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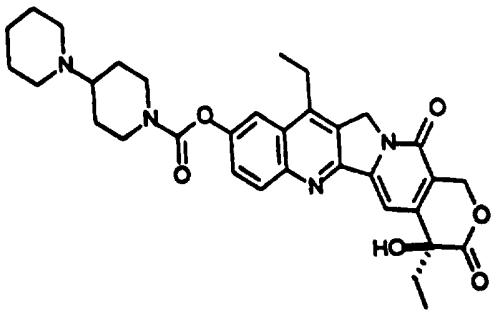
(57) Abstract

This invention discloses and claims novel intermediates and procedures for the synthesis of camptothecin derivatives, such as irinotecan, and other compounds related to the synthesis of CPT-11 of formula (I). Related procedures and compounds are also disclosed, such as a novel method of making mappicine of formula (II).



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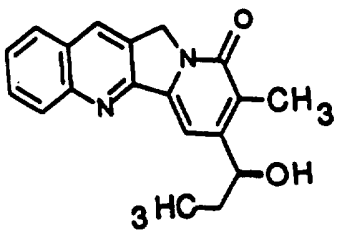

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NOVEL INTERMEDIATES AND PROCESS FOR THE MANUFACTURE OF CAMPTOTHECIN DERIVATIVES (CPT-11) AND RELATED COMPOUNDS

Field of the Invention

This invention discloses and claims novel intermediates and procedures for the synthesis of camptothecin derivatives, such as irinotecan, and other compounds related to the synthesis of CPT-11. Related procedures and compounds are also disclosed, such as a novel method of making mappicine.

Information Disclosure

The compound given the label **14CPT** in this document is mentioned in M. Shamma, D.A. Smithers, V. St. George, Tetrahedron, 1973, 1949-1954.

The asymmetric synthesis of this compound, 14 CPT, is reported in the following documents (grouped by author):

Group 1.

H. Terasawa, M. Sugimori, A. Ejima, H. Tagawa, Chem. Pharm. Bull., 1989, 37, 3382-3385.

A. Ejima, H. Terasawa, M. Sugimori, H. Tagawa, J.C.S. Perkin I, 1990, 27-31.

H. Tagawa, H. Terasawa, A. Ejima, U.S. Patent 4,778,891 (Oct. 18, 1988).

H. Tagawa, H. Terasawa, A. Ejima, EP 220601 (Oct 14, 1986).

Group 2.

M.C. Wani, A.W. Nicholas, M.E. Wall, J. Med. Chem. 1987, 2317-2319.

M.C. Wani, A.W. Nicholas, M.E. Wall, U.S. Patent 5,053,512 (Oct 1, 1990).

M.E. Wall, M.C. Wani, A.W. Nicholas, G. Manikumar, U.S. Patent 4,894,456 (Jan. 16, 1990).

M.E Wall, M.C. Wani, A.W. Nicholas, and G. Manikumar, WO 90/03169 (Sep. 28, 1988).

Background

Camptothecin derivatives, such as irinotecan, are effective anticancer drugs. This invention describes an efficient method of synthetic synthesis for a variety of camptothecin derivatives, including irinotecan or CPT-11, and other useful compounds like mappicine.

Summary of the Invention

This invention comprises compounds, processes, reactions and reagents as shown in the CHARTS, formulas and figures herein. The compounds, processes, reactions and reagents are useful for the manufacture of camptothecin derivatives such as CPT-11 and other related compounds such as mappicine.

Specific compounds selected from the compounds described and labeled in the specification are the compounds in the CHARTS labeled **2G, 3G, 4G, 5G, 6G, 7GG, 7GA, 8GG, 8GA, 8GB, 9GG, 9GA, 10G, 10G(S), 10G(R), 11G, 11G(S), 11G(R), 12GA-1, 12GA-1(S), 12GA-1(R), 12GA-2, 12GA-2(S), 12GA-2(R), 12GB-1, 12GB-1(S), 12GB-1(R), 12GB-2, 12GB-2(S), 12GB-2(R), 12G, 12G(S), 12G(R), 13G, 13G(S), or 13G(R),**

where R_1 is any optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H,

a) any optionally substituted alkyl, including C_{1-8}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-8}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

b) -C(O)-R_3, or

c) -$C(R_7)_2$-O-R_3 where each R_7 is independent of the other;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_5 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, or two R_5 groups may be combined to form cyclopentane or cyclohexane, or substituted derivatives thereof;

where R_6 is optionally substituted C_{1-8} alkyl, lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl,

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups

may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

where R_8 is optionally substituted C_{1-6} alkyl, including lower alkyl, including t-butyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl.

Other specific compounds of the invention are selected from the compounds described and labeled in the specification are **2CPT, 3CPT, 4CPT, 5CPT, 6CPT, 7CPT, 7CPTA, 8CPTG, 8CPTA, 8CPTAB, 9CPTG, 9CPTA, 9CPTB, 10CPT, 10CPT(S), 10CPT(R), 11CPT, 11CPT(S), 11CPT(R), 12CPTA-1, 12CPTA-1(S), 12CPTA-1(R), 12CPTA-2, 12CPTA-2(S), 12CPTA-2(R), 12CPTB-1, 12CPTB-1(S), 12CPTB-1(R), 12CPTB-2, 12CPTB-2(S), 12CPTB-2(R), 12CPT, 12CPT(S), 12CPT(R), 13CPT, 13CPT(S), and 13CPT(R)** where R_1- R_9 is defined above.

Other specific compounds of the invention are selected from the compounds described and labeled in the specification as **6MG, 7MG, 8MG, 9MG, 10MG, 11MG,12MG,13MG**, except where **13MG** has an R_6 that is C_{1-2} alkyl, where the variables have the same definition as the variables above.

Other specific compounds of the invention are selected from the compounds described and labeled in the specification as **5MM, 6MM, 7MM, 8MM, 9MM, 10MM, 11MM, or 12MM**.

In addition to the compounds, various procedures labeled as STEPS are also described and claimed in this invention. Those STEPS include the STEPS described and labeled in the specification as **CHART G** comprising; STEP 2, or STEP 3, or STEP 4, or STEP 5, or STEP 5a, or STEP 5b, or STEP 6, or STEP 7GG, or STEP 7GA, or STEP 8GG, or STEP 8GA, or STEP 8GB, or STEP 9GG, or STEP 9GA, or STEP 9GB, or STEP 10GG, or STEP 10GA, or STEP 10 Resolution, or STEP 11, or STEPS 12, or STEP 13, or STEP 14 or any combination thereof combining two or more STEPS.

Also described and claimed are those STEPS described and labeled in the specification as **CHART CPT** comprising; STEP 7G, or STEP 7A, or STEP 8G, or STEP 8A, or STEP 8B, or STEP 9G, or STEP 9A, or STEP 9B, or STEP 10G, or STEP 10A, or STEP 11, or STEP 12, or STEP 13, or STEP 14 or any combination thereof combining two or more STEPS.

Also described and claimed are those STEPS described and labeled in the specification as **CHART M-G** comprising; STEP 5, or STEP 6, or STEP 7, or STEP 8 or STEP 9, or STEP 10, or STEP 11, or STEP 12, or STEP 13, or any combination

thereof combining two or more STEPS.

Also described and claimed are those STEPS described and labeled in the specification as **CHART M-M** comprising; STEP 5, or STEP 6, or STEP 7, or STEP 8 or STEP 9, or STEP 10, or STEP 11, or STEP 12, or STEP 13, or any combination thereof combining two or more STEPS.

Additional Description of the Invention and Description of the Preferred Embodiment(s).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are identified in two ways: by descriptive names and by reference to structures indicating various chemical entities. In appropriate situations, the proper stereochemistry is also described either with writing or represented in the structures. In some cases, when a molecule has two chiral centers, only the stereochemistry of one chiral center is indicated, unless the stereochemistry of the other chiral center is taught, the stereochemistry of the other chiral chiral center is unresolved or racemic. All the temperatures provided are in degrees centigrade, whether indicated with "^{O}" or "C^{O}" or not. Minute may be written m or min. Hour may be written H or h. Abbreviations are standard or obvious to a chemist unless indicated otherwise. When compounds are added or exposed in any fashion to other compounds they may be said to be "mixed" with those compounds. Usually the purpose in mixing compounds is to promote chemical reactions among one or more of the mixed compounds The following terms may also be used.

OPTIONALLY SUBSTITUTED The term " substituted" or "optionally substituted" usually appears first before "C_{1-8}alkyl" but should be understood to modify all variations of all r groups. The term shall mean a group or radical that is substituted with halogen, lower alkyl, mono- or di(lower alkyl)-substituted lower alkyl, (lower alkyl)thio, halo-substituted lower alkyl, amino-substituted lower alkyl, mono- or di(lower alkyl)-substituted amino, lower alkenyl, lower alkynyl, halogen, lower alkoxy, aryloxy, aryl(lower alkyl), hydroxy, cyano, amino, mono- and di(lower alkyl)amino, or nitro and the like. A chemist ordinarily skilled in the art would know when and how to make such obvious substitutions.

