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(54) Title: STEREOSELECTIVE REDUCTION OF TRITERPENONES

(57) Abstract: The present invention provides for methods of selectively converting triterpen-3-ones to the corresponding triterpen-3-ols. The selectivity of the methods is at least about 80% of the beta-isomer, at the C-3 position. Specifically, the present invention provides for methods of preparing betulinic acid, lupeol, betulin, allobetulin, and oleanan-3- β -ol-28,19-lactone from betulonic acid, lupeone, betulone, allobetulone and oleanan-3- β -one-28,19-lactone, respectively.



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STEREOSELECTIVE REDUCTION OF TRITERPENONES

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Related Applications

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Serial No. 60/688,739, filed June 8, 2005, which is incorporated herein by reference.

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Background of the Invention

Currently, there is a need for methods of preparing triterpenes such as betulinic acid, lupeol, betulin, allobetulin, and oleanan-3- β -ol-28,19-lactone. Additionally, there is a need for methods of selectively converting triterpen-3-ones to the corresponding triterpen-3-ols. Such methods would employ relatively inexpensive, nontoxic and environmentally safe reagents and solvents, compared to known methods.

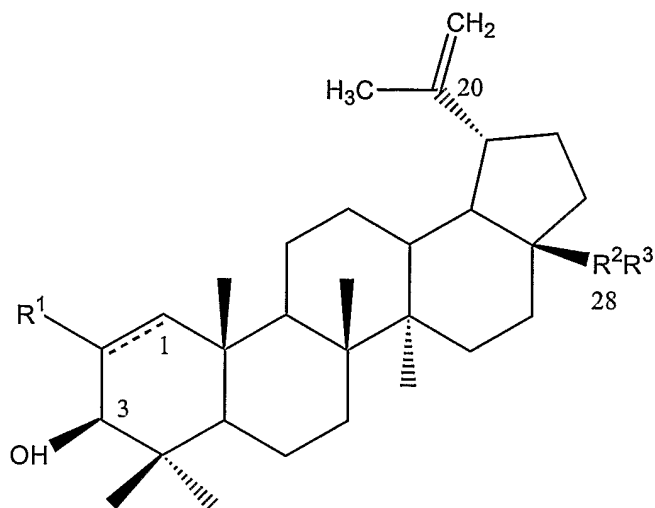
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Summary of the Invention

The present invention provides for methods of preparing betulinic acid, lupeol, betulin, allobetulin, and oleanan-3- β -ol-28,19-lactone. The selectivity of the methods is at least about 80% of the beta-isomer, at the C-3 position. Additionally, the present invention provides for methods of selectively converting triterpen-3-ones to the corresponding triterpen-3-ols. Such methods employ relatively inexpensive, nontoxic and environmentally safe reagents and solvents, compared to known methods.

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The present invention provides a method for preparing a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, wherein

R^1 is hydrogen or hydroxy;

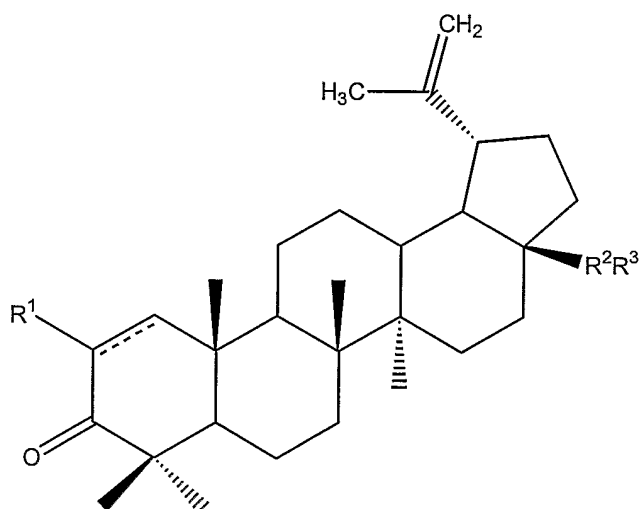
5 R^2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, (C₆-C₁₀)aryl, or (C₁-C₆)alkyl;

R^3 is hydrogen, hydroxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl, O=P(OH)₂, O=P(OH)₂OP(O)(OH)-, (C₁-C₅)alkanoyl, Si(R)₃ wherein each R is H, phenyl or (C₁-C₆)alkyl, C(O)N(R)₂, benzyl, benzoyl, tetrahydropyran-2-yl,

10 1-[(C₁-C₄)alkoxy](C₁-C₄)alkyl, or a glycoside;

or a pharmaceutically acceptable salt thereof;

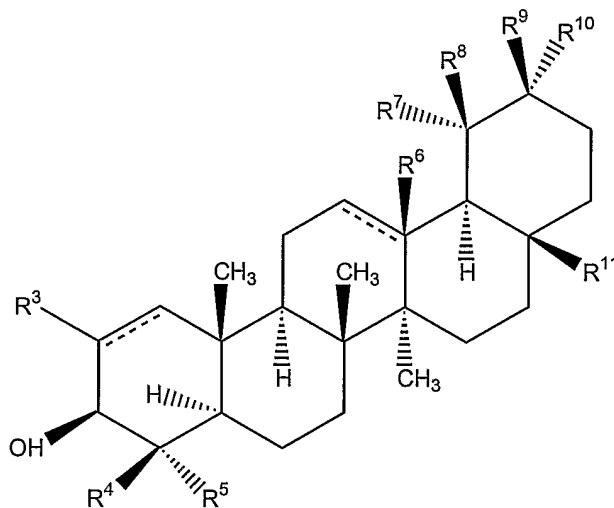
the method comprising contacting a metal alcoholate and a compound of formula (II):



(II)

for a period of time effective to provide the compound of formula (I).

