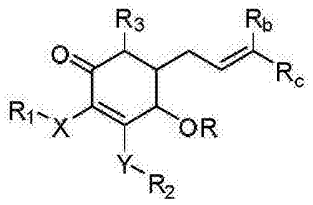
环己烯酮组成物及其制备方法

(57)摘要

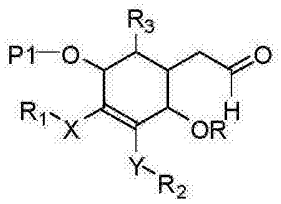
本文提供了制备可用于治疗癌症和/或疾病的环己烯酮化合物的方法。本发明涉及环己烯酮化合物的组成物以及制备环己烯酮化合物的方法。在一方面,提供了用于制备式I的化合物的方法包括使式II反应的步骤。

CN 105263893 A

1. 一种用于制备式 I 的化合物的方法：



(I)，

该方法包括使式 II  的化合物与式 (III)$Ph_3PCHR_bR_cL$(III)

(II)

的化合物在碱的存在下反应的步骤，其中

L 为离去基团，P1 为羟基保护基团；

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R 为 H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或 C(=S)NR_5R_6；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_b和 R_c中的每一个独立地为任选取代的 C_1-C_{12}烷基或 $(CH_2CH=C(CH_3)(CH_2))_m$-R_4，其中

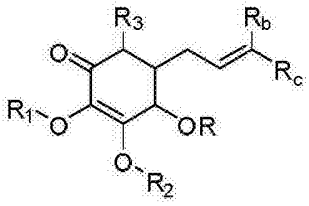
R_4为 H、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

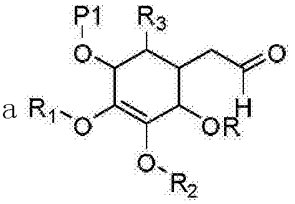
R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；

m = 0-11。

2. 一种用于制备式 Ia 的化合物的方法：



(Ia)，

该方法包括使式 IIa  的化合物与式 (III)$Ph_3PCHR_bR_cL$(III)

(IIa)

的化合物在碱的存在下反应的步骤，

其中 L 为离去基团，P1 为羟基保护基团；

R 为 H、C(= O)OR_5、C(= O)R_5、C(= O)NR_5R_6、C(= O)SR_5、C(= S)R_5或 C(= S)NR_5R_6；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_b和 R_c中的每一个独立地为任选取代的 C_1-C_{12}烷基或 $(CH_2CH=C(CH_3)(CH_2))_m$-R_4，其中

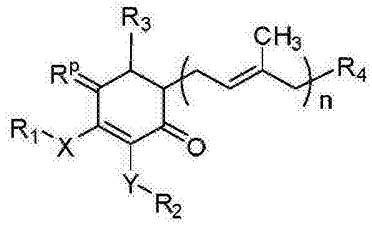
R_4为 H、NR_5R_6、OR_5、OC(= O)R_7、C(= O)OR_5、C(= O)R_5、C(= O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(= O)R_7、C(= O)OR_5、C(= O)R_5、C(= O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

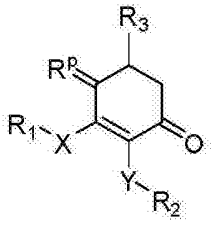
R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；

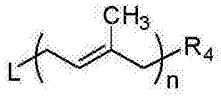
m = 0-11。

3. 一种用于制备式 IV 的化合物的方法：



(IV)，

该方法包括使式 V  (V) 的烯醇或烯醇化物化合物与式

(VI)  (VI) 的化合物在合适的条件下反应，其中

X 和 Y 中的每一个独立地为氧、NR_5或硫；

R^p为氧代保护基团；

L 为离去基团；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

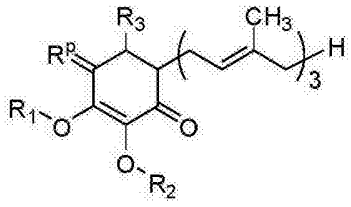
R_4为 NR_5R_6、OR_5、OC(= O)R_7、C(= O)OR_5、C(= O)R_5、C(= O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(= O)R_7、C(= O)OR_5、C(= O)R_5、C(= O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

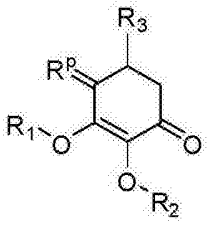
R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；且

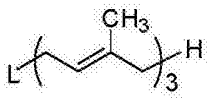
n = 1-12。

4. 一种用于制备式 IVa 的化合物的方法：



(IVa)，

该方法包括使式  (Va)| 的烯醇或烯醇化物化合物与式

(VIa)  (VIa)| 的化合物在合适的条件下反应，其中

R^p为氧代保护基团；

L 为离去基团；且

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基。

5. 根据权利要求 1-4 中任一项所述的方法，其中 R_1、R_2和 R_3中的每一个独立地为 H、甲基、乙基、丙基、丁基、戊基或己基。

6. 根据权利要求 1 或 2 所述的方法，其中所述碱为锂盐。

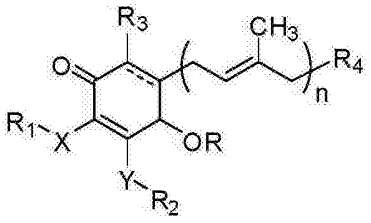
7. 根据权利要求 6 所述的方法，其中所述锂盐为正丁基锂。

8. 根据权利要求 3 或 4 所述的方法，其中所述烯醇化物化合物在碱性条件下制备。

9. 根据权利要求 3 或 4 所述的方法，其中所述烯醇化合物在酸性条件下制备。

10. 根据权利要求 3 或 4 所述的方法，其中R^p为无环或环状缩醛、无环或环状缩酮、二硫代缩醛、二硫代缩酮、环状二硫代缩醛、环状二硫代缩酮、取代的腙、肟、肟衍生物或噁唑烷。

11. 式 X 的化合物：



(X)，

或其药学上可接受的盐、代谢物、溶剂化物或前药，

其中

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R 为 H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或 C(=S)NR_5R_6；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_4为 H、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和R_6中的每一个独立地为H或C_1-C_8烷基；

R_7为C_1-C_8烷基、OR_5或NR_5R_6;虚线表示任选存在的键；

且n＝1-12,条件是当X和Y为氧时,R_1和R_2中的每一个独立地为取代的C_1-C_{12}烷基。

12.根据权利要求11所述的化合物,其中R为氢、C(＝O)C_3H_8、C(＝O)C_2H_5或C(＝O)CH_3。

13.根据权利要求11所述的化合物,其中R_1、R_2和R_3中的每一个独立地为氢、任选地被芳基或杂芳基取代的甲基、乙基、丙基、丁基、戊基、己基、庚基或辛基。

14.根据权利要求13所述的化合物,其中R_1为被苯基取代的甲基。

15.根据权利要求13所述的化合物,其中R_2为被苯基取代的甲基。

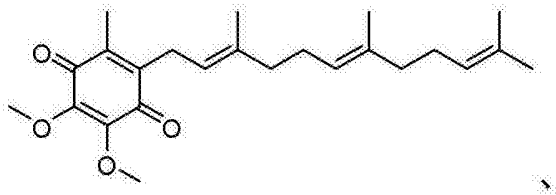
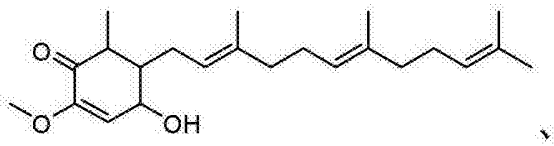
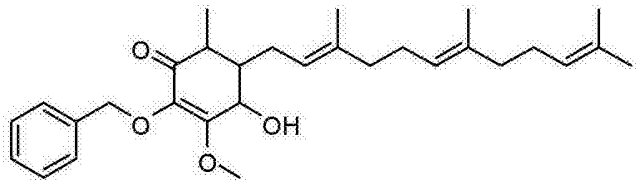
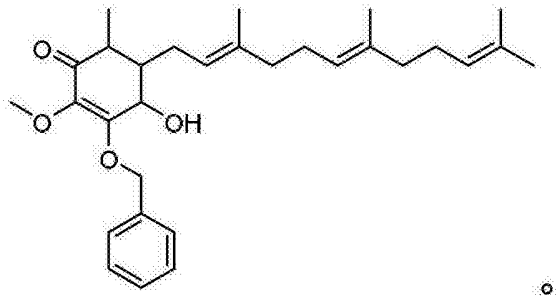
16.根据权利要求11所述的化合物,其中R_4为卤素、NH_2、$NHCH_3$、$N(CH_3)_2$、OCH_3、OC_2H_5、C(＝O)CH_3、C(＝O)C_2H_5、C(＝O)OCH_3、C(＝O)OC_2H_5、C(＝O)$NHCH_3$、C(＝O)NHC_2H_5、C(＝O)NH_2、OC(＝O)CH_3、OC(＝O)C_2H_5、OC(＝O)OCH_3、OC(＝O)OC_2H_5、OC(＝O)$NHCH_3$、OC(＝O)NHC_2H_5或OC(＝O)NH_2。

17.根据权利要求11所述的化合物,其中R_4为$C_2H_5C(CH_3)_2OH$、$C_2H_5C(CH_3)_2OCH_3$、CH_2COOH、C_2H_5COOH、CH_2OH、C_2H_5OH、CH_2Ph、C_2H_5Ph、$CH_2CH＝C(CH_3)(CHO)$、$CH_2CH＝C(CH_3)(C(＝O)CH_3)$、5或6元内酯、芳基或葡糖基,其中该5或6元内酯、芳基和葡糖基任选地被选自NR_5R_6、OR_5、OC(＝O)R_7、C(＝O)OR_5、C(＝O)R_5、C(＝O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基所取代。

18.根据权利要求17所述的化合物,其中R_4为任选地被选自NR_5R_6、OR_5、OC(＝O)R_7、C(＝O)OR_5、C(＝O)R_5、C(＝O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基取代的C_1-C_8烷基。

19.根据权利要求18所述的化合物,其中R_4为$CH_2CH＝C(CH_3)_2$。

20.根据权利要求11所述的化合物,其中所述化合物选自


、

、

和

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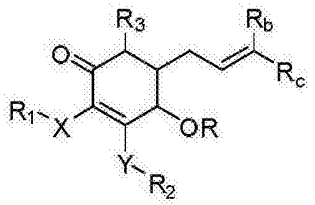
环己烯酮组成物及其制备方法

背景技术

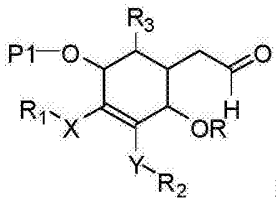
[0001] 本发明涉及环己烯酮化合物的组成物以及制备环己烯酮化合物的方法。

发明内容

[0002] 在一方面，提供了用于制备式 I 的化合物的方法：



(I)，



该方法包括使式 II (II) 的化合物与式 (III) $Ph_3PCHR_bR_cL$ (III) 的化合物在碱的存在下反应的步骤，其中 L 为离去基团，P1 为羟基保护基团；

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R 为 H、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、$C(=O)SR_5$、$C(=S)R_5$或 $C(=S)NR_5R_6$；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_b和 R_c中的每一个独立地为任选取代的 C_1-C_{12}烷基或 $(CH_2CH=C(CH_3)(CH_2))_m$-R_4，其中

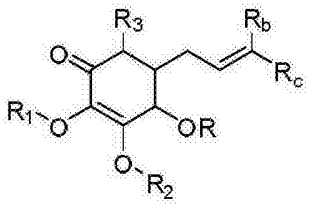
R_4为 H、NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

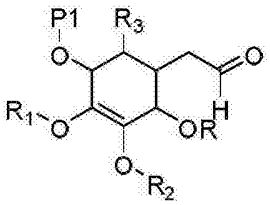
R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；

m = 0-11。

[0003] 在另一方面，提供了用于制备式 Ia 的化合物的方法：



(Ia)，

该方法包括使式 IIa  (IIa) 的化合物与式 (III)$Ph_3PCHR_bR_cL$(III) 的化合物在碱的存在下反应的步骤，

其中 L 为离去基团，P1 为羟基保护基团；

R 为 H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或 C(=S)NR_5R_6；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_b和 R_c中的每一个独立地为任选取代的 C_1-C_{12}烷基或 $(CH_2CH=C(CH_3)(CH_2))_m$-R_4，其中

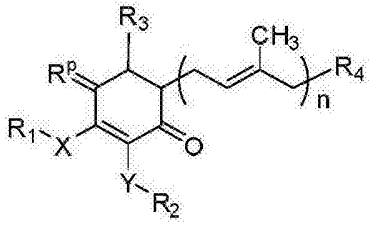
R_4为 H、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

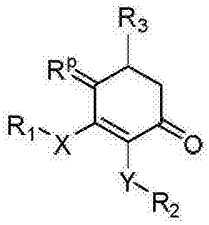
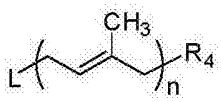
R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；

m = 0-11。

[0004] 在本发明的另一方面，提供了用于制备式 IV 的化合物的方法：

 (IV)，

该方法包括使式 V  (V) 的烯醇或烯醇化物化合物与式 (VI)  (VI) 的化合物在合适的条件下反应，其中

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R^p为氧代保护基团；

L 为离去基团；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_4为 H、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)