ALKYL The parenthetical term (C_n-C_m alkyl) is inclusive such that a compound of (C_1-C_8) would include compounds of 1 to 8 carbons and their isomeric forms. The various carbon moieties are aliphatic hydrocarbon radicals and includes

branched or unbranched forms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, and n-octyl and isomeric forms thereof.

n-ALKYL The parenthetical term (C_n-C_m n-alkyl) is inclusive such that a compound of (C_1-C_8) would include compounds of 1 to 8 carbons in their straight chain unbranched form.

LOWER ALKYL The term "lower alkyl" refers to branched or unbranched saturated hydrocarbon radicals having from one to six carbon atoms. Representatives of such groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, the pentyl isoforms, hexal isoforms and the like.

(LOWER ALKYL)THIO The term "(lower alkyl)thio" refers to a lower alkyl group as defined above, attached to the parent molecular moiety through a sulfur atom. Typical (lower alkyl)thio groups include methylthio, ethylthio, propylthio, iso-propylthio, and the like.

ALKOXY Alkoxy as represented by -OR_1 when R_1 is (C_1-C_8) alkyl refers to an alkyl radical which is attached to the remainder of the molecule by oxygen and includes branched or unbranched forms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentoxy, isopentoxy, n-hexoxy, isohexoxy, n-heptoxy, isoheptoxy, and n-octoxy and the like.

LOWER ALKOXY The term "lower alkoxy" denotes an alkyl group as defined above, attached to the patent molecular moiety through an oxygen atom. Representatives of such groups include methoxy, ethoxy, butyoxy and the like.

ALKENYL Alkenyl refers to a radical of an aliphatic unsaturated hydrocarbon having at least one double bond and includes both branched and unbranched forms such as ethenyl, (-CH=CH_2), 1-methyl-1-ethenyl, 1-propenyl, (-CH_2-CH=CH_2), 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-butenyl, 1-pentenyl, allyl, 3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 3-methyl-allyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 1-methyl-4-hexenyl, 3-methyl-1-hexenyl, 3-methyl-2-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 1-methyl-4-heptenyl, 3-methyl-1-heptenyl, 3-methyl-2-heptenyl, 1-octenyl, 2-octenyl, or 3-octenyl and the like.

ALKYNYL Alkynyl refers to a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, propynyl, and the like.

CYCLOALKYL The parenthetical term (C_{n-m} cycloalkyl) is inclusive

such that a compound of (C_{3-10}) would include radicals of a saturated cyclic hydrocarbon of 3 to 10 carbons in their cyclic chain. The term may also include alkyl-substituted cycloalkyl, such as cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3 diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclodecyl and the like. Each of these moieties may be substituted as appropriate.

HETEROALKYL "Heteroalkyl" refers to a alkyls as described above, only where one, two or three non-adjacent carbon atoms are replaced by heteroatoms such as nitrogen, sulfur and oxygen.

ARYL (C_{6-12}) aryl, refers to a 6 to 12 carbon atom base structure, one or two fused or nonfused aromatic rings, that may be optionally substituted or substituted with one to 3 hydroxy, C_1-C_3 alkoxy, C_1-C_3 alkyl, trifluoromethyl, fluoro, chloro, or bromo groups. Examples of "aryl" are: phenyl, m-methylphenyl, p-trifluoromethylphenyl, α-naphthyl, ß-naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)-tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4-, 2,3,6-, or 2,4,5-)trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-,)trifluorophenyl, (o-, m-, p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro(5- or 6-)methylphenyl and the like. Each of these moieties may be substituted as appropriate.

ALKYLARYL Alkylaryl refers to alkyl chains of one to 8 carbon atoms and isomeric forms thereof which are substituted with aryl groups of 6 to 12 carbon atoms as described above.

HETEROCYCLICS Examples of heterocyclics include: (2-, 3-, or 4-)pyridyl, imidazolyl, indolyl, N^{in}-formyl-indolyl, N^{in}-C_2-C_5alkyl-C(O)-indolyl, [1,2,4]-triazolyl, (2-, 4-, 5-)pyrimidinyl, (2-, 3-)thienyl, piperidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, puryl, phenazyl, carbazolyl, thienyl, and benzothienyl, thienyl, indolyl, iso-quinolyl and the

like. Each of these moieties may be substituted as appropriate.

HETEROARYL Heteroaryl refers to a one or two ring structure, of 5 - 12 ring atoms, where a minimum of one ring is aromatic, only where one, two or three non-adjacent carbon atoms are replaced by heteroatoms such as nitrogen, sulfur and oxygen. Examples can include pyridine, thiophene, furan, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pryidazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl,2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl. Each of these moieties may be substituted as appropriate.

CHIRALITY It will be apparent to those skilled in the art that compounds of this invention may contain one or more chiral centers and may exist in optically active forms including cis-/trans- and/or R- and S- isomeric forms and mixtures thereof. The scope of this invention includes all of these forms, the enantiomeric or diastereomeric forms of the compounds, including optically active forms, in pure form or as mixtures of enantiomers or diastereomers including cis-/trans-isomeric forms. The therapeutic properties of the compounds may to a greater or lesser degree depend on the stereochemistry of a particular compound. Resolution can be accomplished using resolving agents such as optically active dibenzoyltartaric acid, camphorsulfonic acid, bis-o-toluoyltartaric acid, tartaric acid, and diacetyl tartaric acid.

OPTICAL PURITY is sometimes referred to as "% ee."

Procedures and Compounds of the Invention

The procedures below refer to compounds and formula identified in the CHARTS.

PROCEDURES, REACTIONS AND COMPOUNDS OF CHART G

General Description of the Reactions

All of the variables for the procedures described below are defined above, in the Summary of the Invention and in the Definitions. More preferred substituents are disclosed below.

STEP 1. (Citrazinic acid → **1 G**)

The starting material, dichloroisonicotinic acid, is a known compound and is readily prepared from commercially available citrazinic acid.

The methods of preparation and range of acceptable conditions are known and contained in the following references: M.E.Baizer, M. Dub, S. Gister, N.G. Steinberg, *J. Am. Pharm. Assoc*, 1956, 45, 478-480; The use of tetraalkylammonium and tertiary amine salts in this type of reaction is described in Chemical Abstracts, CA 97, 216024 and East German patent, DD 154,538 by E. Schroetter, H. Schick, H. Niedrich, P. Oehme, and L. Piesche. See also, W. H. Levelt and J. P. Wibaut, *Rec. Trav. Chem*, 1929, 44, 466.

In the preferred method, citrazinic acid is heated with phosphorus oxychloride and a tetraalkylammonium chloride or tertiary amine hydrochloride, most preferably tetramethylammonium chloride, to a temperature between 120° and 140° for about 12 to 24 hours. The mixture is then reacted with water to yield the product, **1CPT**.

STEP 2. (**1 G** → **2 G**)

2,6-dichloroisonicotinic acid is dissolved or suspended in an ethereal solvent such as diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane and reacted with an excess of ethylmagnesium halide or ethyllithium in diethyl ether or tetrahydrofuran solution at a temperature between about -30° and about +10°. The excess ethyl magnesium halide or ethyllithium is decomposed by reaction with a dilute acid such as hydrochloric acid, or by reaction first with an ester such as methyl formate or a ketone such as acetone, followed by reaction with a dilute acid such as hydrochloric acid.

Alternatively, the 2,6-dichloroisonicotinic acid may be converted into the acid chloride by reaction with thionyl chloride, or phosphorus pentachloride, and then converted into the Weinreb amide. See, S. Nahm and S. M. Weinreb, *Tet. Lett*, 1981, 3815-3818. The Weinreb amide is then dissolved in reacted with an ethereal solvent such as diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane and reacted with an excess of ethylmagnesium halide or ethyllithium in diethyl ether or

tetrahydrofuran solution at a temperature between about -30° and about +10°. The product is then isolated after reaction of the intermediate complex with a dilute acid such as hydrochloric acid. Preferred R_6 is lower alkyl, including C_{1-4}alkyl and ethyl, aryl and substituted aryl, alkylaryl,and substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl, preferably C_{1-4} alkyl, ethyl, benzyl.

STEP 3. **(2 G → 3 G)**

The alkyl ketone, referred to in **CHART G** p.1, as **2 G**, is reacted with an alcohol or a diol in the presence of trimethylchlorosilane. Alcohols may be diols such as ethylene glycol, 1,3-propanediol, or 2,2-dimethyl-1,3-propanediol, or alcohols such as methanol. The preferred alcohol is ethylene glycol. When ethylene glycol is used the ethylene ketal is produced, other ketals may be produced with other alcohols. A solvent such as methylene chloride may be added. The reaction is run at a temperature between about 0° and about 60°, preferably at about 40°. Preferred R_6 is lower alkyl, including C_{1-4}alkyl and ethyl, aryl and substituted aryl, alkylaryl,and substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl, preferably C_{1-4} alkyl, ethyl, benzyl.