The present invention also provides a method for preparing a compound of formula (III):



5

(III)

or a pharmaceutically acceptable salt, wherein

R^3 is hydrogen, halo, carboxy, mercapto, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or $-O-Y$;

R^4 and R^5 are each independently hydrogen, (C_1-C_6) alkyl, or hydroxy (C_1-C_6) alkyl;

R^6 is hydrogen or is absent when the adjacent --- is a bond;

R^7 is hydrogen or (C_1-C_6) alkyl;

R^8 is hydrogen, (C_1-C_6) alkyl, or hydroxy (C_1-C_6) alkyl and R^{11} is hydrogen, (C_1-C_6) alkyl, carboxy, or hydroxy (C_1-C_6) alkyl; or R^8 and R^{11} together are $-O-C(=X)-$;

R^9 and R^{10} , are each independently hydrogen or (C_1-C_6) alkyl;

each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo ($=O$) or thioxo ($=S$);

each Y is independently H, aryl, $P(O)(Cl)_2$, (C_3-C_8) cycloalkyl, adamantyl, $-SO_2R_a$, $O=P(R_b)_2$, $O=P(R_c)_2OP(O)(R_d)-$, $Si(R_e)_3$, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and $-N(R_f)-$; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo ($=O$), hydroxy, carboxy, halo,

mercapto, nitro, $-N(R_g)(R_h)$, (C_3-C_8) cycloalkyl, (C_3-C_8) cycloalkyloxy, aryl, aryloxy, adamantyl, adamantyloxy, hydroxyamino, trifluoroacetylamino, glycoside, amino acid, or peptide groups; and wherein said chain may optionally be saturated or unsaturated (e.g. containing one, two, three or more, double or

5 triple bonds);

R_a is (C_1-C_6) alkyl or aryl;

R_b , R_c , and R_d are each independently hydroxy, (C_1-C_6) alkoxy, hydroxy (C_2-C_6) alkoxy, adamantyloxy, adamantyl (C_1-C_6) alkoxy, norbornyloxy, 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy (C_1-C_6) alkoxy, 2,3-

10 epoxypropyloxy, benzyloxy, (C_3-C_8) cycloalkyloxy, NR_xR_y , or aryloxy;

R_e is H, aryl or (C_1-C_6) alkyl;

R_f is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, phenyl or benzyl;

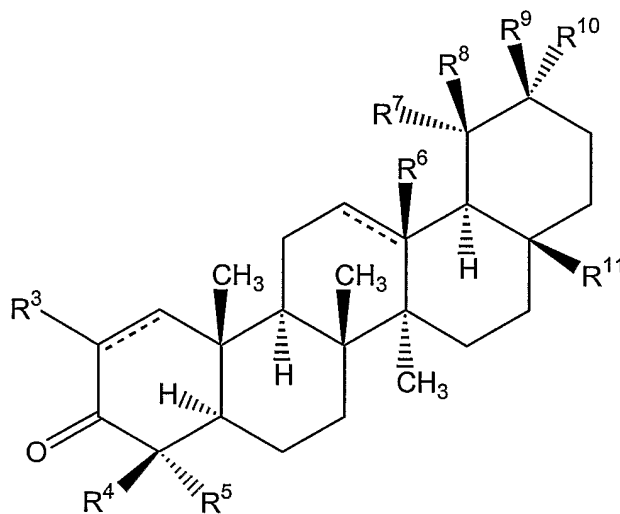
R_g and R_h are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, adamantyl, adamantyl $(C_1-$

15 $C_6)$ alkyl, amino (C_1-C_6) alkyl, aminosulfonyl, (C_1-C_6) alkanoyl, aryl and benzyl; or R_g and R_h together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, aryl or benzyl;

20 or a pharmaceutically acceptable salt thereof.

the method comprising contacting a metal alcoholate and a compound of formula (IV):



(IV)

for a period of time effective to provide the compound of formula (III).

Detailed Description of the Invention

As used herein, the following terms and expressions have the indicated meanings. It will be appreciated that the methods of the present invention can employ and/or provide compounds that can contain asymmetrically substituted carbon atoms, and can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials.

All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. The processes to prepare or manufacture compounds useful in the present invention are contemplated to be practiced on at least a multigram scale, kilogram scale, multikilogram scale, or industrial scale. Multigram scale, as used herein, is preferably the scale wherein at least one starting material is present in 10 grams or more, more preferably at least 50 grams or more, even more preferably at least 100 grams or more. Multikilogram scale, as used herein, is intended to mean the scale wherein more than one kilogram of at least one starting material is used. Industrial scale as used herein is intended to mean a scale which is other than a laboratory scale and which is sufficient to supply product sufficient for either clinical tests or distribution to consumers.

One diastereomer of a compound disclosed herein may display superior activity compared with the other. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Tucker, et al., J. Med. Chem., 37:2437 (1994). A chiral compound described herein may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g. Huffman, et al., J. Org. Chem., 60:1590 (1995).

The present invention is intended to include all isotopes of atoms occurring on the compounds useful in the present invention. Isotopes include those atoms having the same atomic number but different mass numbers. By

way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 (^{13}C) and C-14 (^{14}C).

Definitions

5 As used herein, “pharmaceutically acceptable salts” refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as
10 carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric
15 and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

20 The pharmaceutically acceptable salts of the compounds useful in the present invention can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an
25 organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985), the disclosure of which is hereby incorporated by reference.

30 The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the

tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

“Stable compound” and “stable structure” are meant to indicate a
5 compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated by the present invention.

“Substituted” is intended to indicate that one or more hydrogens on the atom indicated in the expression using “substituted” is replaced with a selection
10 from the indicated group(s), provided that the indicated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl,
15 alkylsulfonyl and cyano. When a substituent is keto (i.e., =O) or thioxo (i.e., =S) group, then 2 hydrogens on the atom are replaced.

The term “alkyl” refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more
20 preferably 1 to 30 carbon atoms, and even more preferably 1 to 26 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, stearyl, octyl, decyl, lauryl, myristyl, palmityl, and the like.

The alkyl can optionally be substituted with one or more alkoxy, halo,
25 haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR_xR_x or COOR_x , wherein each R_x is independently H or alkyl.

30 The alkyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), sulfonyl (SO) or sulfoxide (SO₂).

The alkyl can optionally be at least partially unsaturated, thereby providing an alkenyl or alkynyl.

The term "alkoxy" refers to the groups alkyl-O-, where alkyl is defined herein. Preferred alkoxy groups include, e.g., methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The alkoxy can optionally be substituted with one or more alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Preferred aryls include phenyl, naphthyl and the like.

The aryl can optionally be substituted with one or more alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The cycloalkyl can optionally be substituted with one or more alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano.