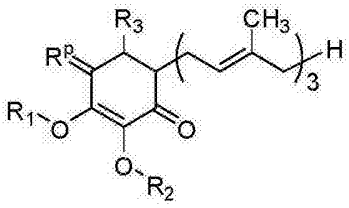
R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和R_6中的每一个独立地为H或C_1-C_8烷基；

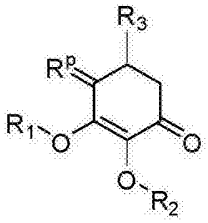
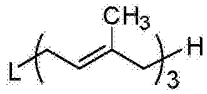
R_7为C_1-C_8烷基、OR_5或NR_5R_6；

且n=1-12。

[0005] 在本发明的另一方面，提供了用于制备式IVa的化合物的方法：



(IVa)，

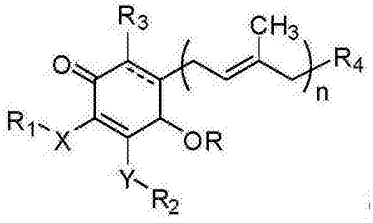
该方法包括使式Va  (Va)的烯醇或烯醇化物化合物与式(VIa)  (VIa)的化合物在合适的条件下反应，其中

R^p为氧代保护基团；

L为离去基团；且

R_1、R_2和R_3中的每一个独立地为H或任选取代的C_1-C_{12}烷基。

[0006] 在一方面，提供了式X的化合物：



(X)，或其药学上可接受的盐、代谢物、溶剂化物或前药，其中

X和Y中的每一个独立地为键、氧、NR_5或硫；

R为H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或C(=S)NR_5R_6；

R_1、R_2和R_3中的每一个独立地为H或任选取代的C_1-C_{12}烷基；

R_4为H、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基所取代；

R_5和R_6中的每一个独立地为H或C_1-C_8烷基；

R_7为C_1-C_8烷基、OR_5或NR_5R_6；虚线表示任选存在的键；

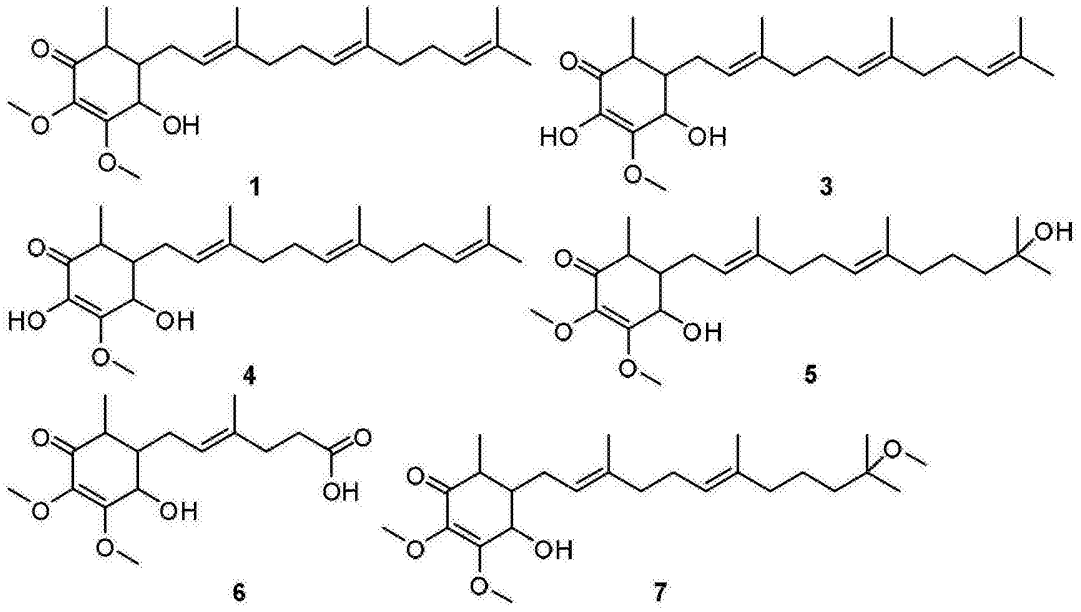
且n=1-12，条件是当X和Y为氧时，R_1和R_2中的每一个独立地为取代的C_1-C_{12}烷基。

援引并入

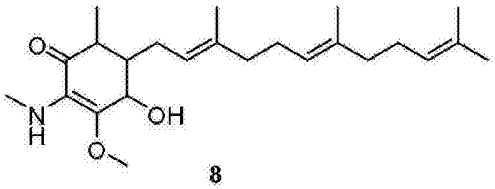
[0007] 本说明书中所提到的所有出版物、专利和专利申请均通过引用并入本文，其程度等同于特别地且单独地指出每个单独的出版物、专利或专利申请通过引用而并入。

具体实施方式

[0008] 可从牛樟芝 (Antrodia camphorata) 的提取物中分离环己烯酮化合物。例如，从有机溶剂提取物中分离化合物 1 和 3-7。



[0009] 在一些实施方案中，某些环己烯酮化合物可通过合成方式制备。以下是一些非限制性的实例。



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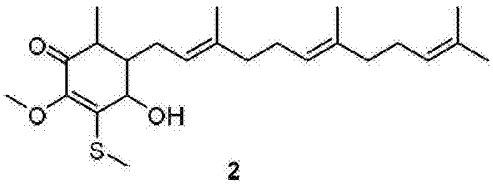

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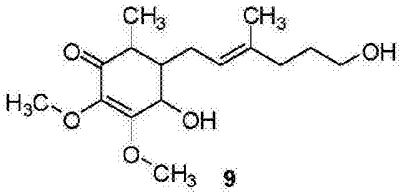

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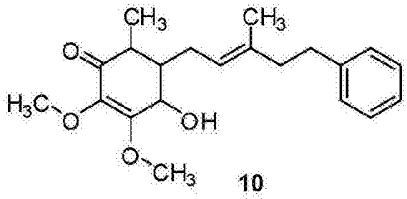

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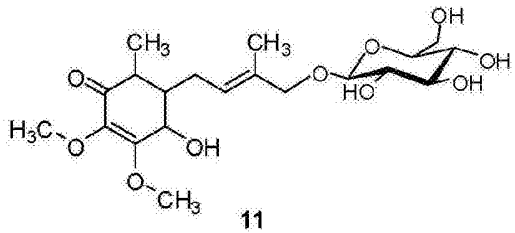

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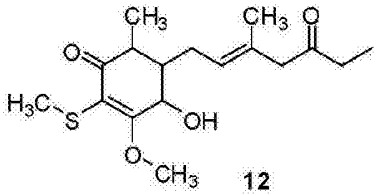

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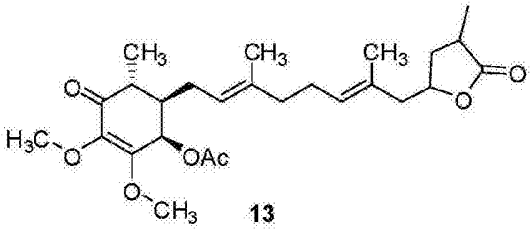
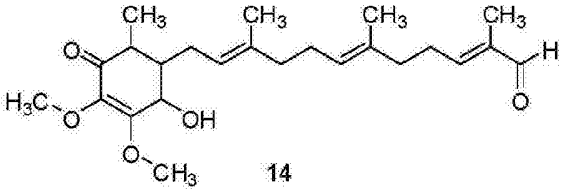
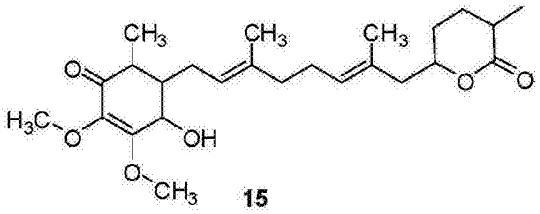


13



14



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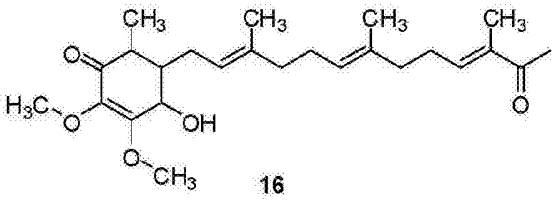

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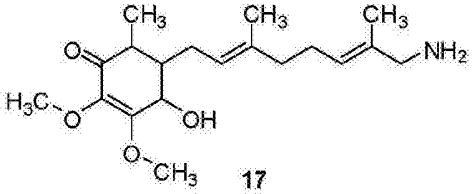

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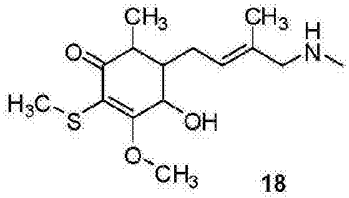

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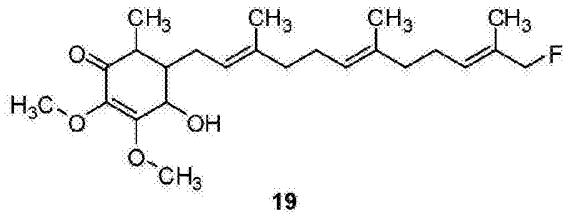
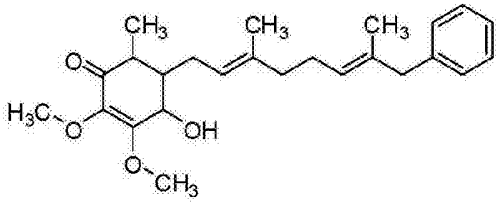


19



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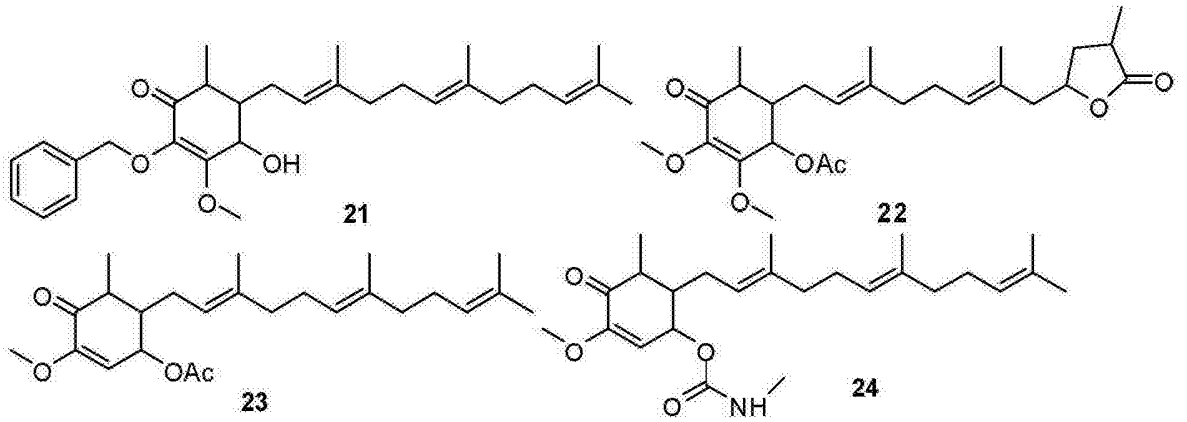
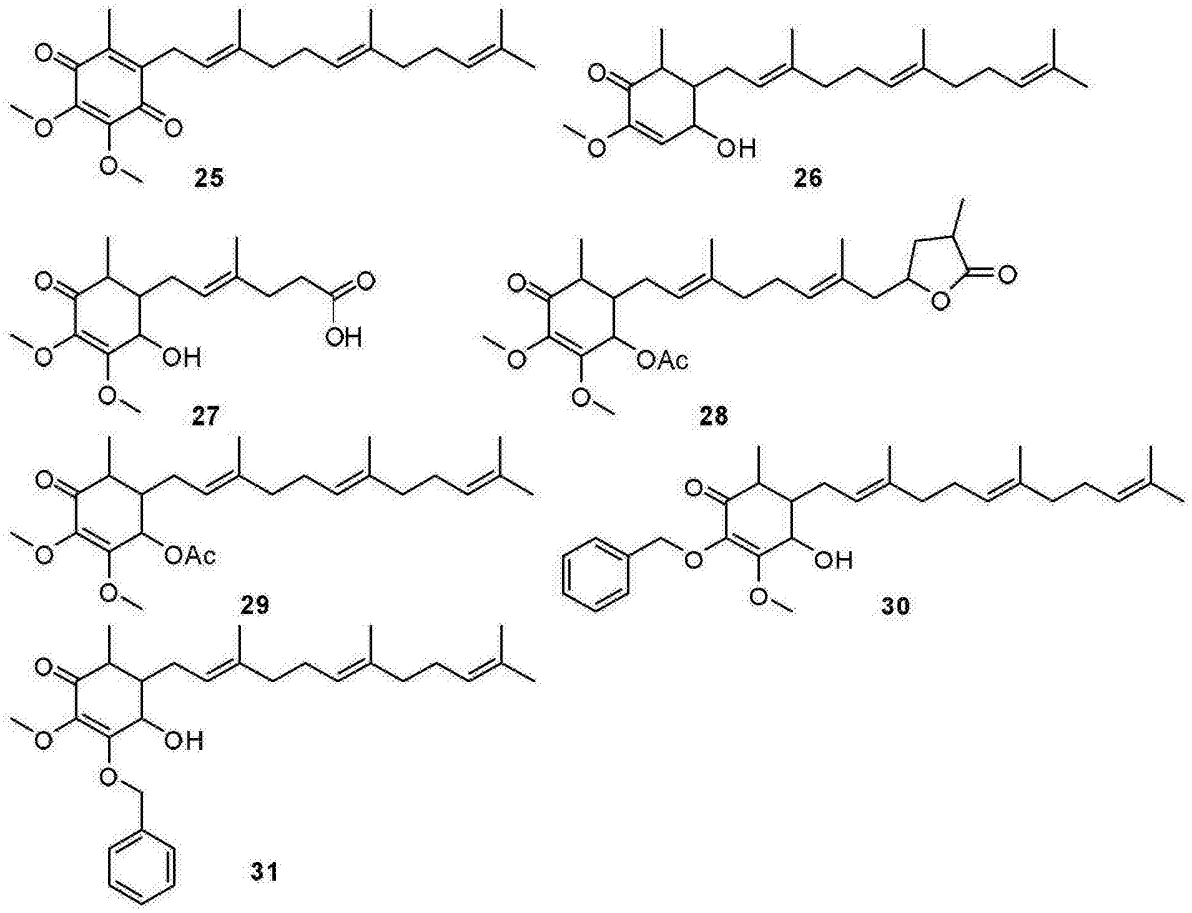
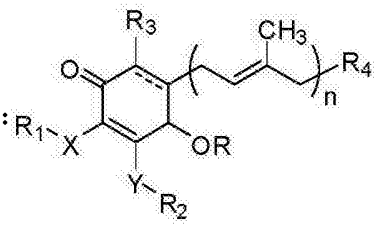