STEP 4. **(3 G → 4G)**

The compound in **CHART G** p.1 labeled **3 G** is reacted with a sodium or potassium alkoxide, either in an excess of the alcohol or a solvent such as tetrahydrofuran or 1,2-dimethoxyethane. The reaction may be run at a temperature between about 20° and 80°. The alkoxide, or the preferred R_1 group of **CHART G**, may be any of the previously defined lower alkyl, cycloalkyl, C_{3-10} cycloalkyl, alkenyl, aryl, and aryalkyl, including benzyl and substituted benzyl, groups. The more preferred R_1 groups are methyl and benzyl.

STEP 5a (optional) and **STEP 5b.** **(4G → 5G)**

STEP 5a. Ortho-directed metallation reactions have been reviewed, see V. Snieckus, Chem. Rev., 1990, Vol. 90, pp. 879-933, incorporated by reference.

The compound in **CHART G p.1** labeled **4 G** is dissolved in a solvent and reacted with an alkyllithium base or arylllithium base to form the pyridyl anion. The resulting anion is then reacted with an electrophile and the product is isolated after further reaction with a dilute acid. Suitable solvents for the reaction are ethers such as diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane or hydrocarbons such as toluene, hexane, heptane, cyclohexane, or isooctane, or mixtures of any of these or similar solvents.

The alkyllithium may be methyllithium, n-butyllithium, sec-butyllithium or t-butyllithium. The reaction temperature may be between about -40° and about +50°. The electrophile may be an alkyl halide such as methyl iodide, dimethyl sulfate, chloromethylmethyl ether, benzyl chloromethyl ether, or benzyl bromide; aldehydes or ketones such as formaldehyde, acetone, benzaldehyde or other similar compounds; or amides such as formamides including dimethylformamide, N-formylpiperidine, or N formylmorpholine or N-methylformanilide or similar formamides. The acid used for product isolation may be hydrochloric acid, acetic acid, sulfuric acid, or other moderate to strong acids.

The preferred solvent is heptane, the preferred base is n-butyllithium, and the preferred amide is N-formylpiperidine. The reaction is preferably run between about -5° and about +5°. Purification of the product may be accomplished by crystallization, chromatography, or through the formation of the bisulfite addition compound, which may be decomposed by reaction with either acid or base.

Note that **STEP 5a** may be omitted, **STEP 5b** may be used without **STEP 5a**, to produce **5G**.

STEP 5b.

The aldehyde of **STEP 5a** is reduced to the alcohol with a hydride reducing agent such as sodium borohydride. The reaction may be run using an alcohol such as methanol or 2-propanol as the solvent, or may be run under two-phase conditions with water and an organic phase consisting of heptane, methylene chloride or methyl t-butylether, or mixtures of these and similar solvents. A phase transfer catalyst such as tetrabutylammonium chloride may be added but is not essential.

STEP 5a and STEP 5b. **(4 G → 5 G)**

Preferred R_2, shown in **CHART G**, may be H, or a) any optionally substituted C_{1-8}alkyl, alkylaryl, C_{1-8}alkyl-aryl, including C_{1-8}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl; b) -C(O)-R_3, or c) -C(R_7)$_2$-O-R_3 where each R_7 is independent of the other; and where R_3 and R_7 are defined above, in the Summary of Invention. This series of reactions proceeds with **CHART G** p.2, STEP 6, immediately below, only when R_2 is b) -C(O)-R_3, or c) -C(R_7)$_2$-O-R_3 where each R_7 is independent of the other. When R_2 is H or any optionally substituted C_{1-8}alkyl, alkylaryl, C_{1-8}alkyl-aryl, including C_{1-8}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl; then the reactions proceed according to **CHART M-G** and **CHART M-M** and may result in the production of mappicine or mappicine analogues.

STEP 6. (5 G → 6 G)(CHART G - continued)

The alcohol is reacted with a base, and an alkylating agent in an appropriate solvent to yield the product. Bases may be hydrides such as sodium hydride or potassium hydride, or alkoxide bases such as potassium t-butoxide.

Suitable solvents are ethereal solvents such as tetrahydrofuran or 1,2-dimethoxyethane or alcohols such as t-butanol. The temperature may be between about 15° and about 80°. The preferred base is potassium t-butoxide and the preferred solvents are THF or MTBE at a temperature preferably between about 20° and about 40°.

Alternatively, the reaction may be performed under phase transfer conditions using water and an organic solvent such as methylene chloride, or hydrocarbons such as hexane, heptane, or toluene or similar solvents. The base may be a hydroxide such as sodium or potassium hydroxide, or sodium or potassium carbonate. A phase transfer catalyst such as tetrabutylammonium chloride may be added and the preferred temperature range is between about 10° and about 30°.

ALTERNATIVE STEPS

There are 2 different Step 7 reactions, series 7GG and 7GA; 3 different Step 8 reactions, series 8GG, 8GA, 8GB; 3 different Step 9 reactions, series 9GG, 9GA, 9GB and 2 different step 10 reactions, series 10GG and 10GA followed by a Step 10 resolution procedure. See Chart G, p. 2, 3, 4.

STEP 7 GG and STEP 10 GA. (6 G → 7 GG) and (9 GA → 10 G).

Carbonylation reactions of aryl halides catalyzed by palladium-zero are well known, see, J. K. Stille and P. K. Wong, *J. Org. Chem.*, 1975, 40, 532-534, but aryl chlorides generally have low reactivity in these reactions. In contrast to simple aryl chlorides, 2- chloropyridines are known to undergo facile insertion reactions with palladium-zero. Various coupling reactions of 2-chloropyridines catalyzed by palladium-zero are known but carbonylation reactions of 2-chloropyridines catalyzed by palladium-zero have not been reported in the literature.

Compounds represented by **6G** are reacted with carbon monoxide and an alcohol in the presence of a soluble palladium II salt (such as palladium acetate), a phosphine ligand (such as 1,3-bisdiphenylphosphinopropane), and a base such as sodium or potassium acetate, sodium or potassium carbonate, triethylamine, or tri n-butylamine in a polar aprotic solvent such as dimethyl formamide or acetonitrile.

The preferred R_3 group, shown in **CHART G** p.2 & 3, may be any of the previously defined, H, lower alkyl, cycloalkyl, alkenyl, aryl, and aryalkyl, including

benzyl and substituted benzyl, groups. The more preferred R_3 groups are methyl and benzyl.

The preferred R_4 group of the alcohol, shown in **CHART G** p.2 & 3, may be any of the previously defined, H, lower alkyl, cycloalkyl, alkenyl, aryl, and aryalkyl, including benzyl and substituted benzyl, groups. The more preferred R_4 group is n-propyl. The temperature range is between about 50° to and about 100°.

The preferred R_7 group is independently H, lower alkyl, aryl, alkylaryl, substituted aryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

Some references describing the insertion reactions mentioned in **STEP 7**, above, are: a) K. Isobe and S. Kawaguchi, Heterocycles, 1981, 16, 1603-1612; b) N. Sato, A. Hayakawa, and R Takeuchi, *J. Het. Chem.* 1990, 503-506; c) M. Ishikura, M. Kamada, and M. Terashima, *Synthesis*, 1984, 936-938; and d) K. Isobe, K. Nanjo, Y. Nakamura, and S. Kawaguchi, *Bul. Chem. Soc. Japan*, 1986, 59, 2141-2149.

STEP 7 GA and **STEP 8 GG**. **(6 G → 7 GA)** also for **(7 GG → 8 GG)**

The ketal is hydrolyzed by reaction with water in the presence of a strong acid such as trifluoroacetic acid. The trifluoroacetic acid concentration may be between about 50% and 90% and the reaction temperature between about 15° and about 30°. Alternatively, the ketal may be removed by an exchange reaction with a ketone such as acetone or 2-butanone catalyzed by a strong acid such as p-toluenesulfonic acid or an acidic ion exchange resin such as amberlyst A-15 resin. The preferred temperature for the exchange reaction is about the reflux temperature of the ketone.

STEP 8GA. (7GA → 8GA)

Compound 8GA is dissolved in a solvent and reacted with a vinyllithium or a vinylmagnesium halide. Suitable solvents are ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, or MTBE, either alone or as mixtures, or as mixtures with hydrocarbons such as toluene, heptane, or cyclohexane. The reaction temperature may be between about -78° and about 25°. The product is isolated after further reaction with a dilute acid such as hydrochloric, sulfuric, or acetic acids. The preferred reagent is vinylmagnesium bromide in tetrahydrofuran as the solvent at a temperature of about -40° to about 25° followed by quenching with hydrochloric acid. Preferred R_5 is independently, H, lower alkyl, aryl, substituted aryl, or two R_5 groups may be combined to form cyclopentane or cyclohexane, or

substituted derivatives thereof.