The cycloalkyl can optionally be at least partially unsaturated, thereby providing a cycloalkenyl.

The term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

5 "Haloalkyl" refers to alkyl as defined herein substituted by 1-4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12,12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, and the like.

 The term "heteroaryl" is defined herein as a monocyclic, bicyclic, or
10 tricyclic ring system containing one, two, or three aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio,
15 alkylsulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include, but are not limited to, 2*H*-pyrrolyl, 3*H*-indolyl, 4*H*-quinoliziny, 4*nH*-carbazolyl, acridinyl, benzo[*b*]thienyl, benzothiazolyl, β -carbolinyl, carbazolyl, chromenyl, cinnaoliny, dibenzo[*b,d*]furanyl, furazanyl, furyl, imidazolyl, imidizolyl, indazolyl, indolisiny, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl,
20 isothiazolyl, isoxazolyl, naphthyridinyl, naphtho[2,3-*b*], oxazolyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidinyl, pyrrolyl, quinazoliny, quinolyl, quinoxaliny, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, triazolyl, and xanthenyl. In one embodiment the term "heteroaryl" denotes a
25 monocyclic aromatic ring containing five or six ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from the group non-peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, alkyl, phenyl or benzyl. In another embodiment heteroaryl denotes an ortho-fused bicyclic
30 heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, or tetramethylene diradical thereto.

The heteroaryl can optionally be substituted with one or more alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano.

The term "heterocycle" refers to a saturated or partially unsaturated ring system, containing at least one heteroatom selected from the group oxygen, nitrogen, and sulfur, and optionally substituted with alkyl or C(=O)OR^b, wherein R^b is hydrogen or alkyl. Typically heterocycle is a monocyclic, bicyclic, or tricyclic group containing one or more heteroatoms selected from the group oxygen, nitrogen, and sulfur. A heterocycle group also can contain an oxo group (=O) attached to the ring. Non-limiting examples of heterocycle groups include 1,3-dihydrobenzofuran, 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2*H*-pyran, 2-pyrazoline, 4*H*-pyran, chromanyl, imidazolidinyl, imidazoliny, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuclidine, and thiomorpholine.

The heterocycle can optionally be substituted with one or more alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

Another class of heterocyclics is known as "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating units of the formula $[-(\text{CH}_2)_a\text{A}-]$ where a is equal to or greater than 2, and A at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, $[-(\text{CH}_2)_3\text{-NH-}]_3$, $[-((\text{CH}_2)_2\text{-O})_4\text{-}((\text{CH}_2)_2\text{-NH})_2]$ and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "alkanoyl" refers to $\text{C}(=\text{O})\text{R}$, wherein R is an alkyl group as previously defined.

The term "acyloxy" refers to $-\text{O}-\text{C}(=\text{O})\text{R}$, wherein R is an alkyl group as previously defined. Examples of acyloxy groups include, but are not limited to, acetoxo, propanoyloxy, butanoyloxy, and pentanoyloxy. Any alkyl group as defined above can be used to form an acyloxy group.

The term "alkoxycarbonyl" refers to $\text{C}(=\text{O})\text{OR}$, wherein R is an alkyl group as previously defined.

The term "amino" refers to $-\text{NH}_2$, and the term "alkylamino" refers to $-\text{NR}_2$, wherein at least one R is alkyl and the second R is alkyl or hydrogen. The term "acylamino" refers to $\text{RC}(=\text{O})\text{N}$, wherein R is alkyl or aryl.

The term "oxy" refers to $-\text{O}-$ and the term "thio" refers to $-\text{S}-$.

As to any of the above groups, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

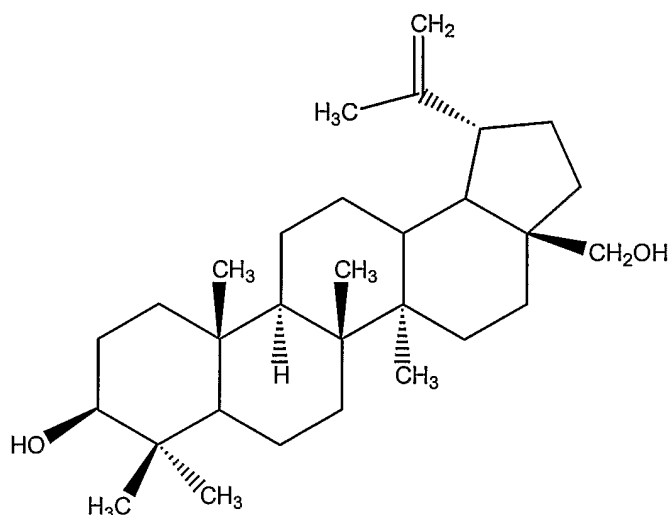
Selected substituents within the compounds described herein are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log

P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

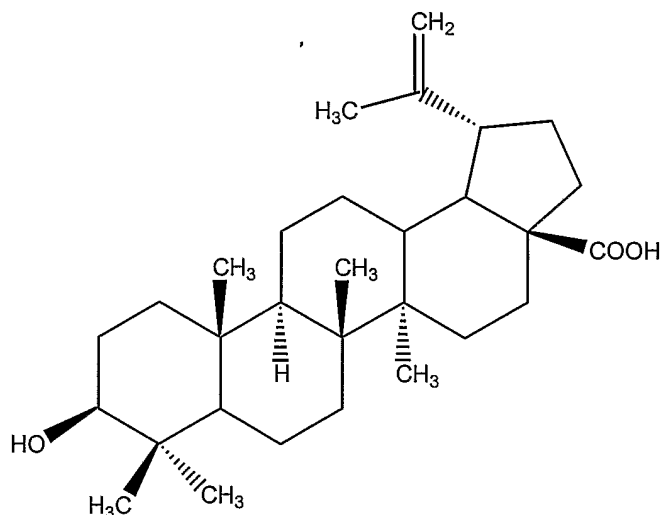
Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

As used herein, "triterpene" or "triterpenoid" refers to a plant secondary metabolite that includes a hydrocarbon, or its oxygenated analog, that is derived from squalene by a sequence of straightforward cyclizations, functionalizations, and sometimes rearrangement. Triterpenes or analogues thereof can be prepared by methods known in the art, i.e., using conventional synthetic techniques or by isolation from plants. Suitable exemplary triterpenes and the biological synthesis of the same are disclosed, e.g., in R.B. Herbert, The Biosynthesis of Secondary Plant Metabolites, 2nd. ed. (London: Chapman 1989). The term "triterpene" refers to one of a class of compounds having approximately 30 carbon atoms and synthesized from six isoprene units in plants and other organisms. Triterpenes consist of carbon, hydrogen, and optionally oxygen. Most triterpenes are secondary metabolites in plants. Most, but not all, triterpenes are pentacyclic. Examples of triterpenes include betulin, allobetulin, lupeol, friedelin, and all sterols, including lanosterol, stigmasterol, cholesterol, β -sitosterol, and ergosterol.