[0010] 从牛樟芝的提取物中分离的许多环己烯酮化合物提供某些生物学效应。特别地，制备化合物 25 至 31 并相对于化合物 1 进行测试，以确定它们的生物学性质。



[0011] 在一些实施方案中，提供了式X的化合物：  (X)，或其药学上可接受的盐、代谢物、溶剂化物或前药，其中环的虚线为单键或双键；

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R 为 H、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、$C(=O)SR_5$、$C(=S)R_5$或 $C(=S)NR_5R_6$；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_4为 H、NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

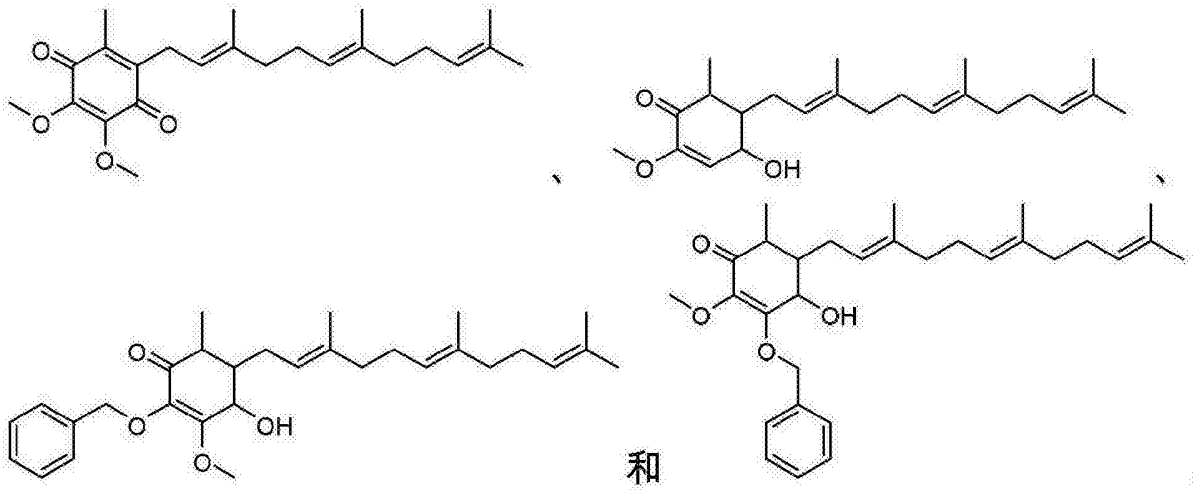
R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；虚线表示任选存在的键；

且 n = 1-12，条件是当 X 和 Y 为氧时，R_1和 R_2中的每一个独立地为取代的 C_1-C_{12}烷基。

[0012] 在某些实施方案中，从牛樟芝的有机溶剂提取物中分离式 (X) 的化合物。在一些实施方案中，该有机溶剂选自醇（例如，甲醇、乙醇、丙醇等）、酯（例如，乙酸甲酯、乙酸乙酯等）、烷烃（例如，戊烷、己烷、庚烷等）、卤代烷烃（例如，氯甲烷、氯乙烷、氯仿、二氯甲烷等）等。在某些实施方案中，该有机溶剂是醇。在某些实施方案中，该醇是乙醇。在一些实施方案中，从牛樟芝的水性提取物中分离式 (X) 的化合物。在一些实施方案中，通过本文所公开的方法以合成方式制备式 (X) 的化合物。在其他实施方案中，通过本领域中容易获得的其他方法，如经由合成或半合成方法制备式 (X) 的化合物。

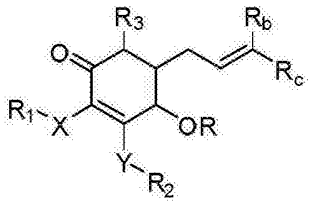
[0013] 在一些实施方案中，X 和 Y 中的每一个独立地为键。在一些实施方案中，R 为 H、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$。在某些实施方案中，R 为 H 或 $C(=O)R_5$。在某些实施方案中，R 为 H、$C(=O)C_3H_8$、$C(=O)C_2H_5$或 $C(=O)CH_3$。在一些实施方案中，R_1、R_2和 R_3中的每一个独立地为氢或取代的 C_1-C_{12}烷基。在一些实施方案中，R_1、R_2和 R_3中的每一个独立地为氢或者被芳基或杂芳基取代的 C_1-C_{12}烷基。在某些实施方案中，R_1为被苯基或吡啶基取代的甲基、乙基、丙基、丁基、戊基或己基。在某些实施方案中，R_1为 CH_2-Ph。在某些实施方案中，R_1为 H、甲基、乙基、丙基、丁基、戊基或己基，条件是 X 和 Y 之一为键。在某些实施方案中，R_2为被苯基或吡啶基取代的甲基、乙基、丙基、丁基、戊基或己基。在某些实施方案中，R_2为 CH_2-Ph。在某些实施方案中，R_2为 H、甲基、乙基、丙基、丁基、戊基或己基，条件是 X 和 Y 之一为键。在一些实施方案中，R_3为 H、甲基、乙基、丙基、丁基、戊基或己基。在一些实施方案中，R_4为 H、卤素、NH_2、$NHCH_3$、$N(CH_3)_2$、OCH_3、OC_2H_5、$C(=O)CH_3$、$C(=O)C_2H_5$、$C(=O)OCH_3$、$C(=O)OC_2H_5$、$C(=O)NHCH_3$、$C(=O)NHC_2H_5$、$C(=O)NH_2$、$OC(=O)CH_3$、$OC(=O)C_2H_5$、$OC(=O)OCH_3$、$OC(=O)OC_2H_5$、$OC(=O)NHCH_3$、$OC(=O)NHC_2H_5$或 $OC(=O)NH_2$。在一些实施方案中，R_4为 $C_2H_5C(CH_3)_2OH$、$C_2H_5C(CH_3)_2OCH_3$、CH_2COOH、C_2H_5COOH、CH_2OH、C_2H_5OH、CH_2Ph、C_2H_5Ph、$CH_2CH=C(CH_3)(CHO)$、$CH_2CH=C(CH_3)(C(=O)CH_3)$、5 或 6 元内酯、$C_2$-$C_8$烯基、$C_2$-$C_8$炔基、芳基和葡糖基，其中该 5 或 6 元内酯、$C_2$-$C_8$烯基、$C_2$-$C_8$炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代。在某些实施方案中，R_4为 $CH_2CH=C(CH_3)_2$。在某些实施方案中，式 (X) 的化合物选自



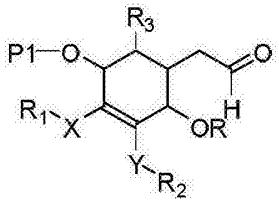
和 。

[0014]]由于通过纯化从牛樟芝获得环己烯酮化合物的高成本，和/或为了制备所需的类似物以用于进一步的临床试验，本文中描述了制备环己烯酮化合物的合成方法。

[0015] 根据本发明，提供了用于制备式 I 的化合物的方法：



(I)，

该方法包括使式 (II)  (II) 的化合物与式 (III)$Ph_3PCHR_bR_cL$(III) 的化合物在碱的存在下反应的步骤，其中 L 为离去基团，P1 为羟基保护基团；

X 和 Y 中的每一个独立地为键、氧、NR_5或硫；

R 为 H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或 C(=S)NR_5R_6；

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基；

R_b和 R_c中的每一个独立地为氢、任选地被 $(CH_2CH=C(CH_3)(CH_2))_m$-R_4取代的 C_1-C_{12}烷基，其中

R_4为氢、NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；

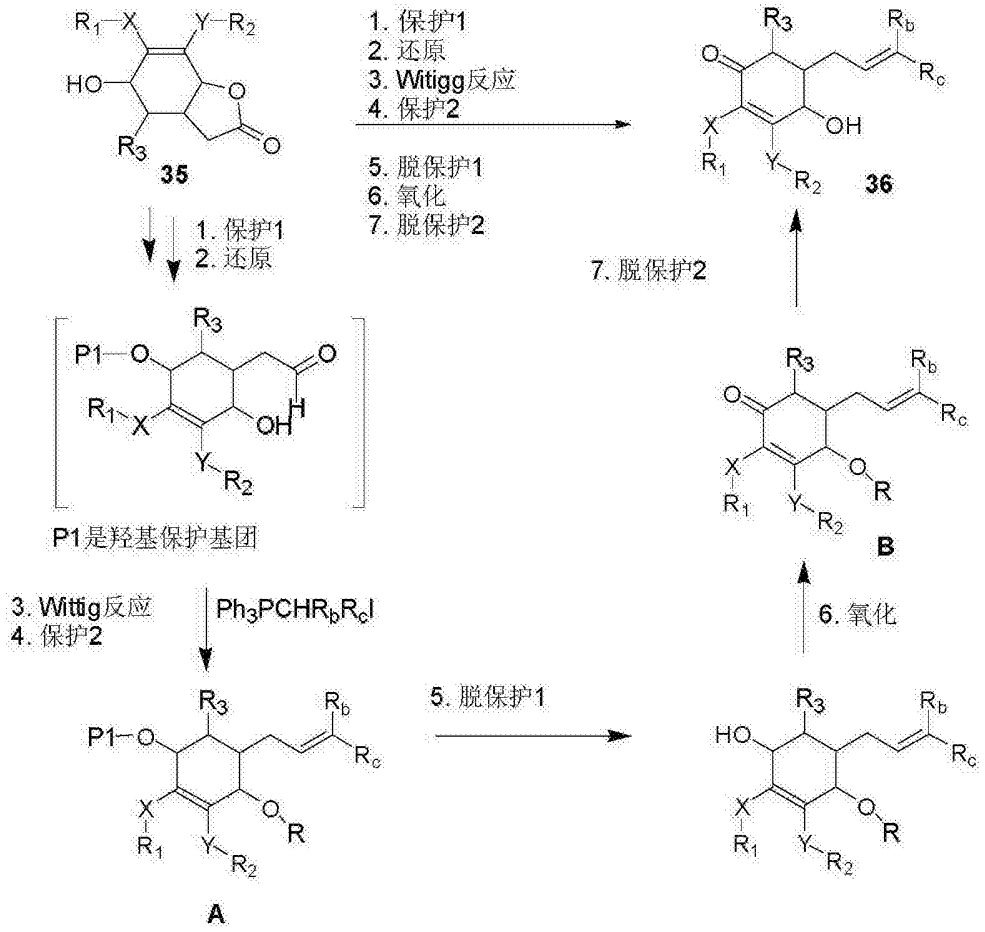
R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；