STEP 8GB and **STEP 9GG.** **(7 GA → 8 GB** and **8 GG → 9 GG)**

The Wittig reaction is performed by reaction the ketone with an ylide solution prepared from a methyl triphenylphosphonium salt, preferably the bromide and a strong base, such as n-butyllithium, potassium t-butoxide, or potassium bis trimethylsilylamide, in a solvent such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, or DMF. The preferred base is potassium bis trimethylsilylamide and the preferred solvent is DMF. The reaction temperature is between about -5° and about 25°. Reaction time is between about 5 min and about 2 hours.

STEP 9GA. (8GA → 9GA)

9GA is dissolved in a solvent and reacted with ozone to produce an intermediate. Depending on the solvent composition, this intermediate may be an ozonide or a mixture of hydroperoxides. The intermediate is reacted with a suitable reducing agent to produce the product, either directly or stepwise through the intermediacy of an aldehyde. The temperature for the reaction may be between about -78° and about 25°. Suitable solvents for the reaction are chlorinated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane, or other multiply chlorinated ethane or ethylene derivatives, either alone, as mixture, or as mixtures with alcohols such as methanol. The preferred solvent is a mixture of methylene chloride and methanol at a temperature from about -78° to about -40° for the initial reaction with ozone, and a temperature of about 0° to 25° for the reduction of the intermediate. The preferred reducing agent is sodium borohydride.

STEP 9GB and **STEP 10GG.** **(8 GB → 9 GA** and **9 GG → 10 GG).**

The alkene is converted into the diol by osmylation under standard conditions, see, V. VanRheenen, R. C. Kelley, and D. Y. Cha, Tet. Lett., 1976, 1973, with catalytic osmium tetroxide and a stoichiometric cooxidant such as trimethylamine N-oxide or N-methylmorpholine-N-oxide in either aqueous THF or, preferably, t-butanol as the solvent. The reaction temperature may be between about 15° and about 50°, preferably about 40°, for about 12-48 hours.

An alternative to the racemic osmylation is the use of an asymmetric osmylation, as described by Sharpless, for the conversion of **9CPT** directly into 10G (R) or (S). Specific references for the Sharpless asymmetric osmylation are:

G.A. Crispino, A. Makita, Z.-M. Wang, K.B. Sharpless, Tet. Lett., 1994, 543-546.

G.A. Crispino, K.-S. Jeong, H.C. Kolb, Z.-M. Wang, D. Xu, K.B. Sharpless, J. Org.

Chem., 1993, 3785-3786 and the many references cited in this paper.

K.B. Sharpless, W.K. Amberg, U.S. Patent 5,227,543.

K.B. Sharpless, M. Beller, B. Blackburn, Y. Kawanami, H.-L. Kwong, Y. Ogino, T. Shibata, T. Ukita, L. Wang, PCT WO 92/20677.

J. Hartung, K.B. Sharpless, PCT WO 93/07142.

STEP 10. Resolution (10 G → 10 G (R or S)).

The racemic diol like **10 G** may be treated with an acetylating reagent like vinyl acetate, isopropenyl acetate, acetic anhydride or ethyl acetate in an organic solvent in the presence of a lipase. Possible solvents include ether, or hexane and the lipase may be a *cepaica* like *Pseudomonas cepaica*. Using this process one can obtain a single acetate isomer and a single diol isomer. The reaction is usually conducted between 25^0 to 45^0 C at a substrate concentration of 15-40 mg/mL. The products of the reaction can be separated by crystallization using common organic solvents or by conventional silica gel chromatography. The optical purity (% ee) of each enantiomer can be determined by NMR with chiral shift reagents or by chiral HPLC analysis.

STEPS 11-14.

The following reactions may be run with the single enantiomer, or racemic mixtures or other ratios of enantiomeric mixtures. The product of the reactions will depend on the starting materials. **CHART G** p. 4 & 5 and the steps below refer to a single enantiomer for convenience and by way of example. The single enantiomer is usually referred to by a capitol letter "R" or "S." One example is "**10 G (R)**." The racemic mixture is usually referred to by a number followed by the capitol letter "**G**." One example is "**10G**." See **CHART G**. The reactions of this invention are, of course, not limited to what is shown in the Charts, for example , **CHART G** does not show the reaction **STEPS 11** through **13** for the racemic mixtures but it is implied in the CHART and described herein. Similarly the "R" series is not as completely shown as the "S" series. The CHARTS are descriptive aids only and do not represent the complete invention.

STEP 11. (10G → 11G)

The diol may be oxidized to the hydroxy aldehyde using oxidation under Swern type conditions such as DMSO, oxalyl chloride and triethylamine in an aprotic solvent such as methylene chloride at a temperature ranging from about -78^0 to about 25^0. Alternatively, the oxidation can be done with sodium hypochlorite solution catalyzed by TEMPO or a substituted TEMPO such as 4-acetoxy-TEMPO in

a two phase system consisting of water and an aprotic solvent such as methylene chloride. The reaction temperature is preferably between about -5° and about +25° and the reaction time is between about 30 min and about 2 hours.

Swern type conditions are described in A. J. Mancuso and D. Swern Synthesis, 1981, 165-185. A two phase system consisting of water and an aprotic solvent is described in P. L. Anelli, C. Biffi, F. Montanari, and S. Quici, J. Org. Chem, 1987, 52, 2559-2562. Incorporated by reference.

STEP 12. **(11G → 12G)**

Several variations have been used to convert the hydroxyaldehyde, **11G** into **12G**. In the first procedure, the hydroxy aldehyde, **11G** is oxidized to the hydroxy acid, **12GA-1**, with sodium chlorite. The hydroxyacid then can be converted into **12G** by reaction with trimethylsilyl iodide in one pot. The advantage of this procedure is the one step conversion of **11G** into **12G**. Refer to CHART G p. 5, STEP 12, Pathway A, Part 2, path a. The disadvantage of this one step conversion is the relatively low yield and variable reaction times.

A higher yielding procedure removes the benzyl group first, either by hydrogenation or reaction with boron tribromide, and then the methoxy group by reaction with trimethylsilyl iodide. Refer to CHART G p. 5, STEP 12, Pathway A, Part 2, path b-1 and b-2. Obviously, the order of deprotection steps could be reversed.

A second method for the conversion of **11G** into **12G** changes the order of the oxidation and deprotection steps. Refer to CHART G p. 5, STEP 12, Pathway B. The benzyl group is removed by hydrogenation to yield the lactol. The lactol is then oxidized with sodium hypochlorite catalyzed by TEMPO. Cleavage of the methoxy group is done as before with trimethylsilyl iodide. Refer to CHART G p. 5, STEP 12, Pathway B, Parts 1, 2, and 3. The advantage of this sequence is the avoidance of the sodium chlorite oxidation and the hazards associated with it.

Pathways A and B are described in more detail below, Pathway B is preferred. See **CHART G** p. 4 & 5.

STEP 12. Pathway A. **(11G → 12G** Pathway A)

Pathway A has two parts, part 1 and part 2. Part 2 follows part 1. Part 2 of Pathway A also has 2 paths, *path a* and *path b*. *Path a* of Pathway A, part 2, has only one step. *Path b* of Pathway A part 2 has two steps. See **CHART G**, p. 4, note that only one stereoisomer is shown, the other stereoisomers and racemic mixtures are suggested.

Part 1.

Oxidation to form the hydroxy acid is done preferably with sodium chlorite using conditions described in the literature. See, B. S. Bal, W. E. Childers, H. W. Pinnick, Tetrahedron, 1981, 2091-2096. Other additives, such as hydrogen peroxide or sulfamic acid, have also been used to prevent the formation of chlorine dioxide. This produces **12 GA-1**.

Part 2.

Path a.

One step removal of the benzyl and methyl groups is done with trimethylsilyl iodide, either preformed or generated in situ from trimethylsilyl chloride and sodium iodide in methylene chloride or acetonitrile. See, T. Morita, Y. Okamoto, H. Sakurai, J.C.S. Chem. Comm, 1978, 874-875, and M. E. Jung and M. A. Lyster, J. Am. Chem. Soc., 1977, 99, 968. Pyridine may be added but is not required. The reaction temperature is between about 15° and 50° for between 12 and 48 hours. This produces **12 G.**

Path b.

Part 1 of *Path b-1*. The two step removal of the benzyl and methyl groups can be done in two ways. The benzyl group is removed by hydrogenation over a catalyst, preferably a palladium catalyst supported on carbon or other porous substrate, or palladium black. The solvent is preferably an alcohol, most preferably methanol. The reaction is done at about 15° to about 40° under an atmosphere of hydrogen at a pressure of about 1 atmosphere to about 4 atmospheres for about 2-four hours.