As used herein, "betulin" refers to 3 β ,28-dihydroxy-lup-20(29)-ene. Betulin is a pentacyclic triterpenoid derived from the outer bark of paper birch trees (*Betula papyrifera*, *B. pendula*, *B. verucosa*, etc.). The CAS Registry No. is 473-98-3. It can be present at concentrations of up to about 24% of the bark of white birch. Merck Index, twelfth edition, page 1236 (1996). Structurally, betulin is shown below:

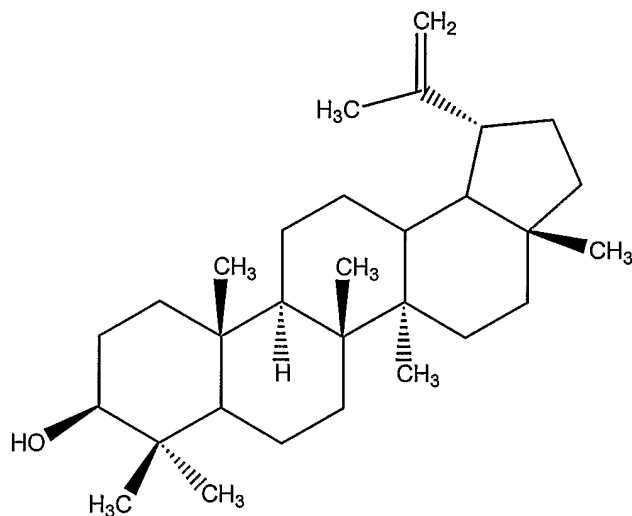


As used herein, "betulinic acid" refers to 3(β)-hydroxy-20(29)-lupaene-28-oic acid; 9-hydroxy-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-eicosahydro-cyclopenta[a]chrysene-3a-carboxylic acid. The CAS Registry No. is 472-15-1. Structurally, betulinic acid is shown below:

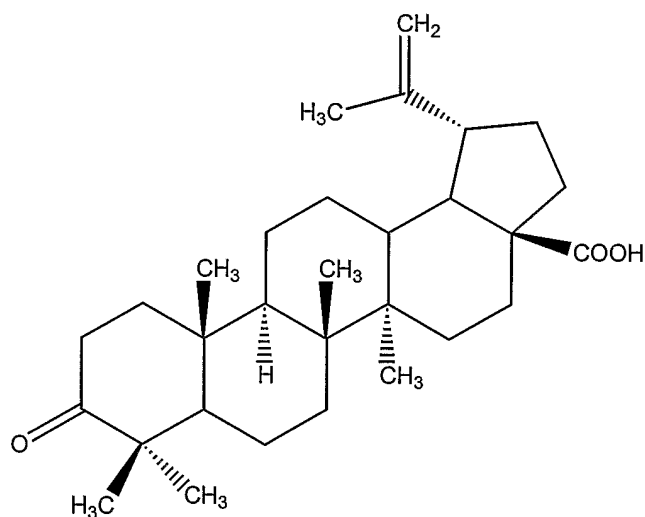


As used herein, "lupeol" refers to lup-20 (29)-en-3 β -ol. Lupeol is also found in birch bark and in other plant sources. Lupeol is present at concentrations of about 1.5-3% of the birch bark and at up to about 8.2% in

Canavalia ensiformis, a plant widespread in the humid tropics of Asia and Africa. Structurally, lupeol is shown below:

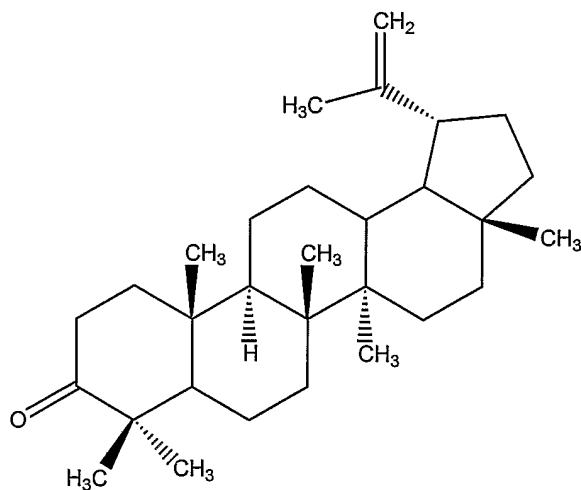


As used herein, “belulonic acid” refers to a compound of the formula

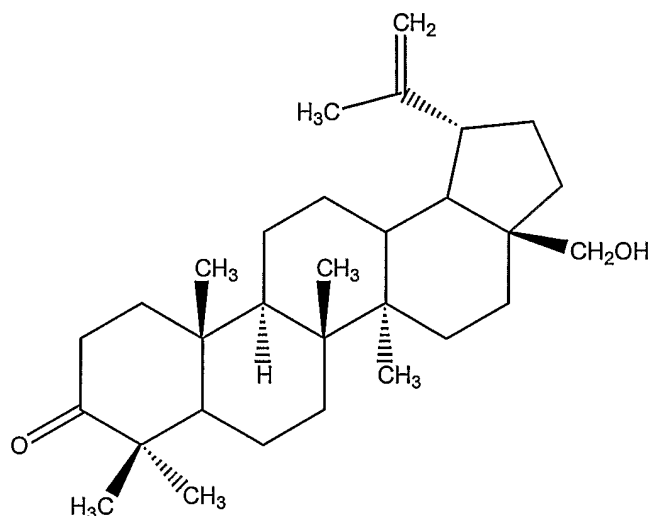


5

As used herein, “lupeone” refers to a compound of the formula



As used herein, "betulone" refers to a compound of the formula



As used herein, "amino acid" refers to the residues of the natural amino acids (e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citrulline, α -methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g. acetyl or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (e.g. as a (C₁-C₆)alkyl, phenyl or benzyl ester or amide; or as an α -methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, T.W. Greene, *Protecting Groups In Organic Synthesis*; Third Edition, Wiley: New York, 1999, and references cited therein). An amino acid can be linked to the remainder of a compound of formula (I)-(VI) through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine.