R_7为 C_1-C_8烷基、OR_5或 NR_5R_6；

m = 0-11。在某些实施方案中，R 为羟基保护基团如甲硅烷基保护基团以及与 P1 相同或不同的其他合适的保护基团。

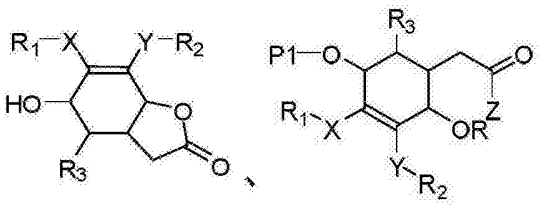
[0016] 式 (II) 的化合物与式 (III) 的化合物之间的反应被称为 Wittig 反应。由于醛通

常是化学不稳定的，因此在一些实施方案中，原位制备式（II）的化合物。方案 I 提供了制备式（I）的化合物的非限制性示例性路线。对化合物 35 的游离羟基基团进行保护，接着进行内酯环的还原以提供式（II）的醛化合物，然后式（II）的醛化合物与 $Ph_3PCHR_bR_cI$ 进行 Wittig 反应以制备中间体 A。在脱保护和氧化后，制备化合物 B（其为式（I）的化合物）。通过脱保护反应可以容易地制备其中 R 为 H 的化合物 36。



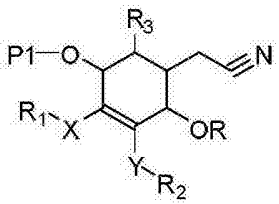
方案 I. 制备式（I）的化合物的示例性合成方案

[0017] 可以由芳基硅烷、羧酸、酰卤、酸酐、酯、内酯、酰胺、腈等的还原来制备醛。在一些情况下，可以由游离羟基基团的氧化来制备醛。本领域技术人员根据本发明可以容易地考虑其他合适的反应来制备式（II）的化合物。在一些实施方案中，由具有结构



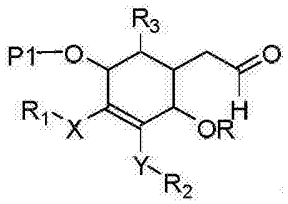
、

或

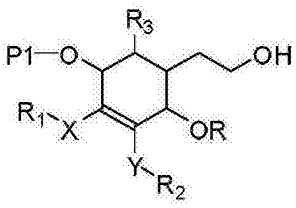
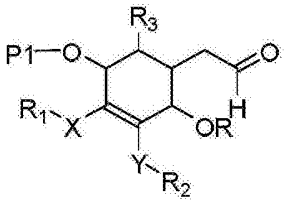


的化合物的还原制备式

（II）



（II）的化合物，其中 Z 为卤素、$OR_5OC(=O)R_7$ 或 NR_5R_6。

[0018] 在一些实施方案中，由具有结构  的化合物的氧化制备式 (II)  (II) 的化合物。

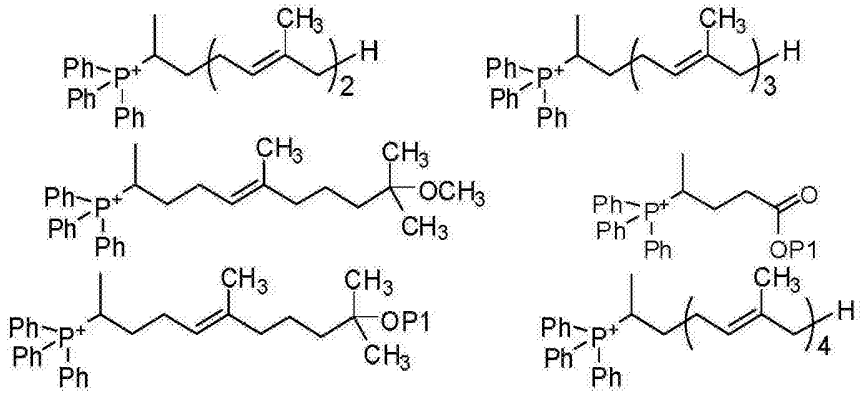
[0019] 在一些实施方案中，R 为可以经受 Wittig 反应条件的任何合适的羟基保护基团。例如，R 为 $C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、$C(=O)SR_5$、$C(=S)R_5$、$C(=S)NR_5R_6$等。

[0020] 在一些实施方案中，所述碱为可以由式 (III) 的化合物形成内鎓盐 (ylide) 的碱，例如，正丁基锂 (n-BuLi) 等。

[0021] 在一些实施方案中，R_1、R_2和 R_3中的每一个独立地为 H、任选地被芳基或杂芳基取代的甲基、乙基、丙基、丁基、戊基或己基。在某些实施方案中，R_1、R_2和 R_3中的每一个独立地为 H 或甲基。

[0022] 本文提供的 Wittig 反应适用于多种异戊二烯单元前体。例如，该反应适用于以下情形：其中 R_b为 CH_3且 R_c为被 $(CH_2CH=C(CH_3)(CH_2))_m-R_4$取代的 CH_2，其中 R_4为氢、NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、卤素、5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基，其中该 5 或 6 元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自 NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和 C_1-C_8卤代烷基的一个或多个取代基所取代；R_5和 R_6中的每一个独立地为 H 或 C_1-C_8烷基；且 R_7为 C_1-C_8烷基、OR_5或 NR_5R_6。

[0023] 例如，非限制性地，技术人员可以使用以下异戊二烯前体，其中 P1 为羟基保护基团。



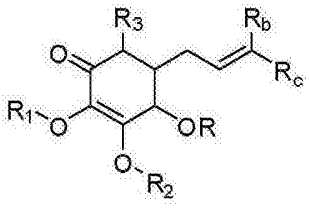
[0024] 在一些实施方案中，提供了制备其中 X 为氧、NR_5或硫的式 (I) 的化合物的方法。例如，X 可以为 O、S、NH、NCH_3、NC_2H_5等。

[0025] 在其他实施方案中，提供了制备其中 Y 为氧、NR_5或硫的式 (I) 的化合物的方法。例如，Y 可以为 O、S、NH、NCH_3、NC_2H_5等。

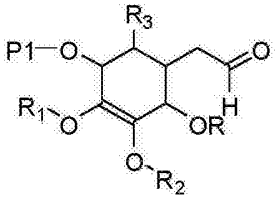
[0026] 在其他实施方案中，提供了制备其中 X 为 O 且 Y 为 O，或者 X 为 O 且 Y 为 S，或者 X

为S且Y为O,或者X为O且Y为NH,或者X为NH且Y为O的式(I)的化合物的方法。

[0027] 在一些实施方案中,提供了用于制备式(Ia)的化合物的方法:



(Ia),

该方法包括使式IIa  (IIa)的化合物与式(III)$Ph_3PCHR_bR_cL$(III)的化合物在碱的存在下反应的步骤,其中

其中L为离去基团,P1为羟基保护基团;

R为H、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C(=O)SR_5、C(=S)R_5或C(=S)NR_5R_6;

R_1、R_2和R_3中的每一个独立地为H或任选取代的C_1-C_{12}烷基;

R_b和R_c中的每一个独立地为氢、任选地被$(CH_2CH=C(CH_3)(CH_2))_m$-R_4取代的C_1-C_{12}烷基,其中

R_4为NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、卤素、5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基,其中该5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自NR_5R_6、OR_5、OC(=O)R_7、C(=O)OR_5、C(=O)R_5、C(=O)NR_5R_6、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基所取代;

R_5和R_6中的每一个独立地为H或C_1-C_8烷基;

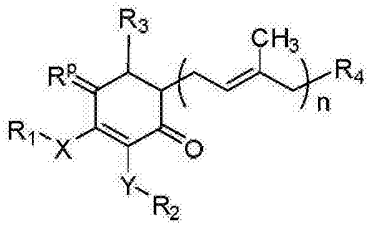
R_7为C_1-C_8烷基、OR_5或NR_5R_6;

m=0-11。

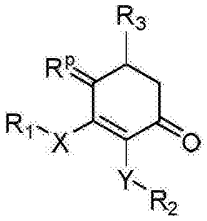
[0028] 在一些实施方案中,提供了制备其中R为H或-C(=O)C_1-C_8烷基且R_1、R_2和R_3中的每一个独立地为H或C_1-C_{12}烷基的式(I)或(Ia)的化合物的方法。

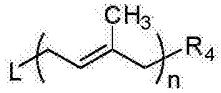
[0029] 在某些实施方案中,R为H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中,R_1为H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中,R_2为H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中,R_3为H、甲基、乙基、丙基、丁基、戊基等。

[0030] 在一些实施方案中,提供了用于制备式IV的化合物的方法:



(IV),

该方法包括使式V  (V)的烯醇或烯醇化物化合物与式

(VI)  (VI)的化合物在合适的条件下反应,其中

X和Y中的每一个独立地为键、氧、NR_5或硫;

R^p为氧代保护基团;

L为离去基团;

R_1、R_2和R_3中的每一个独立地为H或任选取代的C_1-C_{12}烷基;

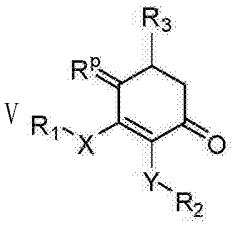
R_4为H、NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、卤素、5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基、葡糖基,其中该5或6元内酯、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、芳基和葡糖基任选地被选自NR_5R_6、OR_5、$OC(=O)R_7$、$C(=O)OR_5$、$C(=O)R_5$、$C(=O)NR_5R_6$、C_1-C_8烷基、C_2-C_8烯基、C_2-C_8炔基、C_3-C_8环烷基和C_1-C_8卤代烷基的一个或多个取代基所取代;

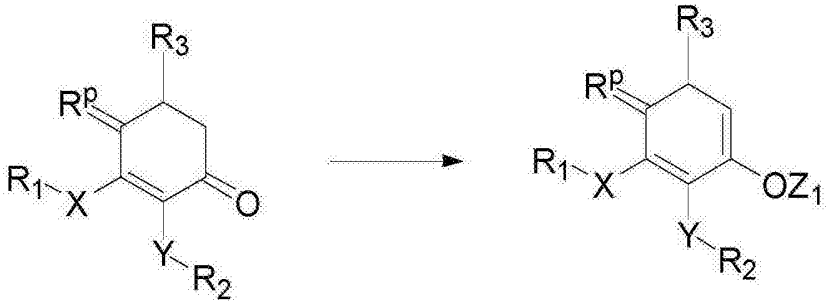
R_5和R_6中的每一个独立地为H或C_1-C_8烷基;

R_7为C_1-C_8烷基、OR_5或NR_5R_6;

且n=1-12。

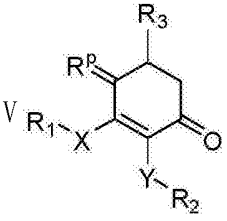
[0031] 在一些实施方案中,在合适的条件(例如,酸促进或甲硅烷基捕获)下制备式

 (V)的烯醇化合物。



[0032] Z_1=H或甲硅烷基保护基团

[0033] 在一些实施方案中,通过使式V的化合物与强碱反应来制备式

 (V)的烯醇化物化合物。技术人员遵循已知程序将容易找到其他合适

的条件来制备式 V 的烯醇或烯醇化物化合物。

[0034] 在某些实施方案中，P 为可以经受用于生成式 V 的烯醇或烯醇化物化合物的酸性或碱性条件的氧代保护基团。例如，P 为对水性和非水性碱稳定、对包括有机金属试剂在内的亲核剂稳定以及对氢化物还原稳定的无环或环状缩酮或无环或环状酮缩硫醇。在一些实施方案中，P 为对水性和非水性酸稳定、对包括有机金属试剂在内的亲核剂稳定以及对氢化物还原稳定的无环或环状酮缩硫醇。在某些实施方案中，P 为 1,3- 二噻戊环等。

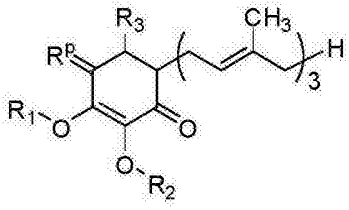
[0035] 在一些实施方案中，L 为在合适的条件下经历 SN1、SN2 或 SNi 反应的离去基团。例如，L 为卤素如 Cl、Br 或 I。在一些情况下，L 为羟基衍生的离去基团如甲苯磺酸基团或甲基磺酸基团。技术人员可遵循容易获得的已知程序使用其他合适的离去基团。

[0036] 在一些实施方案中，提供了制备其中 X 为氧、NR_5或硫的式 (IV) 的化合物的方法。例如，X 可以是 O、S、NH、NCH_3、NC_2H_5等。

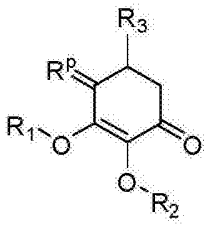
[0037] 在其他实施方案中，提供了制备其中 Y 为氧、NR_5或硫的式 (IV) 的化合物的方法。例如，Y 可以是 O、S、NH、NCH_3、NC_2H_5等。

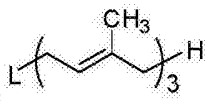
[0038] 在其他实施方案中，提供了制备其中 X 为 O 且 Y 为 O，或者 X 为 O 且 Y 为 S，或者 X 为 S 且 Y 为 O，或者 X 为 O 且 Y 为 NH，或者 X 为 NH 且 Y 为 O 的式 (IV) 的化合物的方法。