Alternatively, the benzyl group may be removed by reaction with boron tribromide in a solvent such as methylene chloride at about -5° to about 20° for about 30 minutes to about 2 hours. Produces **12 GA-2**, alternately labeled **12 GB-2**.

Part 2 of *Path b-2*. Cleavage of the methoxy group to yield **12G** may be accomplished with trimethylsilyl iodide, as described above. (This step is the same as the third step of Pathway B, below.)

STEP 12. Pathway B. (**11G** → **12G**, Pathway B)

Pathway B has 3 steps.

Part 1. The benzyl, or other appropriate group, is removed by hydrogenation over a catalyst, preferably a palladium catalyst supported on carbon or other porous substrate, or palladium black. The solvent is preferably an alcohol, most preferably methanol. The reaction is done at about 15° to about 40° under an

atmosphere of hydrogen at a pressure of about 1 atmosphere to about 4 atmospheres for about 12 to about 96 hours. This produces **12 GB-1**.

Part 2. The lactol is then oxidized under the same conditions for the formation of the hydroxy aldehyde:using either oxidation under Swern conditions such as DMSO, oxalyl chloride and triethylamine in an aprotic solvent such as methylene chloride at a temperature ranging from -78° to about 25°.

Alternatively, the oxidation is done with sodium hypochlorite solution catalyzed by TEMPO or a substituted TEMPO such as 4-acetoxy-TEMPO in a two phase system consisting of water and an aprotic solvent such as methylene chloride. The reaction temperature is between about -5° and about +25° and the reaction time is between about 30 minutes and 2 hours. This produces **12 GB-2** alternately labeled **12 GB-1**.

Part 3. Removal of the methyl group is done with trimethylsilyl iodide, either preformed or generated in situ from trimethylsilyl chloride and sodium iodide, in methylene chloride or acetonitrile. The conditions are described above. This produces **12 G**.

STEP 13. **(12G → 13G)**

12G is reacted with an acrylate ester, such as methyl, ethyl, or t-butyl acrylate in the presence as a base such as potassium hydride, sodium hydride, potassium t-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, or tertiary amines such as diisopropylethyl amine in a polar aprotic solvent such as dimethyl sulfoxide, DMF, or acetonitrile at a temperature between about 20° and 100°. See **CHART G**, p. 5. The preferred conditions are reaction with t-butyl acrylate and cesium carbonate in DMSO at about 50°. The product may be isolated as the toluene solvate. This gives the ketoester, compounds 13G.

STEP 14. **(13G → 14G)**

The ketoester, which may exist primarily or exclusively in the enol form, is converted into **14G** by reaction with a strong acid such as trifluoroacetic acid at a temperature of about 80° to about 110° for about 10 minutes to about 6 hours. A solvent such as toluene may be added. The preferred conditions are a mixture of toluene and trifluoroacetic acid at 100-110° for 1-4 hours.

All references cited in the description of the Charts are incorporated by reference. Using the procedures described above and substituting appropriate starting materials anyone reasonably skilled in the art should be able to make the compounds and reactions of this invention. One embodiment of this invention is

described by the reactions, procedures and structures of **CHART CPT-11**. This embodiment only illustrates and should not limit the invention in any manner.

PROCEDURES, REACTIONS AND COMPOUNDS OF CHART CPT-11

STEP 1. (citrazinic acid → **1CPT**)

Citrazinic acid (152.0g, 0.98mole) and tetramethylammonium chloride (107.71g, 1.02mole) were suspended in phosphorus oxychloride (450g, 273mL, 2.9mole) and heated in a 130°C bath. The solids dissolved with a slight exotherm when the internal temperature reached about 75°C, yielding a clear brown solution. The reaction was heated at 130°C for 18 hours, then heated to 145°C for 2 hours. The mixture was cooled to room temperature, poured onto 2kg of ice, and stirred for 2 hours. The solids were dissolved in 1.5L of ethyl acetate. The organic solution was dried over sodium sulfate, filtered, and evaporated to yield 146.9g (78%) of a light brown solid.

mp 195-197°C (dec). (lit.[1] mp. 205-207°C).

^{1}H NMR (300.13 MHz, DMSO-d_6) δ 7.80 (s, 2H).

^{13}C NMR (75.47 MHz, DMSO-d_6) δ 122.87, 144.60, 150.13, 163.66.

Nominal mass spectrum calculated m/z 192, found m/z 192.

References.

1. M.E.Baizer, M. Dub, S. Gister, N.G. Steinberg, J. Am. Pharm. Assoc, 1956, 45, 478-480.

2. The use of tetraalkylammonium salts in this type of reaction is described in DDR patent 154538.

STEP 2. (**1CPT** → **2CPT**)

1CPT (6.6g, 0.034mole) was mixed with 82mL of THF and the mixture cooled to -40°C. Ethylmagnesium chloride (52mL, 104mmole, 2M in THF) was added over the course of about 15 min, keeping the internal reaction temperature at less than -30°C. The cooling bath was removed, and the resulting dark brown mixture was allowed to warm to 0°C and stirred at 0° C for one hour. The reaction mixture was recooled to -25°C and methyl formate (3.2mL, 52 mmole) was added. After 15 min at -25°C, 20mL of 6M hydrochloric acid was added and the mixture was allowed to warm to room temperature. The phases were separated and the lower aqueous phase was extracted 3 x 10mL with THF. The combined THF phases were washed 2 x with a mixture of 15mL 1N NaOH and 15mL sat NaCl, and then once with 15mL of sat NaCl solution. The organic phase was dried over sodium

sulfate and then concentrated to an oil. Toluene (50mL) was added and the mixture was concentrated to an oil, and the process repeated to yield 6.01g (84%) of brown oil which crystallized under vacuum.

mp 60-63°C.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.17 (t, J=7.1Hz, 3H), 2.88 (q, J=6.6Hz, 2H), 7.61 (s, 2H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.50, 32.61, 120.88, 147.66, 151.83, 197.15.

Nominal mass spectrum calculated *m/z* 204, found *m/z* 204.

STEP 3. (2CPT → 3CPT)

2CPT (90.2g, 0.44mole), ethylene glycol (650mL), and trimethylsilyl chloride (140mL, 1.1mole) were mixed and stirred at room temperature. White crystals gradually formed in the mixture. After about 12 hours the reaction was complete. The reaction was neutralized by the addition of 1L of 1N NaOH solution and extracted 3 x 250mL with 1:1 ethyl acetate/heptane. The organic extracts were combined, dried over sodium sulfate and evaporated. The crystalline residue was dried under high vacuum to yield 109.71g (100%) of the product.

mp 91°C.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.80 (t, J=7.4Hz, 3H), 1.78 (q, J=7.4Hz, 2H), 3.72 (t, J=7.0Hz, 2H), 3.99 (t, J=7.0Hz, 2H), 7.27 (s, 2H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.45, 32.77, 65.10, 108.94, 120.30, 150.57, 158.06.

Nominal mass spectrum calculated *m/z* 248, found *m/z* 248.

STEP 4. (3CPT → 4CPT)

3CPT (57.5g, 0.23mole) was dissolved in methanol (170mL). Sodium methoxide (80mL, 0.35mole, 25% wt soln. in methanol) was added and the reaction brought to reflux in an 85°C oil bath. After 20 hours the reaction mixture was allowed to cool to room temperature and then quenched with 250mL of water. The two-phase mixture was diluted with 200mL of methylene chloride and partitioned. The aqueous phase was extracted with two more 100mL portions of methylene chloride. The organic extracts were combined, dried over MgSO4, filtered, and concentrated to an amber oil which crystallizes upon seeding to yield 50.43g (89%) as a light yellow solid.

mp 47°C.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.88 (t, J=7.4Hz, 3H), 1.85 (q, J=7.5Hz, 2H), 3.78 (t, J=6.9Hz, 2H), 3.93 (s, 3H), 4.02 (t, J=7.1Hz, 2H), 6.73 (s, 1H), 6.98 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.62, 32.53, 54.04, 64.79, 106.25, 109.23, 113.83, 148.33, 157.27, 163.94.

Nominal mass spectrum calculated *m/z* 243 , found *m/z* 244 (m+1).

STEP 5. (**4CPT → 5CPT**)

4CPT (73.05g, 0.299 mole) was dissolved in 1400mL of heptane and cooled to -10°C. n-Butyllithium (294mL, 0.588mole, 2.5M in hexane) was added over 10 min keeping the internal temperature < 5°C. The orange mixture is stirred at 0°C for 30 min after completion of the butyllithium addition. The mixture was then cooled to -30°C and N-formylpiperidine (66.0mL, 0.588mole) was added. The mixture was allowed to warm to 0°C and stirred at 0°C for 1hr. The deep red mixture was quenched by the addition of 600mL of 1N HCl. The phases were separated and the aqueous phase extracted with 2 x 250mL of MTBE. The organic phases were combined to yield a solution of **5aCPT**. A portion of this solution was chromatographed on silica using 4:1 hexane/ethyl acetate to yield a purified sample of **5aCPT** for characterization.