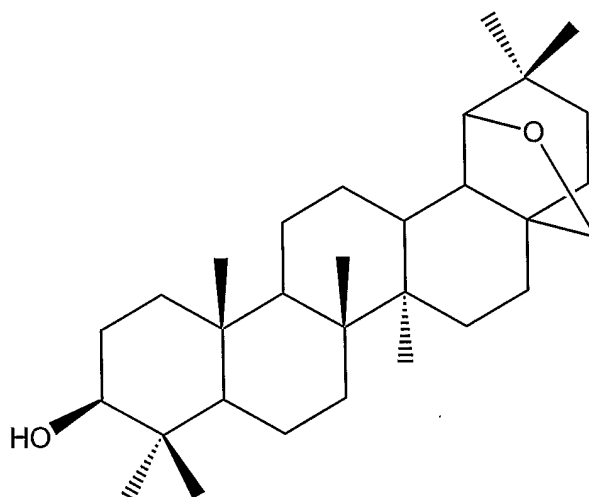
The term "peptide" describes a sequence of 2 to 25 amino acids (e.g. as defined hereinabove) or peptidyl residues. The sequence may be linear or cyclic. For example, a cyclic peptide can be prepared or may result from the formation of disulfide bridges between two cysteine residues in a sequence. A peptide can

be linked to the remainder of a compound of formula (I)-(VI) through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of a cysteine. Preferably a peptide comprises 3 to 25, or 5 to 21 amino acids. Peptide derivatives can be prepared as disclosed in U.S. Patent Numbers 4,612,302; 4,853,371; and
5 4,684,620.

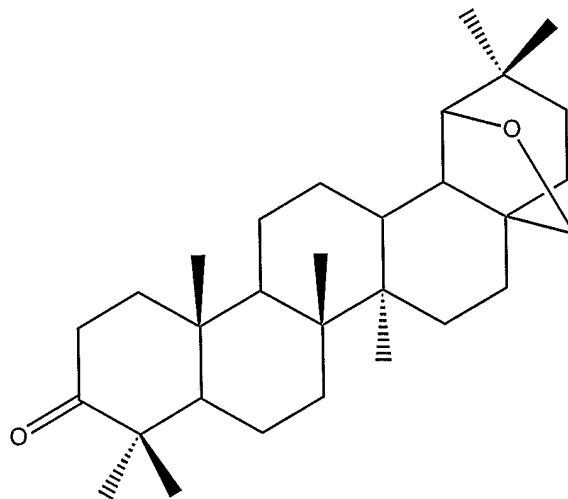
The term "polyethyleneimine" refers to the group $(-\text{NHCH}_2\text{CH}_2-)_x[-\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)\text{CH}_2\text{CH}_2-]_y$. Polyethyleneimine can be attached to a compound through either of the nitrogen atoms marked with hash marks.
10 marks. "Poly(ethylene glycol)" refers to the compound $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$. It can be attached to a compound through its terminal hydroxyl.

The term "direct bond" refers to a group being absent.

As used herein, "allobetulin" refers to a compound of the formula



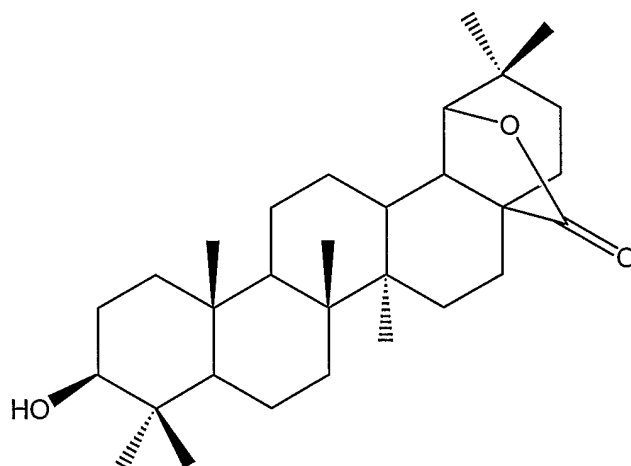
15 As used herein, "allobetulone" refers to a compound of the formula



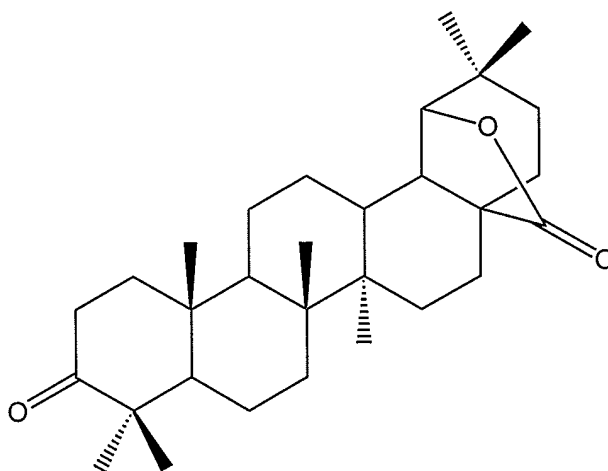
As used herein, “metal alcoholate” or “alcoholate” refers to an organic alcohol wherein the hydroxy hydrogen has been replaced with a metal, e.g., $(\text{CH}_3\text{CH}_2\text{O})_3\text{Al}$. Metal alcoholates are suitable reagents for triterpene purification because it is believed that metal alcoholates bind strongly and irreversibly to acids and tannins, therefore providing complete discoloration of the total extract. Suitable specific metal alcoholates include, e.g., sodium methoxide (NaOMe), sodium ethoxide (NaOEt), potassium methoxide (KOMe), potassium ethoxide (KOEt), aluminum *iso*-propoxide [$\text{Al}(\text{i-OPr})_3$], aluminum *tert*-butoxide [$\text{Al}(\text{t-OBu})_3$], and aluminum methoxide [$\text{Al}(\text{OMe})_3$].