[0039] 在一些实施方案中，提供了用于制备式 IVa 的化合物的方法：



(IVa)，

该方法包括使式 V  (Va) 的烯醇或烯醇化物化合物与式

(VIa  (VIa)) 的化合物在合适的条件下反应，其中

R^P为氧代保护基团；

L 为离去基团；且

R_1、R_2和 R_3中的每一个独立地为 H 或任选取代的 C_1-C_{12}烷基。

[0040] 在一些实施方案中，提供了制备其中 R 为 H 或 -C(=O)C_1-C_8烷基且 R_1、R_2和 R_3中的每一个独立地为 H 或 C_1-C_{12}烷基的式 (IV) 或 (IVa) 的化合物的方法。

[0041] 在某些实施方案中，R 为 H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中，R_1为 H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中，R_2为 H、甲基、乙基、丙基、丁基、戊基等。在某些实施方案中，R_3为 H、甲基、乙基、丙基、丁基、戊基等。

通过亲电子剂与亲核剂反应形成共价键

[0042] 在某些实施方案中，使用各种亲电子剂或亲核剂对本文所述的化合物进行修饰以形成新的官能团或取代基。标题为“共价键及其前体的实例”的表 1 列出了用于制备修饰

化合物的共价键和前体官能团的所选非限制性实例。前体官能团显示为亲电子基团和亲核基团。

表 1 :共价键及其前体的实例

共价键产物	亲电子剂	亲核剂
羧酰胺	活化酯	胺/苯胺
羧酰胺	酰基叠氮	胺/苯胺
羧酰胺	酰基卤	胺/苯胺
酯	酰基卤	醇/酚
酯	酰基腈	醇/酚
羧酰胺	酰基腈	胺/苯胺
亚胺	醛	胺/苯胺
腙	醛或酮	肼

肟	醛或酮	羟胺
烷基胺	烷基卤	胺/苯胺
酯	烷基卤	羧酸
硫醚	烷基卤	硫醇
醚	烷基卤	醇/酚
硫醚	烷基磺酸酯	硫醇
酯	烷基磺酸酯	羧酸
醚	烷基磺酸酯	醇/酚
酯	酸酐	醇/酚
羧酰胺	酸酐	胺/苯胺
苯硫酚	芳基卤	硫醇
芳胺	芳基卤	胺
硫醚	氮丙啶(Azindines)	硫醇
硼酸酯	硼酸酯	二醇
羧酰胺	羧酸	胺/苯胺
酯	羧酸	醇
肼	酰肼	羧酸
N-酰基脲或酸酐	碳二亚胺	羧酸
酯	重氮烷	羧酸
硫醚	环氧化物	硫醇
硫醚	卤代乙酰胺	硫醇
氨基三嗪 (Ammotriazines)	卤代三嗪	胺/苯胺
三嗪基醚	卤代三嗪	醇/酚
脒	亚胺酯	胺/苯胺
脲	异氰酸酯	胺/苯胺

氨基甲酸酯	异氰酸酯	醇/酚
硫脲	异硫氰酸酯	胺/苯胺
硫醚	马来酰亚胺	硫醇
亚磷酸酯	亚磷酰胺	醇
甲硅烷基醚	甲硅烷基卤化物	醇
烷基胺	磺酸酯	胺/苯胺
硫醚	磺酸酯	硫醇
酯	磺酸酯	羧酸
醚	磺酸酯	醇
磺酰胺	磺酰卤	胺/苯胺
磺酸酯	磺酰卤	酚/醇

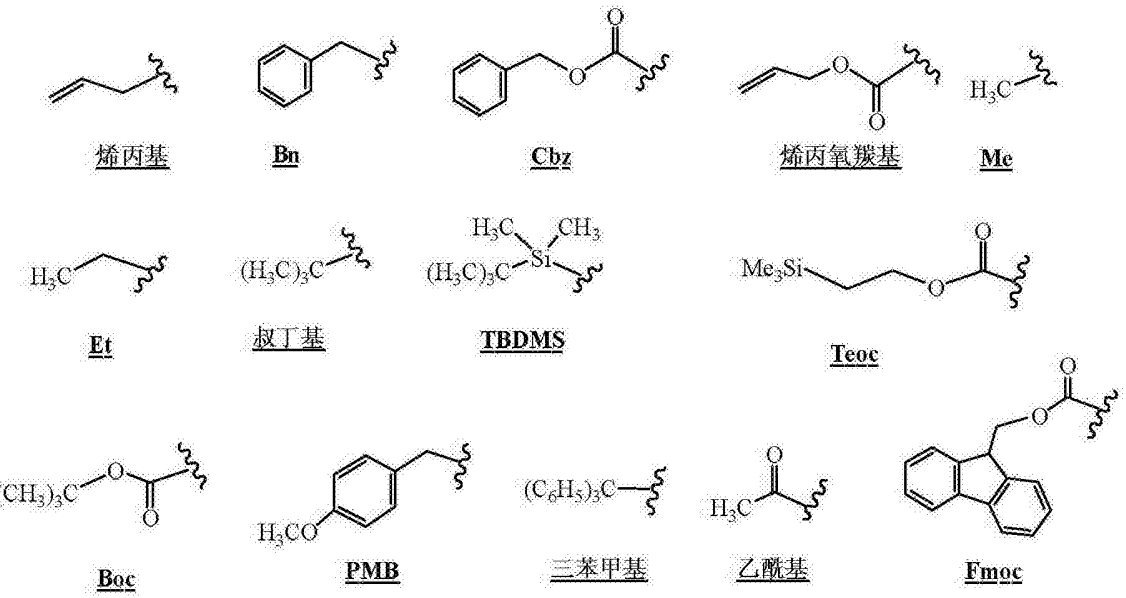
保护基团的使用

[0043] 在所描述的反应中，在某些实施方案中有必要保护反应性官能团，例如羟基、氨基、硫醇或羧基基团（其中这些在最终产物中是所期望的），以避免它们不必要地参与反应。保护基团用来封闭一些或所有反应性部分，并防止这些基团参与化学反应直至保护基团被除去。在一个实施方案中，可通过不同的手段除去各保护基团。在完全不同的反应条件下裂解的保护基团满足差异性去除的要求。在一些实施方案中，通过酸、碱和/或氢解来去除保护基团。诸如三苯甲基、二甲氧基三苯甲基、缩醛和叔丁基二甲基甲硅烷基的基团是酸不稳定的，并在某些实施方案中用于在用可通过氢解去除的 Cbz 基团和/或碱不稳定的 Fmoc 基团保护的氨基基团的存在下保护羧基和羟基反应性部分。在其他实施方案中，羧酸和羟基反应性部分在胺的存在下用碱不稳定的基团，例如但不限于甲基、乙基和乙酰基进行封端，该胺用酸不稳定的基团如氨基甲酸叔丁酯或用对酸和碱均稳定但可水解除去的氨基甲酸酯进行封端。

[0044] 在另一个实施方案中，羧酸和羟基反应性部分用可水解除去的保护基团如苄基基团进行封端，而能够与酸氢键结合的胺基团用碱不稳定的基团如 Fmoc 进行封端。在另一个实施方案中，如本文所示例的，羧酸反应性部分通过转化成简单的酯化合物而得到保护，或在又一个实施方案中，羧酸反应性部分用可氧化除去的保护基团如 2,4- 二甲氧基苄基进行封端，而共存的氨基基团用氟化物不稳定的甲硅烷基氨基甲酸酯进行封端。

[0045] 烯丙基封端基团在酸保护基团和碱保护基团的存在下是有用的，因为前者是稳定的，并任选地随后通过金属或 pi- 酸催化剂除去。例如，烯丙基封端的羧酸任选地在酸不稳定的氨基甲酸叔丁酯或碱不稳定的乙酸胺保护基团的存在下用 Pd(0) 催化的反应进行脱保护。再一种形式的保护基团是化合物或中间体附着于其上的树脂。只要残基附着于树脂上，该官能团即被封端而不能反应。一旦从树脂上释放，则官能团即可进行反应。

[0046] 一般来说，仅举例而言，封端/保护基团为：



[0047] 其他保护基团以及适用于保护基团的产生及其去除的技术的详述描述于 Greene 和 Wuts,Protective Groups in Organic Synthesis, 第 3 版 .,John Wiley&Sons,New York,NY,1999 以及 Kocienski,Protective Groups,Thieme Verlag,New York,NY,1994 中，这些文献以此公开内容通过引用并入本文。

[0048] 术语“药学上可接受的盐”是指不对其所施用的生物体引起显著的刺激并且不消除化合物的生物活性和性质的该化合物的制剂。在一些实施方案中，通过使本文提供的化合物与酸反应来获得药学上可接受的盐。还通过使本文提供的化合物与碱反应形成盐来获得药学上可接受的盐。

[0049] 本文所述的化合物可形成为和 / 或用作药学上可接受的盐。药学上可接受的盐的类型包括但不限于 :(1) 酸加成盐，其通过使化合物的游离碱形式与药学上可接受的以下酸反应而形成 :无机酸，例如，盐酸、氢溴酸、硫酸、磷酸、偏磷酸等 ;或有机酸，例如，乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、三氟乙酸、酒石酸、柠檬酸、苯甲酸、3-(4- 羟基苯甲酰) 苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1,2- 乙二磺酸、2- 羟基乙磺酸、苯磺酸、甲苯磺酸、2- 萘磺酸、4- 甲基双环 -[2.2.2] 辛 -2- 烯 -1- 甲酸、葡庚糖酸、4,4'- 亚甲基双 (3- 羟基 -2- 烯 -1- 甲酸)、3- 苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、粘康酸、丁酸、苯基乙酸、苯基丁酸、丙戊酸等 ;(2) 当母体化合物中存在的酸性质子被金属离子例如碱金属离子 (例如，锂、钠、钾)、碱土金属离子 (例如，镁或钙) 或铝离子替代时形成的盐。在一些情况下，本文所述的化合物可以与诸如但不限于乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N- 甲基葡糖胺、二环己胺、三 (羟甲基) 甲胺的有机碱配位。在其他情况下，本文所述的化合物可以与诸如但不限于精氨酸、赖氨酸等氨基酸形成盐。用来与包含酸性质子的化合物形成盐的可接受的无机碱包括但不限于氢氧化铝、氢氧化钙、氢氧化钾、碳酸钠、氢氧化钠等。

[0050] 如本文所用的术语“离去基团”可以是在有机合成中通常被称为离去基团的任何基团，例如但不限于 :卤素如氟、氯、溴和碘，烷基磺酰氧基基团如甲磺酰氧基、三氟甲磺酰氧基和乙磺酰氧基，芳基磺酰氧基基团如苯磺酰氧基和对甲苯磺酰氧基。优选的“离去基

团”是卤素，如氟、氯、溴和碘。

[0051] 应当理解，对药学上可接受的盐的提及包括其溶剂加成形式或晶体形式，特别是溶剂化物或多晶型物。溶剂化物包含化学计量或非化学计量的量的溶剂，并且可以在结晶过程中与药学上可接受的溶剂如水、乙醇等形成。当溶剂是水时形成水合物，或者当溶剂是醇时形成醇化物。本文所述化合物的溶剂化物可以在本文所述的过程中方便地制备或形成。此外，本文提供的化合物可以以非溶剂化以及溶剂化形式存在。通常，对于本文提供的化合物和方法而言，溶剂化形式被认为等同于非溶剂化形式。

[0052] 除非另有定义，本文使用的所有技术和科学术语均具有与所请求保护的主题有关的标准含义。在本文中的术语存在多种定义的情况下，以本部分中的定义为准。当提到URL或其他这样的标识符或地址时，应理解这样的标识符可能变化，且因特网上的特定信息可能时有时无，但可以通过搜索因特网找到等同信息。对此的提及证明了这样的信息的可获得性和公开传播。

[0053] 应当理解，上述一般性描述和下面的详细描述仅是示例性和说明性的，而对所请求保护的任何主题并不具有限制性。在本申请中，除非另外特别说明，否则单数的使用包括复数。必须指出，除非上下文另外明确指出，否则如在说明书和所附的权利要求书中使用的，单数形式“一个”、“一种”和“该”包括复数的指示对象。在本申请中，除非另有说明，否则“或”的使用意指“和/或”。此外，术语“包括”以及其他形式如“包含”、“含有”和“包括的”的使用并非是限制性的。

[0054] 除非另有说明，否则采用质谱法、NMR、HPLC、蛋白质化学、生物化学、重组DNA技术和药理学的常规方法。除非提供了具体的定义，否则采用与分析化学、合成有机化学以及医学和药物化学结合使用的标准命名法以及分析化学、合成有机化学以及医学和药物化学的标准实验室程序和技术。在某些情况下，标准技术用于化学合成、化学分析、药物制备、配制和递送以及患者的治疗。在某些实施方案中，标准技术用于重组DNA、寡核苷酸合成以及组织培养和转化（例如，电穿孔、脂质转染）。在一些实施方案中，例如，使用制造商试剂盒的说明书或如通常所完成的或如本文所述的那样进行反应和纯化技术。