Water (250mL), tetrabutylammonium chloride (8.3g, 0.029 mole), and sodium borohydride (11.3g, 0.29 mole) were added to the solution of **5aCPT** and the mixture was vigorously stirred at room temperature. After about 18 hours the reduction was complete. 20mL of acetone were added and the mixture was stirred at room temperature for 30 min. The aqueous phase was removed and the organic phase was washed once with 500mL of water. The organic phase was evaporated to an oil. The oil was chromatographed on 800g of silica using 4:1 hexane/ethyl acetate. Yield of product was 57.30g, 71% chemical. 15.0g (20%) of essentially pure **4CPT** was also recovered.

5aCPT

^{1}H NMR (300.13 MHz, CDC_{13}) δ 0.96 (t, J=9.0Hz, 3H), 2.03 (q, J=9.0Hz, 2H), 3.75 (m, 2H), 4.00 (m, 2H), 4.00 (s, 3H), 7.13 (s, 1H), 10.44 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.32, 33.28, 54.81, 64.78, 109.66, 114.67, 117.20, 150.83, 157.52, 161.75, 190.80.

Nominal mass spectrum calculated *m/z* 271, found *m/z* 271.

5CPT

mp 49-56°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.84 (t, J=7.5Hz, 3H), 1.87 (q, J=7.0Hz, 2H), 3.74 (m, 2H), 3.92 (s, 3H), 3.97 (m, 2H), 4.72 (s, 1H), 7.05 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.46, 33.01, 54.50, 56.16, 64.98, 110.25, 114.53, 119.15, 147.39, 154.50, 163.00.

Nominal mass spectrum calculated *m/z* 273, found *m/z* 273.

STEP 6. (5CPT → 6CPT, CHART CPT p.2)

5CPT (503.98g, 1.841mole) was dissolved in 1330 mL of THF in a 12L flask equipped with a mechanical stirrer, an addition funnel, and a thermocouple with adaptor. 1188 mL of 20% solution of potassium t-butoxide solution in THF to the flask, keeping the internal temperature less than 30°. The mixture was stirred for 30 min, then benzyl bromide (230.0mL, 2.117mole) was added through the addition funnel, keeping the internal temperature less than 30°. After completion of the benzyl bromide addition, the mixture was stirred at 20-30° for 1 hour.

After one hour, 38mL of 40% aqueous dimethylamine solution was added and the mixture was stirred at 20-30° for 30 min. 276mL of 1N HCl and 2L of ethyl acetate were added and the phases were separated. The organic phase was washed 3 x 1L with water and then evaporated to an oil. Yield of product: 663.5g, 99.3% chemical yield.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.75 (t, J=7.4Hz, 3H), 1.82 (q, J=7.4Hz, 2H), 3.61 (m, 2H), 3.82 (s, 3H), 3.85 (m, 2H), 4.48 (s, 2H), 4.57 (s, 2H), 6.97 (s, 1H), 7.23 (m, 5H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.50, 32.96, 54.47, 62.83, 64.73, 73.20, 110.12, 114.8, 116.42, 127.54, 127.76, 128.24, 138.43, 147.91, 155.62, 163.74.

Nominal mass spectrum calculated *m/z* 363, found *m/z* 364 (m+1).

There are two different possible **STEP 7** reactions, series G and A, and three different possible **STEP 8** reactions. See, **Chart CPT p.2**

STEP 7G. (6CPT → 7CPTG)

6CPT (66.45g, 183mmole), palladium acetate (2.05g, 9.13 mmole), DPPP (4.14g, 10.0mmole), potassium carbonate (37.86g, 274mmole), n-propanol (665mL) and DMF (332mL) were charge to a flask. The flask was purged with nitrogen and then with carbon monoxide. The mixture was heated to 90° under an atmosphere of carbon monoxide for about 16 hours. The reaction was cooled and vented. The solids were removed by filtration through celite and the celite was washed with 350mL of THF. The combined filtrates and washing were concentrated to a volume of about 400mL. Water (700mL) and MTBE (700mL) were added. The aqueous phase was separated and extracted with 350mL of MTBE. The combined MTBE

solutions were extracted 4 x 350mL with water, dried over sodium sulfate, and evaporated to yield 68.03g (89% chem) of a light orange oil after column chromatography (silica gel: 230-400 mesh, eluent: 80:20 heptane/ethyl acetate.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.87 (t, J=7.4Hz, 3H), 0.98 (t, J=7.4Hz, 3H), 1.77 (m, 2H), 1.93 (q, J=7.4Hz, 2H), 3.71 (m, 2H), 3.94 (m, 2H), 3.99 (s, 3H), 4.26 (t, J=6.7Hz, 2H), 4.59 (s, 2H), 4.74 (s, 2H), 7.29 (m, 5H), 7.82 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.5, 10.42, 22.02, 33.08, 54.07, 63.08, 64.72, 66.98, 73.29, 110.26, 117.05, 122.14, 127.51, 127.99, 128.22, 138.45, 144.70, 153.62, 163.88, 165.29.

Nominal mass spectrum calculated *m/z* 415, found *m/z* 416 (m+1).

Step 7A. (6CPT → 7CPTA)

6CPT (50.0g, 0.137mole) was dissolved in 50% aqueous trifluoroacetic acid (250mL) and stirred at room temperature for 48hrs. Water (200mL) and ethyl acetate (200mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 X 200mL). The combined organics were washed with saturated sodium bicarbonate solution (500mL) until residual TFA is removed and then washed with water (200mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to give 42.6g (97%) of product.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.04 (t, 7.2Hz, 3H), 2.71 (q, 7.2Hz, 2H), 3.95 (s, 3H), 4.47 (s, 2H), 4.56 (s, 2H), 6.77 (s, 1H), 7.29 (m, 5H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.39, 36.15, 54.56, 63.16, 73.43, 113.35, 115.73, 127.86, 127.97, 128.51, 137.50, 147.81, 153.07, 161.38, 204.47.

Nominal mass spectrum calculated *m/z* 319, found *m/z* 320 (m+1).

There are 3 possible different **STEP 8** reactions, series G, A and B, see **Chart CPT p.2 & 3**

STEP 8G. (7CPTG → 8CPTG)

7CPTG (68.02g, 163.7mmole) was dissolved at room temperature in 384mL of 50% aqueous TFA. The mixture was stirred at room temperature for 21 hours. 880mL of water was added and the mixture was extracted 2 x 500mL with ethyl acetate. The organic phases were combined and washed 2 x 500ml with water and then neutralized with sat. sodium bicarbonate solution. The organic phase was then dried over sodium sulfate and evaporated to yield 59.86g (98.4%) of the product as a light yellow oil.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.96 (m, 6H), 1.72 (m, 2H), 2.68 (q, J=7.2Hz, 2H),

3.96 (s, 3H), 4.23 (t, J=6.7Hz, 2H), 4.42 (s, 2H), 4.58 (s, 2H), 7.24 (m, 5H), 7.48 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.55, 10.41, 21.99, 36.21, 54.13, 63.83, 67.22, 73.56, 115.50, 121.49, 127.86, 127.97, 128.19, 128.37, 137.32, 144.87, 150.96, 161.31, 164.54.

Nominal mass spectrum calculated *m/z* 371, found *m/z* 372 (m+1).

STEP 8A. (7CPTA → 8CPTA)

7CPTA (1.00g, 3.13mmole) was dissolved in 5 mL THF and cooled to -40°C under nitrogen. Vinylmagnesium bromide (2.9mL, 4.4mmole, 1.5M in THF) was added . The reaction was maintained at -40°C for one hour, and then allowed to warm to room temperature. After 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and diluted with ethyl acetate (10 mL). The aqueous layer was extracted with 10 mL of ethyl acetate which was combined with the previous organic layer and dried over sodium sulfate. Filtration and concentration yielded 1.098g (100% yield) of light amber oil.

^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.87 (t, J=7.32Hz, 3H), 1.79 - 2.00 (m, 2H), 3.93 (s, 3H), 4.54 (s, 2H), 4.83 (s, 2H), 5.16 (dd, J=0.99Hz, 10.59Hz, 1H), 5.25 (dd, J=0.99, 17.23Hz, 1H), 6.01 (dd, J=10.59, 17.23Hz, 1H), 6.94 (s, 1H), 7.30 - 7.37 (m, 5H).

^{13}C NMR (75.468 MHz, $CDCl_3$): δ 7.7, 34.2, 54.5, 62.6, 72.4, 78.0, 114.0, 115.6, 115.9, 127.9, 128.0, 137.2, 143.0, 148.2, 159.2, 163.1.