As used herein, “aluminum *iso*-propoxide” refers to a compound of the formula $\text{Al}(\text{i-OPr})_3$.

As used herein, “oleanan-3- β -ol-28,19-lactone” refers to a compound of the formula



As used herein, “oleanan-3-one-28,19-lactone” refers to a compound of the formula



As used herein, "contacting" refers to the act of touching, making contact, or of bringing within immediate proximity.

As used herein, "washing" refers to the process of purifying a solid mass (e.g., crystals) by passing a liquid over and/or through the solid mass, as to
5 remove soluble matter. The process includes passing a solvent, such as distilled water, over and/or through a precipitate obtained from filtering, decanting, or a combination thereof. For example, in one embodiment of the invention, washing includes contacting solids with water, vigorously stirring (e.g., for two hours), and filtering. The solvent can be water, can be an aqueous solvent system, or
10 can be an organic solvent system. Additionally, the washing can be carried out with the solvent having any suitable temperature. For example, the washing can be carried out with the solvent having a temperature between about 0 °C and about 100 °C.

As used herein, "stereoselective reduction," "selectively converting a
15 triterpen-3-one to the corresponding triterpen-3-ol" or "selectively reducing a triterpen-3-one to the corresponding triterpen-3-ol" refers to the conversion of the functional group at the C-3 position of a triterpene, e.g., reduction of the ketone to the corresponding beta (β) C-3 hydroxyl triterpene. In one embodiment, the ratio of beta (β) C-3 hydroxyl triterpene to alpha (α) C-3
20 hydroxyl triterpene is at least about 90:10. In another embodiment of the invention, the ratio of beta (β) C-3 hydroxyl triterpene to alpha (α) C-3 hydroxyl triterpene is at least about 95:5. In another embodiment of the invention, the ratio of beta (β) C-3 hydroxyl triterpene to alpha (α) C-3 hydroxyl triterpene is at least about 98:2. In another embodiment of the invention, the ratio of beta (β) C-
25 3 hydroxyl triterpene to alpha (α) C-3 hydroxyl triterpene is at least about 99:1.

Any patent, patent document, or reference disclosed herein is incorporated into reference into this invention and forms part of this invention.

The following example is introduced in order that the invention may be more readily understood. It is intended to illustrate the invention but not limit its
30 scope.

Examples

Example 1: Stereoselective Reduction of Betulonic Acid into 3- β -Betulinic Acid

In a 250 ml glass reactor 5 g of betulonic acid (11.0 mmol) was dissolved
5 in 100 ml THF followed by the addition of 9 g of aluminum isopropoxide (44.0
mmol) and 10 ml benzyl alcohol (96.75 mmol). The resulting mixture was
refluxed (65 °C) with constant vigorous stirring for 2 hours. Then solvent was
removed on a rotor evaporator (40 °C; 100 mbar), the resulting pale yellow solid
mass was transferred into a 250 ml flask containing 130 ml of xylenes preheated
10 at 70 °C, and stirred well until complete dissolution. Under constant stirring,
aqueous NaOH (0.6 g dissolved in 2 ml water) was added to this solution
through a dropping funnel, and boiled at about 130 °C for 1 hour. It was then
filtered off when cold, washed with cold xylenes, and the residue was dried
under vacuum at 50 °C for 2 hours. The dried pale yellow solid mixture was
15 taken into a 330 ml beaker, followed by the addition of 200 ml aqueous acetic
acid (10%). Then it was homogenized in a homogenizer (8000 rpm, 10 minutes),
filtered off, several times washed with cold water, and finally the residue was
dried in a vacuum oven (50 °C; 350 mbar) for 2 hours. The resulting off-white
dried residue was taken into a 300 ml beaker containing 100 ml THF, well
20 homogenized in a homogenizer (8000 rpm, 5 minutes), and filtered off. The
filtrate was evaporated off under reduced pressure, and finally the off-white solid
product was dried in a vacuum oven (50 °C; 350 mbar; 12 hours) to obtain 4.85
g (10.6 mmol) 3- β -Betulinic Acid of at least about 80 percent purity. Conversion
is almost 100 percent and yield is about 96.3 molar percent.

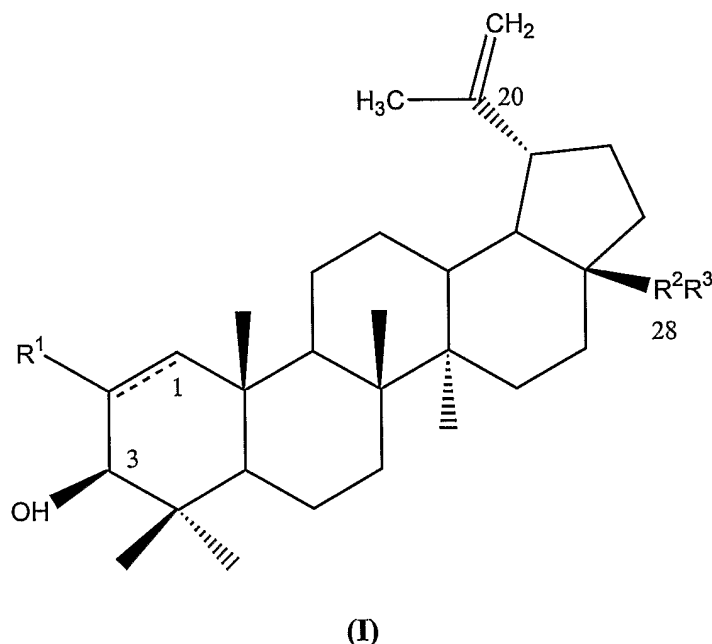
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Obviously, numerous modifications and variations of the present
invention are possible in light of the above teachings. It is therefore to be
understood that within the scope of the appended claims, the invention may be
practiced otherwise than as specifically described herein.