[0055] 如在整个申请和所附权利要求书中所使用的，以下术语具有以下含义：

[0056] 如本文所用的术语“烷基”意指含有1-10个碳原子的直链、支链或环状（在这种情况下，它也被称为“环烷基”）烃。烷基的说明性实例包括但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、正戊基、异戊基、新戊基、正己基、3-甲基己基、2,2-二甲基戊基、2,3-二甲基己基、正庚基、正辛基、正壬基和正癸基。

[0057] 如本文所用的术语“C1-C6烷基”意指含有1-6个碳原子的直链、支链或环状（在这种情况下，它也被称为“环烷基”）烃。烷基的代表性实例包括但不限于甲基、乙基、正丙基、异丙基、环丙基、正丁基、仲丁基、叔丁基、环丁基、正戊基、异戊基、新戊基、环戊基和正己基。

[0058] 如本文所用的术语“烷硫基(thioalkyl)”意指通过硫原子附加至母体分子部分上的如本文所定义的烷基基团。烷硫基的说明性实例包括但不限于甲硫基、乙硫基、丁硫基、叔丁硫基和己硫基。

[0059] 如本文所用的术语“卤代”或“卤素”意指-Cl、-Br、-I或-F。

[0060] 如本文所用的，术语“亚磺酰基”指-S(=O)-R，其中R选自烷基、环烷基、芳基、杂

芳基（通过环碳键合）和杂环烷基（通过环碳键合）。

[0061] 如本文所用的，术语“磺酰基”指 -S(=O)$_2$-R，其中 R 选自烷基、环烷基、芳基、杂芳基（通过环碳键合）和杂环烷基（通过环碳键合）。

[0062] 术语“任选取代的”或“取代的”意指所提及的基团可以被单独地和独立地选自烷基、环烷基、芳基、杂芳基、杂脂环基、羟基、烷氧基、芳氧基、烷基硫基、芳基硫基、烷基亚砜、芳基亚砜、烷基砜、芳基砜、氰基、卤素、硝基、卤代烷基、氟烷基、氟烷氧基和氨基（包括单取代和二取代的氨基基团）及其保护衍生物的一个或多个另外的基团所取代。举例而言，任选的取代基可以是卤素 (halide)、-CN、-NO$_2$或 L$_s$R$_s$，其中各 L$_s$独立地选自键、-O-、-C(=O)-、-C(=O)O-、-S-、-S(=O)-、-S(=O)$_2$-、-NH-、-NHC(=O)-、-C(=O)NH-、S(=O)$_2$NH-、-NHS(=O)$_2$、-OC(=O)NH-、-NHC(=O)O- 或 -(C_1-C_6亚烷基)-；且各 R$_s$选自 H、烷基、氟烷基、杂烷基、环烷基、芳基、杂芳基或杂环烷基。可以形成上述取代基的保护衍生物的保护基团可以在诸如上述的 Greene 和 Wuts 的来源中找到。在一些实施方案中，任选的取代基选自卤素、-CN、-NH$_2$、-OH、-N(CH$_3$)$_2$、烷基、氟烷基、杂烷基、环烷基、杂环烷基、芳基、杂芳基、烷氧基、芳氧基、烷基硫基、芳基硫基、烷基亚砜、芳基亚砜、烷基砜和芳基砜。在一些实施方案中，任选的取代基是卤素、-CN、-NH$_2$、-OH、-NH(CH$_3$)、-N(CH$_3$)$_2$、烷基、氟烷基、杂烷基、烷氧基、氟烷氧基、-S- 烷基或 -S(=O)$_2$烷基。在一些实施方案中，任选的取代基选自卤素、-CN、-NH$_2$、-OH、-NH(CH$_3$)、-N(CH$_3$)$_2$、-CH$_3$、-CH$_2$CH$_3$、-CF$_3$、-OCH$_3$和 -OCF$_3$。在一些实施方案中，取代的基团被前述基团中的一个或两个所取代。在一些实施方案中，取代的基团被前述基团中的一个所取代。在一些实施方案中，脂族碳原子（无环或环状，饱和或不饱和的碳原子，不包括芳族碳原子）上的任选的取代基包括氧代（=O）。

[0063] 术语“保护的胺”指具有可去除的保护基团的胺，该保护基团针对合成过程中不希望的反应改变胺的反应性并将在随后被除去。胺保护基团的实例包括但不限于叔丁氧基羰基 (BOC)、9- 芴甲基羰基 (Fmoc)、三苯甲基 (Tr) 和苄氧羰基 (Cbz)。例如，为了保护和活化根据本发明的具有 6- 氨基部分的嘧啶环系统，可以使用双 -BOC 或双 -FMOC、CBZ、烯丙氧羰基 (alloc)、乙氧羰基 (Teoc)、甲基 / 乙基 - 氧基羰基、双 - 乙酰基或 N- 琥珀酰基或 N- 邻苯二甲酰基，以及它们的单 -N 保护的类似物。

实施例

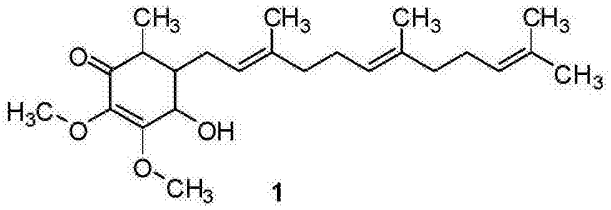
实施例 1. 由牛樟芝制备示例性环己烯酮化合物

[0064] 将 100 克来自牛樟芝的菌丝体、子实体或二者的混合物置于烧瓶中。将适量的水和醇 (70％ -100％醇溶液）加至该烧瓶中，并于 20-25℃下搅拌至少 1 小时。通过滤器和 0.45μm 滤膜过滤该溶液并收集滤液作为提取物。

[0065] 对牛樟芝的滤液进行高效液相色谱 (HPLC) 分析。在 RP18 柱上进行分离，流动相由甲醇 (A) 和 0.3％乙酸 (B) 组成，梯度条件为：在 95％ -20％ B 中 0-10min，在 20％ -10％ B 中 10-20min，在 10％ -10％ B 中 20-35min，在 10％ -95％ B 中 35-40min，流速为 1ml/min。用紫外线 - 可见光检测器监测柱的流出物。

[0066] 对在 25 至 30min 时收集的级分进行收集并浓缩，以得到 4- 羟基 -2,3- 二甲氧基 -6- 甲基 -5-(3,7,11- 三甲基十二碳 -2,6,10- 三烯基）环己 -2- 烯酮（化合物 1），一种浅黄棕色液体产物。对化合物 1 的分析显示分子式为 $C_{24}H_{38}O_4$，分子量为 390，熔点为 48 至 52℃。NMR 谱显示 ^{1}H-NMR($CDCl_3$) δ (ppm) = 1.51, 1.67, 1.71, 1.75, 1.94, 2.03, 2.07, 2.22

,2.25,3.68,4.05,5.07 和 5.14 ;^{13}C-NMR($CDCl_3$) δ (ppm) = 12.31,16.1,16.12,17.67,25.67,26.44,26.74,27.00,39.71,39.81,40.27,43.34,59.22,60.59,120.97,123.84,124.30,131.32,135.35,135.92,138.05,160.45 和 197.12。



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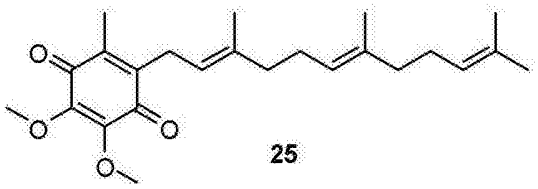
化合物 1 :4- 羟基 -2,3- 二甲氧基 -6- 甲基 -5-(3,7,11- 三甲基十二碳 -2,6,10- 三烯基) 环己 -2- 烯酮

[0067] 从在动物研究中用化合物 1 喂养的大鼠的尿液样品中获得化合物 27——化合物 1 的代谢物。化合物 27 被确定为分子量为 312($C_{16}H_{24}O_6$) 的 4- 羟基 -2,3- 二甲氧基 -6- 甲基 -5-(3- 甲基 -2- 己烯酸) 环己 -2- 烯酮。从纯化过程获得化合物 25,其被确定为 2,3- 二甲氧基 -5- 甲基 -6-((2E,6E)-3,7,11- 三甲基十二碳 -2,6,10- 三烯基) 环己 -2,5- 二烯 -1,4- 二酮 (分子量为 386.52,$C_{24}H_{34}O_4$)。



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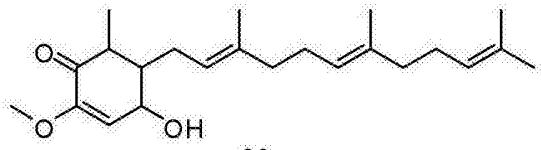
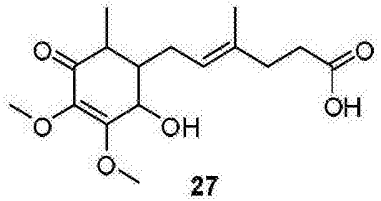
[0068] 通过纯化过程还制备了化合物 26——4- 羟基 -2- 甲氧基 -6- 甲基 -5-((2E,6E)-3,7,11- 三甲基十二碳 -2,6,10- 三烯基) 环己 -2- 烯酮,其分子量为 350.53($C_{23}H_{36}O_3$)。还制备了化合物 28。



26

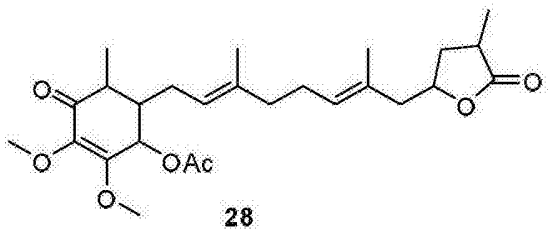
[0069] ^{1}H(500MHz ;CD_3OD) δ 1.16(3H,d,J = 6.9Hz),1.58(3H,s),1.60(3H,s),1.62(3H,s),1.65(3H,s),1.77-1.83(1H,m),1.93-2.20(2H,m),2.00-2.20(7H,m),2.23-2.31(1H,m),2.63-2.71(1H,m),3.59(3H,s),4.64(1H,dd,J = 5.5 和 3.7Hz),5.07-5.12(2H,m),5.21(1H,t,J = 7.3Hz),5.91(1H,d,J = 5.7Hz) ;^{13}C(125MHz ;CD_3OD) δ 13.1,16.2,17.8,17.8,25.9,27.4,27.8,28.2,40.9,43.4,47.5,48.5,49.8,55.3,65.0,116.6,123.3,125.3,125.4,132.1,136.0,138.1,152.0,198.7。



27

[0070] [α]$^{24}_D$ 66.9(c 0.69,MeOH) ;^{1}H(600MHz ;CD_3OD) δ 1.14(3H,d,J = 6.9Hz),1.65-1.70(1H,m),1.67(3H,s),2.24(2H,t,J = 7.4Hz),2.32(2H,t,J = 7.4Hz),2.43(2H,t,J =

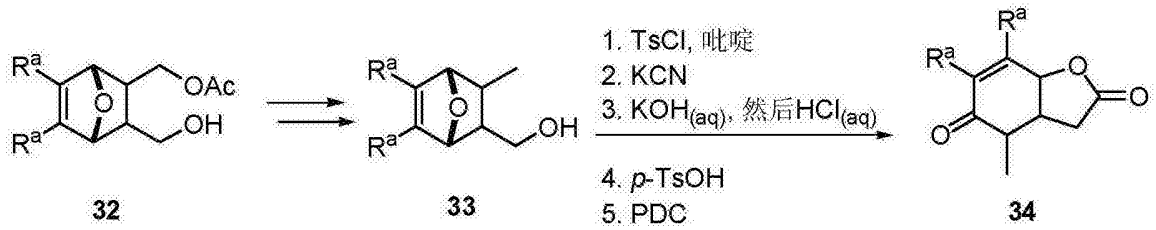
7.4Hz),2.44-2.50(m,1H),3.57(3H,s),4.04(3H,s),4.36(1H,d,J = 3.5Hz),5.29(1H,t,J = 7.1Hz);^{13}C(150MHz;CD_3OD)δ12.8,16.2,28.1,33.8,35.8,41.4,45.6,58.6,60.7,66.8,123.4,137.1,137.2,164.9,177.3,199.4。



28

[0071] EI-MS,m/z 486[M+Na]$^+$;^{1}H(600MHz;CD_3OD)δ1.19(3H,d,J = 7.0Hz),1.24(3H,d,J = 7.4Hz),1.60(3H,s),1.69(3H,s),1.93-2.00(2H,m),2.00-2.04(1H,m),2.05-2.08(2H,m),2.11(3H,s),2.13-2.20(2H,m),2.20-2.25(m,1H),2.26-2.31(2H,m),2.40(1H,dd,J = 13.8Hz 和 7.0Hz),2.50-2.56(1H,m),2.73-2.80(1H,m),3.63(3H,s),4.00(3H,s),4.69-4.74(1H,m),5.17(1H,t,J = 6.7Hz),5.31(1H,t,J = 7.0Hz),5.75(1H,d,J = 3.1Hz);^{13}C(150MHz;CD_3OD)δ13.1,16.0,16.2,16.5,20.9,27.1,28.0,35.0,35.6,40.5,42.5,44.2,45.9,60.3,61.1,70.4,78.8,122.5,129.2,131.7,138.3,138.7,160.5,171.4,182.7,199.0。