Nominal mass spectrum: calculated m/z 347, found 348 (M+1).

There are three different possible **STEP 9** reactions, series G, A and B, see **CHART CPT p.3.**

STEP 9G. (8CPTG → 9CPTG)

Methyltriphenylphosphonium bromide (2.14g, 6.0mmole) was dissolved in 15 mL of DMF and stirred at room temperature. Potassium bis- trimethylsilylamide solution (10mL, 5.0mmole, 0.5M in toluene) was added and the yellow solution with suspended white solids was stirred at room temperature for 10 min. A solution of 8CPTG (1.48g, 4.0mmole) in 5mL of THF was added all at once, giving a deep red color that rapidly faded to brown. The mixture was stirred for 10 min. Additional ylide solution was added until all of the 8CPTG was consumed. The reaction was quenched by the addition of 10mL of 1N HCl. 20 mL of MTBE were added and the

phases were separated. The aqueous phase was extracted 2 x 20mL with MTBE. The combined organic phases were washed 3 x 20mL with water, dried over sodium sulfate, and evaporated to a volume of about 15mL (slight triphenylphosphine oxide crystallization). The solution was chromatographed on silica (about 20g) with 4:1 hexane/ethyl acetate to yield 1.39g of product (92% chemical).

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.85 (m, 6H), 1.59 (m, 2H), 2.20 (q, J=7.4Hz, 2H), 3.89 (s, 3H), 4.12 (t, J=6.7Hz, 2H), 4.33 (s, 2H), 4.42 (s, 2H), 4.89 (s, 1H), 5.06 (s, 1H), 7.17 (m, 5H), 7.35 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 10.43, 12.07, 22.02, 30.23, 53.95, 63.79, 67.00, 73.03, 114.66, 118.67, 121.40, 127.60, 127.90, 128.26, 138.21, 144.49, 147.58, 155.33, 163.11, 165.25.

Nominal mass spectrum calculated *m/z* 369, found *m/z* 369.

STEP 9A. (**8CPTA → 9CPTA**)

8CPTA (0.500g, 1.43mmole) was dissolved in 40mL of 1:1 methanol:methylene chloride and cooled to -70°C. and then purged with oxygen for 15 minutes. A stream of ozone from a Welsbach ozone generator was passed through the solution until the solution turned blue. The solution was then purged with oxygen for five minutes to remove excess ozone, and then purged for ten minutes with nitrogen. The -78°C solution was then treated with sodium borohydride (0.250g, 6.61mmole) as a solution in 5mL 50% aqueous methanol. After fifteen minutes, the reaction was allowed to warm to room temperature over the course of an hour. After one hour at room temperature, the reaction was quenched with of 1M HCl solution (10mL) and partitioned. The aqueous phase was extracted with 20mL and 10mL portions of methylene chloride, which were combined with the initial organic layer and dried over sodium sulfate. Filtration and concentration yielded 0.491g (99% chemical yield) of **9CPTA**.

^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.82 (t, J=7.20Hz, 3H), 1.86 (dd, J=7.20Hz, 14.71Hz, 2H), 3.69 (s, 2H), 3.96 (s, 3H), 4.19 - 4.31 (m, 2H), 4.28 (s, 2H), 4.59 (s, 2H), 7.20 (s, 1H), 7.40 - 7.29 (m, 5H).

^{13}C NMR (75.468 MHz, $CDCl_3$): δ 7.61, 35.44, 54.50, 62.97, 73.40, 75.26, 84.72, 113.71, 114.13,127.91, 128.18, 128.35, 137.48, 148.56, 158.01, 163.46.

Nominal mass spectrum calculated m/z, 351, found m/z.

STEP 9B. (**8CPTB → 9CPTA**)

Use similar reagents and conditions described in **STEP 9CPTG**.

STEP 10G. (**9CPTG → 10CPTG**)

9CPTG (100.0g, 0.271mole), trimethylamine N-oxide dihydrate (90.24g, 0.81 mole) and osmium tetroxide (0.68g, 2.7mmole), and 300mL of t-butanol were charged to a flask.The mixture was heated to 40°. After 24 hours, the mixture was cooled to 20-25°. 300mL of water and 110g of sodium metabisulfite were added and the mixture was stirred for 30 min at room temperature. The mixture was extracted 4 x 200mL with ethyl acetate. The organic phases were combined and stirred with 50g of 70-230 mesh silica for 1 hour. The silica was filtered and washed with 100 mL of ethyl acetate. The filtrate was stirred with 100g of magnesol for 30 min and then the slurry was filtered over 50g magnesol. The filtrates were combined and concentrated to an oil. 200mL of toluene and 800mL of heptane were added and the mixture was allowed to crystallize at -20° for 18 hours. The solids were filtered and washed with 200mL of heptane. The yield of **10CPT** was 83.5g. Additional **10CPT** could be recovered from the filtrates and washings by chromatography.

^1H NMR (300.13 MHz, $CDCl_3$) δ 0.74 (t, J=7.4Hz, 3H), 1.03 (t, J=7.4Hz, 3H), 1.80 (m, 4H), 3.69 (d, J=11.2Hz, 1H), 3.86 (d, J=11.2Hz, 1H), 4.01 (s, 3H), 4.31 (t, J=6.7Hz, 2H), 4.88 (d, J=10.7Hz, 1H), 4.96 (d, J=10.7Hz, 1H), 7.33 (m, 5H), 7.64 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.55, 10.41, 22.01, 31.71, 54.16, 62.95, 67.13, 70.86, 72.69, 80.12, 117.83, 122.25, 128.00, 128.42, 137.14, 144.74, 155.82, 163.16, 165.23.

Nominal mass spectrum calculated m/z 403, found m/z 404 (m+1).

STEP 10A. (9CPTA → 10CPTA)

9CPTA (2.13g, 6.0mmole) was dissolved in 1-propanol (25mL) and DMF (50mL) in a flask equipped with a purge line and magnetic stirring. Solid potassium carbonate (1.24g, 9.0mmole), palladium(II)acetate (67mg, 0.3mmole), and DPPP (124mg, 0.3mmole) were charged to the vessel which was then purged with carbon monoxide and heated to 85°C for 15 hours. The reaction mixture was then cooled to room temperature and purged with nitrogen. The solution was filtered over celite and the celite washed with ethyl acetate (3 x 50 mL). The combined filtrate and washings were concentrated under vacuum to an oil. The oil was diluted with ethyl acetate (100mL), and the resulting solution was washed with water (50mL) and then concentrated under vacuum. The product was isolated by column chromatography (silica gel, 230 - 400 mesh, 1:4 ethyl acetate:hexane eluent) to yield 1.40g (58%) **10CPT**.

After **STEPS 10** are performed the optical isomers may be resolved, this is referred to in the CHARTS as STEP 10 resolution, see **Chart CPT p.4.**

STEP 10 Resolution.

To **10CPT** (8.0 g, 20 mmol) suspended in 200 mL of methyl tert-butyl ether is added 8.0 g of PS-30 catalyst (Pseudomonas cepaica lipase immobilized on equal weight of Celite 521) and 1.85 mL (20 mmol) of vinyl acetate. The resulting suspension was magnetically stirred at room temperature for 24 h. The catalyst was removed by filtration, the catalyst washed with methyl tert-butyl ether (3 x 100 mL), and the organic solvent concentrated under vacuum to approximately 25 mL. The solution was kept was 0-5° C, the resulting solid collected by filtration, and washed with hexane (3 x 25 mL) to give 2.75 g of 10CPT (s-enantiomer), $[a]_D^{25}$ = +3.25° in chloroform (>99% ee HPLC Chiralpak AD column, 90:10 hexane-isopropanol, 1 ml/min, 254 nm).

STEP 11. (10CPT → 11CPT)

10CPT (0.565g, 1.4mmole), 4-acetoxy-TEMPO (0.006g, 0.028mmole), potassium bromide (0.0167g, 0.14mmole), and sodium bicarbonate (0.0153g, 0.182mmole) were charged to a flask. Methylene chloride (7mL) and water (1mL) were added and the mixture was stirred at room temperature for 5 min. A solution of sodium hypochlorite (1.6 mL, 0.95M) was added via syringe pump over about 40 min. At the end of this addition reaction was quenched by the addition of 5% aqueous sodium metabisulfite solution. The aqueous phase was separated and extracted 2 x 5mL with methylene chloride. The combined organic phases were dried over sodium sulfate and evaporated to yield 0.601g of a brown syrup. Chemical yield essentially 100%.