30

What is claimed is:

1. A method for preparing a compound of formula (I):



or a pharmaceutically acceptable salt, wherein

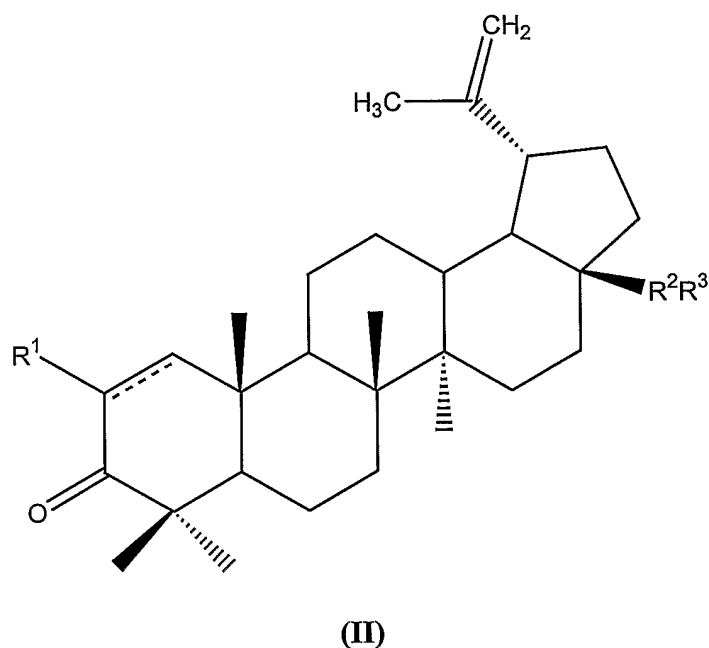
R^1 is hydrogen or hydroxy;

R^2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, (C₆-C₁₀)aryl, or (C₁-C₆)alkyl;

R^3 is hydrogen, hydroxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl, O=P(OH)₂, O=P(OH)₂OP(O)(OH)-, (C₁-C₅)alkanoyl, Si(R)₃ wherein each R is H, phenyl or (C₁-C₆)alkyl, C(O)N(R)₂, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[(C₁-C₄)alkoxy](C₁-C₄)alkyl, or a glycoside;

or a pharmaceutically acceptable salt thereof;

the method comprising contacting a metal alcoholate and a compound of formula (II):



for a period of time effective to provide the compound of formula (I).

- 5 2. The method of claim 1 wherein the bond between carbons 1 and 2 is a single bond.

3. The method of claim 1 wherein R^1 is hydrogen.

- 10 4. The method of claim 1 wherein R^2 is carbonyl or a direct bond.

5. The method of claim 1 wherein R^3 is hydroxy, (C_1-C_6) alkyl, or hydroxy (C_1-C_6) alkyl.

- 15 6. The method of claim 1 wherein R^3 is hydroxy, methyl, or hydroxyl methyl.

7. The method of claim 1 wherein
- 20 R^1 is hydrogen;
- R^2 is carbonyl or a direct bond; and
- R^3 is (C_1-C_6) alkyl or hydroxyl (C_1-C_6) alkyl.

8. The method of claim 1 wherein:

R^1 is hydrogen;

R^2 is carbonyl or a direct bond; and

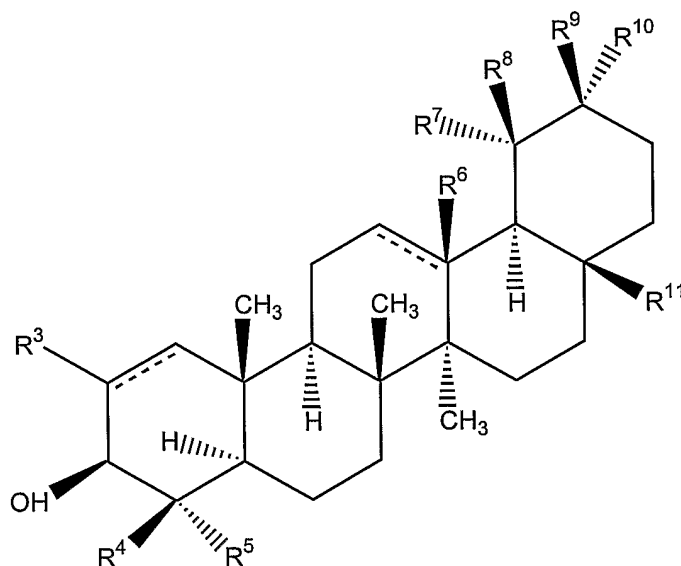
R^3 is methyl or hydroxymethyl.

5 9. The method of claim 1 wherein the compound of formula (I) is betulinic acid, lupeol, or betulin.

10. The method of claim 1 wherein the compound of formula (II) is betulonic acid, lupeone, or betulone.

10

11. A method for preparing a compound of formula (III):



(III)

15 or a pharmaceutically acceptable salt, wherein

R^3 is hydrogen, halo, carboxy, mercapto, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or $-O-Y$;

R^4 and R^5 are each independently hydrogen, (C_1-C_6) alkyl, or hydroxy (C_1-C_6) alkyl;

20 R^6 is hydrogen or is absent when the adjacent --- is a bond;

R^7 is hydrogen or (C_1-C_6) alkyl;

R^8 is hydrogen, (C₁-C₆)alkyl, or hydroxy(C₁-C₆)alkyl and R^{11} is hydrogen, (C₁-C₆)alkyl, carboxy, or hydroxy(C₁-C₆)alkyl; or R^8 and R^{11} together are -O-C(=X)-;

R^9 and R^{10} , are each independently hydrogen or (C₁-C₆)alkyl;

5 each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo (=O) or thioxo (=S);

each Y is independently H, aryl, P(O)(Cl)₂, (C₃-C₈)cycloalkyl, adamantyl, -SO₂R_a, O=P(R_b)₂, O=P(R_c)₂OP(O)(R_d)-, Si(R_e)₃, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or
 10 unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and -N(R_f)-; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo (=O), hydroxy, carboxy, halo, mercapto, nitro, -N(R_g)(R_h), (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkyloxy, aryl, aryloxy, adamantyl, adamantyloxy, hydroxyamino, trifluoroacetyl amino,
 15 glycoside, amino acid, or peptide groups; and wherein said chain may optionally be saturated or unsaturated;

R_a is (C₁-C₆)alkyl or aryl;