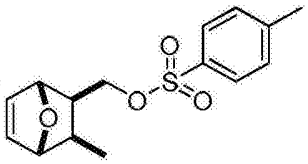
实施例2:示例性环己烯酮核心的制备



32 33 34

R^a = H,CH_3,OMe,OBn

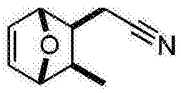
[0072] 通过已知方法(例如,J.Org.Chem.2004,69,8789-8795)由化合物32制备化合物33(R^a = H)。通过以下步骤制备示例性中间体34a(R^a = H)。可以相应地制备其他示例性核心中间体(分别为34b-d,R^a = CH_3、OMe、OBn等)。

步骤1.[(1R,2R,3R,4S)-3-甲基-7-氧杂双环[2.2.1]庚-5-烯-2-基]甲基4-甲基-苯-1-磺酸酯  的制备

[0073] 向在冰浴下的化合物21(8.3g,59mmol)在CH_2Cl_2(210mL)中的溶液中添加Et_3N(21.0mL,148mmol)、4-DMAP(1.0g,8.9mmol)和TsCl(16.9g,88.8mmol)。使混合物升温至室温并搅拌16h,用H_2O(100mL×3)和盐水(100mL)洗涤。将有机层经Na_2SO_4干燥并真空浓缩。将残余物通过硅胶柱色谱法(EtOAc:己烷,1:3,R_f 0.46)纯化,以提供呈无色油的14.8g(50.2mmol,85%)。EI-MS,m/z 317[M+Na]$^+$;[α]$^{24}_D$-14.8(c 2.34,$CHCl_3$);^{1}H(600MHz;$CDCl_3$)δ1.04(3H,d,J = 7.3Hz),1.83-1.90(1H,m),1.91-1.97(1H,m),2.51(3H,s),4.02(1H,t,J = 9.8Hz),4.22(1H,dd,J = 9.5 和 5.4Hz),4.49(1H,s),4.75(1H,s),6.32(1H,dd,J = 5.8Hz 和 1.6Hz),6.41(1H,dd,J = 5.8 和 1.6Hz),7.43(2H,d,J = 8.2Hz),7.87(2H,d,J

= 8.2Hz) ;^{13}C(150MHz ;$CDCl_3$) δ 14.1, 21.4, 33.6, 39.2, 71.0, 80.0, 84.5, 127.6, 129.7, 132.6, 134.4, 135.9, 144.7。

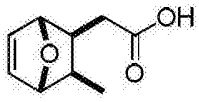
步骤 2. 2-[(1R, 2S, 3R, 4S)-3- 甲基 -7- 氧杂双环 [2.2.1] 庚 -5- 烯 -2- 基] 乙腈



的制备

[0074] 向在冰浴下的化合物 21(8.3g, 59mmol) 在 CH_2Cl_2(210mL) 中的溶液中添加 Et_3N(21.0mL, 148mmol)、4-DMAP(1.0g, 8.9mmol) 和 TsCl(16.9g, 88.8mmol)。使混合物升温至室温并搅拌 16h, 用 H_2O(100mL×3) 和盐水 (100mL) 洗涤。将有机层经 Na_2SO_4 干燥并真空浓缩。将残余物通过硅胶柱色谱法 (EtOAc: 己烷, 1:3, R_f 0.46) 纯化, 以提供呈无色油的 14.8g(50.2mmol, 85%)。EI-MS, m/z 317[M+Na]$^+$;[α]$^{24}_D$-14.8(c 2.34, $CHCl_3$) ;^{1}H(600MHz ; $CDCl_3$) δ 1.04(3H, d, J = 7.3Hz), 1.83-1.90(1H, m), 1.91-1.97(1H, m), 2.51(3H, s), 4.02(1H, t, J = 9.8Hz), 4.22(1H, dd, J = 9.5 和 5.4Hz), 4.49(1H, s), 4.75(1H, s), 6.32(1H, dd, J = 5.8Hz 和 1.6Hz), 6.41(1H, dd, J = 5.8 和 1.6Hz), 7.43(2H, d, J = 8.2Hz), 7.87(2H, d, J = 8.2Hz) ;^{13}C(150MHz ;$CDCl_3$) δ 14.1, 21.4, 33.6, 39.2, 71.0, 80.0, 84.5, 127.6, 129.7, 132.6, 134.4, 135.9, 144.7。

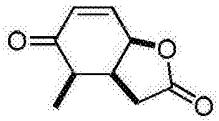
步骤 3. 2-[(1R, 2S, 3R, 4S)-3- 甲基 -7- 氧杂双环 [2.2.1] 庚 -5- 烯 -2- 基] 乙酸



的制备

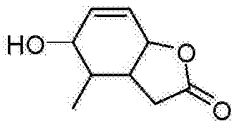
[0075] 将在步骤 2 中制备的腈 (6.7g, 45mmol) 在 1N 氢氧化钾溶液 (480mL, 480mmol) 中加热至回流 4h。4h 后, 浓缩该混合物。使残余物在冰浴中冷却, 用浓 $HCl_{(水溶液)}$ 酸化至 pH 1, 并用 EtOAc(300mL×3) 萃取。将合并的有机部分经 Na_2SO_4 干燥并真空浓缩以产生酸 (7.4g, 44mmol, 98%)。TLC R_f 0.63(EtOAc: 己烷, 2:1) ;EI-MS, m/z 191[M+Na]$^+$;[α]$^{24}_D$-7.03(c 1.95, $CHCl_3$) ;^{1}H(600MHz ;$CDCl_3$) δ 1.00(3H, d, J = 7.3Hz), 1.77-1.84(1H, m), 1.98-2.04(1H, m), 2.39(1H, dd, J = 16.9 和 10.0Hz), 2.51(1H, dd, J = 16.9 和 5.4Hz), 4.45(1H, s), 4.65(1H, s), 6.31(2H, s) ;^{13}C(150MHz ;$CDCl_3$) δ 15.3, 33.5, 34.0, 35.9, 82.8, 84.8, 135.1, 135.6, 179.2。

步骤 4. (3aS, 4R, 7aR)-4- 甲基 -2, 3, 3a, 4, 5, 7a- 六氢 -1- 苯并呋喃 -2, 5- 二酮



34a 的制备

[0076] 将从步骤 3 得到的酸 (500mg, 2.97mmol) 和 p-TSA(57mg, 0.30mmol) 在甲苯 (20mL) 中的溶液在 100℃加热 3h。3h 后, 将混合物真空浓缩以得到羟基内酯化合物 35a(450mg) ; TLC R_f 0.46(EtOAc: 己烷, 2:1) ;EI-MS, m/z 191[M+Na]$^+$。

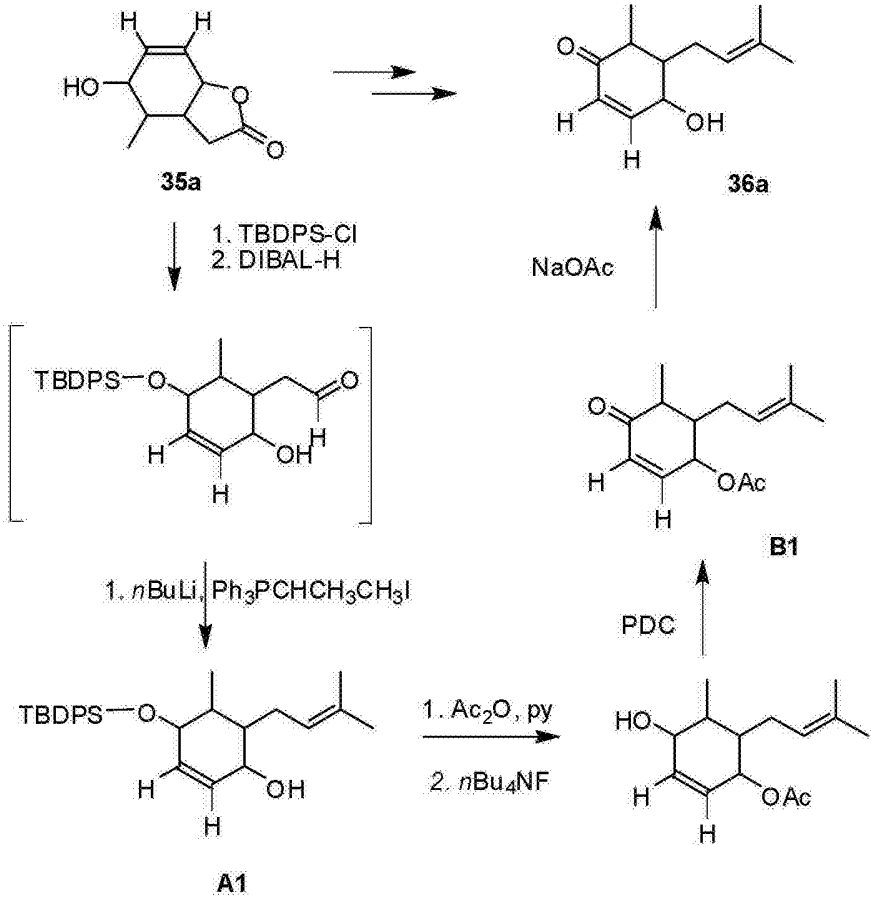


(35a)

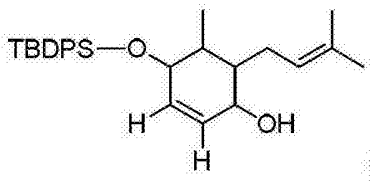
[0077] 向粗羟基内酯 35a(450mg) 在 CH_2Cl_2(15mL) 中的搅拌溶液中添加 PDC(2.0g, 5.4mmol)。将混合物在室温下搅拌过夜, 用 EtOAc(30mL) 稀释, 并过滤。将残余物真空浓缩并通过硅胶柱色谱法 (EtOAc: 己烷, 1:1, TLC R_f 0.38) 纯化以提供呈白色固体的化合物 34a, 294mg(1.77mmol, 60 %, 2 步) ;EI-MS, m/z 189[M+Na]$^+$;[α]$^{24}_D$-269.3(c

2.03, $CHCl_3$) ; ^1H(600MHz ; $CDCl_3$) δ 1.15(3H, d, J = 6.9Hz), 2.17(1H, dd, J = 17.4 和 12.7Hz), 2.53(1H, dd, J = 17.4 和 8.5Hz), 2.78(1H, dd, J = 6.7 和 5.5Hz), 3.26-3.35(1H, m), 5.32(1H, dt, J = 7.2 和 1.9Hz), 6.18(1H, dd, J = 10.3 和 1.3Hz), 6.68(1H, dt, J = 10.3 和 1.9Hz) ; ^{13}C(150MHz ; $CDCl_3$) δ 12.9, 29.6, 41.1, 75.2, 131.1, 141.1, 174.4, 197.7。

实施例 3 : 由内酯 35a 制备示例性化合物 36a



[0078] 由化合物 35a 按以下步骤制备化合物 36a。首先用叔丁基二苯基氯硅烷 (TBDPS-Cl)(也可以使用对强碱性条件呈惰性的其他非限制性示例性的合适的羟基保护基团, 例如, MOM、MEM、THP 保护基团等) 保护羟基基团。然后将所得化合物首先通过 DIBAL-H 还原, 并随后在碱性条件 (n-BuLi) 下与 $Ph_3PCH(CH_3)(CH_3)I$ 反应 (Wittig 反应) 以得到中间体 A1。首先用乙酸基团 (条件 : Ac_2O, 吡啶) 保护中间体 A1 的羟基基团, 并随后用 n-Bu_4NF 除去甲硅烷基保护基团 TBDPS。随后用 PDC 氧化裸露的羟基基团以得到化合物 B1。对乙酸基团的脱保护得到化合物 36a。可以类似地制备一系列的化合物 36。



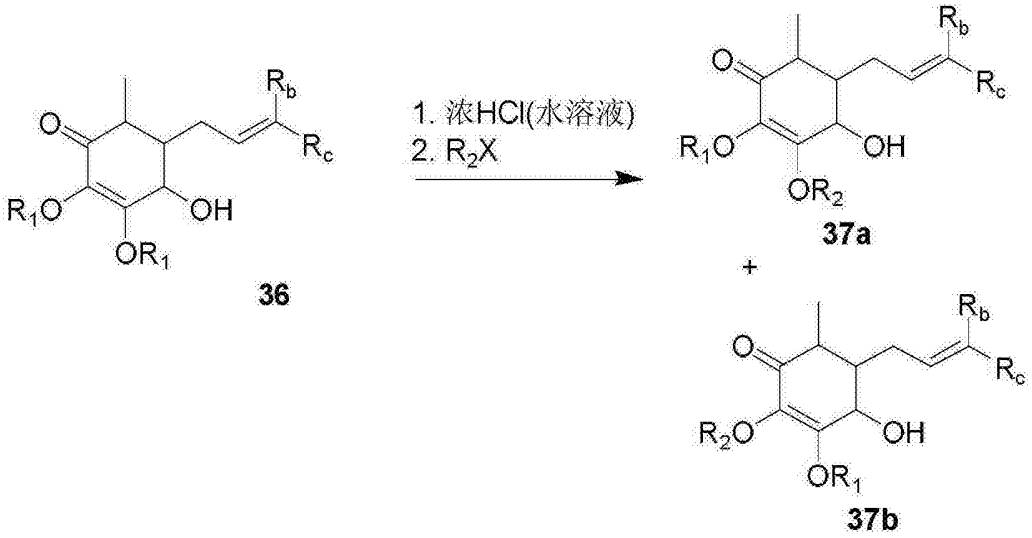
(A1)