R_b, R_c, and R_d are each independently hydroxy, (C₁-C₆)alkoxy, hydroxy(C₂-C₆)alkoxy, adamantyloxy, adamantyl(C₁-C₆)alkoxy, norbornyloxy,
 20 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy(C₁-C₆)alkoxy, 2,3-epoxypropyloxy, benzyloxy, (C₃-C₈)cycloalkyloxy, NR_xR_y, or aryloxy;

R_e is H, aryl or (C₁-C₆)alkyl;

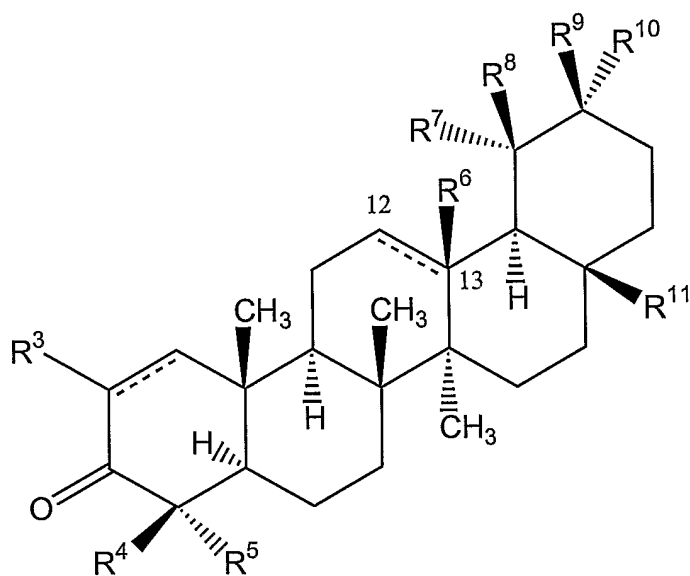
R_f is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkanoyl, phenyl or benzyl;

R_g and R_h are each independently selected from the group consisting of
 25 hydrogen, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, adamantyl, adamantyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, aminosulfonyl, (C₁-C₆)alkanoyl, aryl and benzyl; or R_g and R_h together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, (C₁-C₆)alkyl, (C₁-
 30 C₆)alkanoyl, aryl, or benzyl;

or a pharmaceutically acceptable salt thereof.

the method comprising contacting a metal alcoholate and a compound of formula (IV):



(IV)

5 for a period of time effective to provide the compound of formula (III).

12. The method of claim 11 wherein the bond between carbons 1 and 2 is a single bond.

10 13. The method of claim 11 wherein R³ is hydrogen.

14. The method of claim 11 wherein R⁴ is methyl.

15. The method of claim 11 wherein R⁵ is methyl.

15

16. The method of claim 11 wherein R⁶ is hydrogen and the bond between carbons 12 and 13 is a single bond.

17. The method of claim 11 wherein R⁷ is hydrogen.

20

18. The method of claim 11 wherein R⁸ and R¹¹ together are -O-CH₂- or -O-C(=O)-.

19. The method of claim 11 wherein R^9 is methyl.

20. The method of claim 11 wherein R^{10} is methyl.

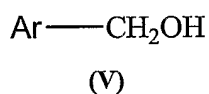
5 21. The method of claim 11 wherein the compound of formula (III) is allobetulin or oleanan-3- β -ol-28,19-lactone.

22. The method of claim 11 wherein the compound of formula (IV) is allobetulone or oleanan-3-one-28,19-lactone.

10

23. The method of any one of claims 1-22, wherein the metal alcoholate is aluminum iso-propoxide.

24. The method of any one of claims 1-23, wherein the contacting occurs in
15 the presence of a compound of formula (V):

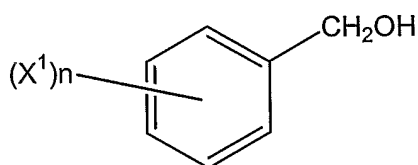


wherein Ar is aryl or heteroaryl.

20

25. The method of any one of claims 1-23, wherein the contacting occurs in the presence of a compound of the formula: $\text{Ph}-\text{CH}_2\text{OH}$.

26. The method of any one of claims 1-23, wherein the contacting occurs in
25 the presence of a compound of the formula



wherein,

each X^1 is independently halo, nitro, hydroxyl, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, COOR^{17} , or $\text{NR}^{16}\text{R}^{17}$, wherein each of R^{16} and R^{17} are independently

30 H or (C_1-C_6) alkyl; and

n is 0, 1, 2, 3, 4 or 5.

27. The method of any one of claims 1-26, wherein the contacting occurs in the presence of a solvent.
- 5 28. The method of any one of claims 1-26, wherein the contacting occurs in the presence of a solvent selected from the group of tetrahydrofuran (THF), dioxane, acetonitrile, dimethylformamide (DMF), dimethylacetamide (DMA), ethyl ether, ethylacetate, or a combination thereof.
- 10 29. The method of any one of claims 1-28, wherein the contacting occurs at a temperature of at least about 50 °C.
30. The method of any one of claims 1-29, having a yield of at least 95 molar percent.
- 15 31. The method of any one of claims 1-30, having a purity of at least 95 percent, as determined by HPLC.
32. The method of any one of claims 1-31, further comprising purifying the
20 compound of formula (I) or (III).
33. The method of any one of claims 1-31, further comprising purifying the compound of formula (I) or (III) by washing the compound of formula (I) or (III).
- 25 34. The method of any one of claims 1-31, further comprising purifying the compound of formula (I) or (III) by washing the compound of formula (I) or (III) with an aqueous acid, an aqueous base, a non-polar aprotic solvent, a polar aprotic solvent, or a mixture thereof.
- 30

35. The method of any one of claims 1-34, wherein the metal alcoholate is employed in at least about 2 molar equivalents, in relation to the compound of formula (II) or (IV).
- 5 36. The method of any one of claims 1-34, wherein the metal alcoholate is employed in at least about 4 molar equivalents, in relation to the compound of formula (II) or (IV).
37. The method of any one of claims 1-36, wherein the contacting occurs for
10 at least about 2 hours.
38. The method of any one of claims 1-37, wherein the compound of formula (II) or (IV) is employed in at least about 1 kilogram.
- 15 39. The method of any one of claims 1-38, wherein at least about 1 kilogram of the compound of formula (I) or (III) is obtained.