[0079] ^1H(600MHz ; CD_3Cl) δ 0.77(3H, d, J = 7.3Hz), 1.07(9H, s), 1.65(3H, s), 1.73(3H, s), 1.84-1.90(1H, m), 2.02-2.10(1H, m), 2.21-2.28(2H, m), 3.93(1H, t, J = 4.0Hz), 4.18(1H, br), 5.20-5.25(1H, m), 5.66(1H, dd, J = 9.9Hz 和 4.5Hz), 5.85(1H, dd, J = 9.9Hz 和

4.0Hz),7.37-7.41(4H,m),7.42-7.46(2H,m),7.66-7.70(4H,m)。

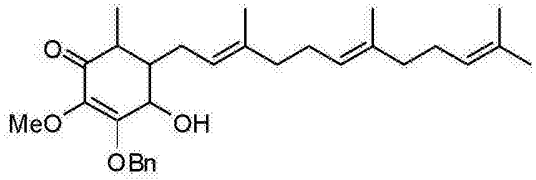
实施例 4:由化合物 36 制备示例性化合物 37a 和 37b

[0080] 通过与 R_2X(X 为离去基团如卤素或甲苯磺酸基)和浓 HCl 水溶液反应制备所需化合物 37a 和 37b。



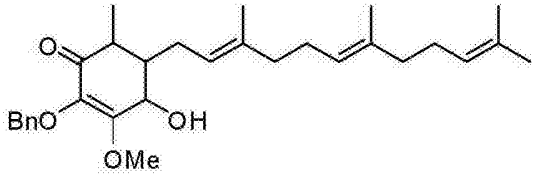
[0081] 相应地制备以下化合物。

化合物 31:3-(苄氧基)-4-羟基-2-甲氧基-6-甲基-5-[(2E,6E)-3,7,11-三甲基十二碳-2,6,10-三烯-1-基]环己-2-烯-1-酮



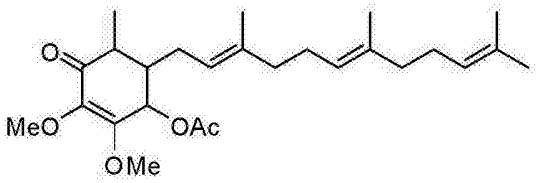
[0082] 向冷却至 0℃的在 MeOH 50mL 中的 (4S,5S,6S)-4-羟基-2,3-二甲氧基-6-甲基-5-[(2E,6E)-3,7,11-三甲基十二碳-2,6,10-三烯-1-基]环己-2-烯-1-酮 (10.0g,25.6mmol) 中添加浓 $HCl_{(水溶液)}$(22.5mL,270mmol)。将反应在室温下搅拌 30min。30min 后,将混合物真空浓缩。将残余物用 EtOAc(100mL) 稀释,用饱和 $NaHCO_3$(50mL×3) 和盐水 (50mL) 洗涤,经 Na_2SO_4 干燥,过滤,浓缩并通过硅胶柱色谱法 (EtOAc: 己烷,1:5,TLC R_f 0.26) 纯化以得到产物 3.0g(6.4mmol,25%);EI-MS,m/z 489$[M+Na]^+$;$[\alpha]^{24}_D$+18.6(c 2.19,$CHCl_3$);^1H(500MHz;$CDCl_3$) δ 1.16(3H,d,J = 7.0Hz),1.59(6H,s),1.64(3H,s),1.67(3H,s),1.73-1.75(1H,m),1.94-2.00(2H,m),2.00-2.09(7H,m),2.21-2.24(2H,m),2.52-2.56(1H,m),3.66(3H,s),4.35(1H,t,J = 3.6Hz),5.05-5.10(2H,m),5.12(1H,t,J = 7.0Hz),5.28(1H,d,J = 11.9Hz),5.44(1H,d,J = 11.9Hz),7.34-7.39(5H,m);^{13}C(125MHz;$CDCl_3$) δ 12.4,16.0,16.1,17.7,25.7,26.5,26.7,26.9,39.7,39.8,40.4,43.4,60.4,68.1,73.4,121.0,123.9,124.3,127.8,128.4,128.6,131.2,135.2,136.3,136.8,137.9,159.8,197.3。

化合物 30:2-(苄氧基)-4-羟基-3-甲氧基-6-甲基-5-[(2E,6E)-3,7,11-三甲基十二碳-2,6,10-三烯-1-基]环己-2-烯-1-酮



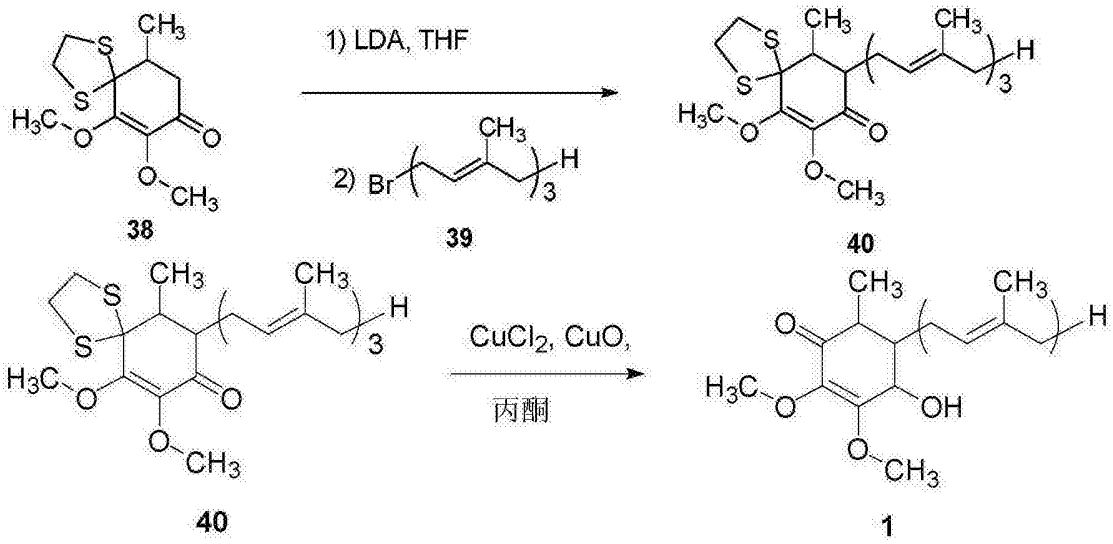
[0083] 6.1g(13mmol,50 %) ;TLC R_f0.26(EtOAc: 己 烷,1:5) ;EI-MS,m/z489[M+Na]$^+$; [α]$^{24}_D$-8.04(c 2.04,$CHCl_3$) ;^{1}H(600MHz ;$CDCl_3$) δ 1.28(3H,d,J = 7.3Hz),1.49(3H,s),1.55(3H,s),1.57(3H,s),1.65(s,3H),1.67-1.77(m,1H),1.90-1.99(2H,m),1.94-1.99(2H,m),1.99-2.05(4H,m),2.05-2.10(1H,m),2.21-2.23(1H,m),2.61-2.65(1H,m),3.57(1H,br),3.67(3H,s),4.97-5.00(1H,m),5.03-5.06(2H,m),5.19(1H,d,J = 11.9Hz),5.46(1H,d,J = 11.9Hz),7.32-7.36(5H,m) ;^{13}C(150MHz ;$CDCl_3$) δ 15.9,16.0,17.6,17.7,24.0,25.6,26.4,26.7,35.4,39.6,39.7,44.9,60.5,70.8,73.4,121.8,123.9,124.3,127.7,128.4,128.6,131.2,133.7,135.1,136.5,137.9,165.7,195.1。

化合物29:2,3-二甲氧基-5-甲基-4-氧代-6-[(2E,6E)-3,7,11-三甲基十二碳-2,6,10-三烯-1-基]环己-2-烯-1-基乙酸酯



[0084] 向冷却至0℃的在吡啶5mL中的(4S,5S,6S)-4-羟基-2,3-二甲氧基-6-甲基-5-[(2E,6E)-3,7,11-三甲基十二碳-2,6,10-三烯-1-基]环己-2-烯-1-酮(500mg,1.38mmol)中添加乙酸酐(300μL,3.19mmol)。将反应在室温下搅拌4h。4h后,将混合物用EtOAc(20mL)稀释,用1N HCl(水溶液)(10mL×2)、饱和$NaHCO_3$(10mL×2)、盐水(20mL)洗涤,经Na_2SO_4干燥,过滤,浓缩并通过硅胶柱色谱法(EtOAc:己烷,1:3,TLC R_f 0.56)纯化以得到产物404mg(0.934mmol,68 %) ;EI-MS,m/z 433[M+H]$^+$;^{1}H(500MHz ;$CDCl_3$) δ 1.19(3H,d,J = 7.0Hz),1.56(3H,s),1.59(6H,s),1.66(3H,s),1.83-1.90(1H,m),1.92-2.10(10H,m),2.08(3H,s),2.20-2.38(1H,m),2.48-2.56(1H,m),3.66(3H,s),3.98(3H,s),5.06-5.13(3H,m),5.74(1H,d,J = 3.2Hz)。

实施例5:通过烯醇化反应制备示例性化合物1



[0085] 由2,3-二甲氧基-5-甲基环己-2-烯-1,4-二酮制备化合物38。在反应烧瓶中，在低温下将化合物38缓慢地添加至LDA的THF溶液中。在形成烯醇化物后，将化合物39在惰性气体条件下缓慢地添加至反应混合物中。将反应在低温下用水猝灭并纯化以得到化合物40。用合适的试剂如在丙酮中的$CuCl_2$、CuO对化合物40进行脱保护以得到化合物1。

实施例6：测定示例性环己烯酮化合物25-31相对于化合物1的细胞毒性作用

[0086] 使用细胞计数试剂盒-8(Cell Counting Kit-8)(CCK-8,Enzo Life Sciences,Farmingdale,NY)测量细胞活力。在该试验中，细胞中的脱氢酶还原WST-8以产生黄色产物（甲臜），该产物在培养基中可溶。生成的甲臜的量与活细胞数成正比。处理后，将CCK-8溶液添加到各孔中并温育4h。使用分光光度计在450nm的吸收波长下测量甲臜的浓度。细胞活力表示为相对于相应对照的百分比。

[0087] 为了确定化合物1的细胞毒性作用是否与Ras突变的存在相关，使用具有野生型Ras(H838、Hep3B和K562)或突变Ras(A549、HepG2和THP-1)的来源于人肺癌(A549和H838)、肝癌(HepG2和Hep3B)和白血病(K562和THP-1)的细胞系。在化合物1处理48h后测量细胞活力。细胞系以及它们按递增顺序排列的IC_{50}为THP-1(2.22μM)<A549(3.24μM)<H838(3.32μM)<Hep3B(3.74μM)<K562(5.12μM)<HepG2(6.42μM)（参见表1）。

[0088] 接着，在H838细胞中测定化合物1类似物（化合物29、30和31）、代谢物（化合物27）以及从丝状牛樟芝分离的类似物（化合物25、26、28）的IC_{50}值。结果表明，化合物1的2'-羟基基团和法尼基基团对于其细胞毒性作用至关重要。此外，化合物31比化合物1的细胞毒性甚至更强（表1）。

[0089] 表1. 通过CCK-8细胞活力试验测定的式X的示例性化合物的IC_{50}值。

化合物	A549	H838	Hep3B	HepG2	K562	THP-1
1	3.24±0.35	2.96±0.05	3.74±0.35	6.42±0.08	5.12±0.83	2.22±0.03
25	-	22.56±6.45	-	-	-	-
26	-	11.34±4.17	-	-	-	-
27	-	>100	-	-	-	-
28	-	>100	-	-	-	-
29	-	>100	-	-	-	-
30	22.61±2.24	25.56±6.54	9.06±3.03	27.03±6.06	-	-
31	6.68±0.75	3.41±1.43	7.46±7.06	8.98±0.97	-	-

数值表示为平均值 ±S.E.M。

[0090] 尽管本文中已经示出并描述了本发明的优选实施方案，但对于本领域技术人员显而易见的是，这些实施方案仅以示例的方式提供。本领域技术人员在不脱离本发明的情况下现将想到多种变化、改变和替代。应当理解，本文中所述的本发明实施方案的各种替代方案可用于实施本发明。目的在于以下述权利要求限定本发明的范围，并由此涵盖这些权利要求范围内的方法和结构及其等同项。