^1H NMR (300.13 MHz, $CDCl_3$) δ 0.91 (t, J=7.5Hz, 3H), 1.03 (t, J=7.5Hz, 3H), 1.83 (m, 2H), 2.10 (m, 2H), 4.02 (s, 3H), 4.35 (t, J=6.6Hz, 2H), 4.55 (s, 2H), 4.68 (d, J=11.7Hz, 1H), 4.87 (d, J=11.7Hz, 1H), 7.35 (m, 5H), 7.78 (s, 1H), 9.62 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.24, 10.43, 22.02, 29.72, 54.30, 63.2, 67.24, 73.12, 82.37, 117.45, 122.48, 128.23, 128.55, 136.67, 145.05, 150.55, 162.88, 164.93, 200.14.

Nominal mass spectrum calculated *m/z* 401, found *m/z* 402 (m+1).

Alternative Reactions.

There are two different reactions routes for **STEPS 12**, called Pathway A or Pathway B. Pathway A has two parts. The second Part of Pathway A, Part 2, has two reaction routes, *path a,* a one step procedure and *path b*, a two step procedure. Pathway B has a total of three parts. The second intermediate produced via Pathway A, Part 2, *path b-1*, **12 GA-2**, is the same as the second intermediate produced via Pathway B, Part 2, **12 GB-2**. The third part of Pathway B is the same

as the second step of Pathway A, Part 2, *path b-2*. See **CHART CPT p. 5.**

STEP 12 Pathway A, Part 1. (11CPT → 12CPT A-1)

A solution of **11CPT** (0.206g, 0.5 mmole) in 6mL of t-butanol was mixed with a solution of NaH_2PO_4 (0.035g) in 2mL of water and cooled to 0°. 50% hydrogen peroxide solution (0.043mL) was added, then a solution of sodium chlorite (0.076g, 0.675 mmole) in 0.5mL of water was added all at once. After 5 min, the reaction was quenched by the addition of 1.8mL of 10% aqueous sodium metabisulfite solution. The mixture was partitioned between water and methylene chloride and the aqueous phase extracted 2 x with methylene chloride. The combined organic phases were evaporated to yield 0.200g (93%) of the product **12 CPT A-1**.

^1H NMR (300.13 MHz, $CDCl_3$) δ 1.02 (m, 6H), 1.82 (m, 2H), 2.23 (m, 2H), 3.99 (s, 3H), 4.32 (t, J=6.9Hz, 2H), 4.53 (d, J=11.7Hz, 1H), 4.62 (d, J=11.7Hz, 1H), 4.68 (d, J=11.7Hz, 1H), 4.97 (d, J=11.7Hz, 1H), 7.32 (m, 5H), 7.90 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.83, 10.41, 22.01, 32.15, 54.36, 62.62, 67.31, 72.95, 79.21, 117.39, 121.82, 128.21, 128.52, 136.52, 145.25, 152.55, 162.97, 165.01, 176.06.

Nominal mass spectrum calculated *m/z* 417, found *m/z* 418 (m+1).

STEP 12, Pathway A, Part 2, path a. (one step) **(12 CPT A-1 → 12CPT)**

A solution of **12A-1 CPT** (0.17g, 0.40mmole) and pyridine (0.05mL, 0.6mmole) in 5 mL of acetonitrile was stirred at room temperature. Trimethylsilyliodide (0.2 mL, 1.4mmole) was added and the mixture was stirred overnight at room temperature, then heated at 45° for 48 hours. Hydrochloric acid (5 mL, 6N) was added and the mixture was stirred at room temperature for 15 min. The mixture was extracted 3 x 5 mL ethyl acetate and the combined extracts were washed with 5% sodium bisulfite solution. The ethyl acetate solution was dried over sodium sulfate and evaporated. The residue was chromatographed on silica with 95:5 methylene chloride/methanol to yield 0.083g (69%) of the product as a light yellow oil.

^1H NMR (300.13 MHz, $CDCl_3$) δ 1.02 (m, 6H), 1.80 (m, 4H), 4.36 (t, J=6.0Hz, 2H), 5.22 (d, J=16.5Hz, 1H), 5.60 (d, J=16.5Hz, 1H), 7.40 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.66, 10.33, 21.84, 31.88, 66.07, 68.68, 72.32, 107.10, 124.45, 134.41, 149.99, 159.80, 173.26, 176.63.

Nominal mass spectrum calculated *m/z* 295, found *m/z* 296 (m+1).

STEP 12, Pathway A, Part 2, path b-1. (12 CPT A-1 → 12CPT A-2)

A solution of hydroxy acid **12CPT A-1** (2.64g, 6.3 mmole) in 50 mL of

methanol was stirred with 10% palladium on carbon (0.264g) under an atmosphere of hydrogen at atmospheric pressure for 2 hours at room temperature. The catalyst was removed by filtration through celite and washed with 10 mL of methanol. The combined filtrate and washing were evaporated to yield the product (1.82g, 93%) as a light yellow, very viscous oil.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ d 0.88 (t, J=7.5Hz, 3H), 0.97 (t, J=7.6Hz, 3H), 1.76 (m, 4H), 4.0 (s, 3H), 4.25 (t, J=6.9Hz, 2H), 5.23 (d, J=16.2Hz, 1H), 5.52 (d, J=16.2Hz, 1H), 7.85 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.49, 10.32, 21.89, 31.88, 54.08, 65.53, 67.22, 72.72, 114.79, 115.22, 146.01, 148.91, 158.50, 164.51, 173.53.

STEP 12, Pathway A, Part 2, path b-2. (12 CPT A-2 → 12 CPT)

A solution of hydroxylactone **12CPT A-2** (1.93g, 6.2 mmole) and sodium iodide (1.86g, 12.4 mmole) in 30 mL of acetonitrile was stirred at 0°. Trimethylsilyl iodide (1.6 mL, 12.4 mmole) was added and the mixture was stirred and allowed to warm to room temperature over 12 hours. Additional sodium iodide (0.9g, 6.2 mmole) and trimethylsilyl chloride (0.8 mL, 6.2 mmole) were added and stirring was continued for 6 more hours. 1N hydrochloric acid (10 mL0 was and sodium metabisulfite (0.6g) were added and the mixture was stirred at room temperature for 1 hour. Ethyl acetate (30 mL) was added and the aqueous phase was extracted with an additional 30 mL of ethyl acetate. The combined organic phases were washed with water, dried over sodium sulfate, and evaporated to yield the product as a light yellow solid 1.84g, 100%).

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 1.02 (m, 6H), 1.80 (m, 4H), 4.36 (t, J=6.0Hz, 2H), 5.22 (d, J=16.5Hz, 1H), 5.60 (d, J=16.5Hz, 1H), 7.40 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.66, 10.33, 21.84, 31.88, 66.07, 68.68, 72.32, 107.10, 124.45, 134.41, 149.99, 159.80, 173.26, 176.63.

Nominal mass spectrum calculated m/z 295, found m/z 296 (m+1).

STEP 12, Pathway B, Part 1. (11 CPT → 12 CPT B-1)

Hydroxyaldehyde **11CPT** (2.62g, 6.6 mole) was dissolved in 30 mL of methanol and stirred with 10% palladium on carbon (0.26g) under an atmosphere of hydrogen at atmospheric pressure. After 96 hours the reaction was complete. The catalyst was removed by filtration through celite and washed with 10 mL of methanol. The combined filtrate and washing were evaporated to yield 1.97g (96%) of the product as a white solid.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ , 0.84 (t, J=7.5Hz, 3H), 0.95 (t, J=7.4Hz, 3H), 1.73 (m, 4H), 3.89 (s, 3H), 4.24 (t, J=6.7Hz, 2H), 4.57 (d, J=17.2Hz, 1H), 4.73 (d, J=17.2Hz, 1H), 7.86 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.53, 10.36, 21.94, 31.70, 53.69, 58.31, 67.04, 70.68, 93.26, 116.57, 120.38, 143.54, 148.98, 158.48, 165.34.

STEP 12, Pathway B, Part 2. (12 CPT B-1 → 12 CPT B-2)

A solution of the lactol **12CPT B-1** (1.94g, 6.2 mmole) in 37 mL of methylene chloride was stirred at room temperature with a solution of TEMPO (0.04g, 0.25 mmole), sodium bicarbonate (0.081g, 0.96 mmole), and potassium bromide (0.088g, 0.74mmole) in 3 mL of water. Sodium hypochlorite solution (12%, approximately 12 mL) was added dropwise over 30 min. Sodium bisulfite (1.0g) was added to destroy the excess sodium hypochlorite. The aqueous phase was extracted with methylene chloride (10 mL) and the combined organic phases were washed once with water (10 mL) and dried over sodium sulfate. The solvent was evaporated to yield the product (1.90g, 99%) as an oil that solidified on standing.

^{1}H NMR (300.13 MHz, $CDCl_3$) δ d 0.88 (t, J=7.5Hz, 3H), 0.97 (t, J=7.6Hz, 3H), 1.76 (m, 4H), 4.0 (s, 3H), 4.25 (t, J=6.9Hz, 2H), 5.23 (d, J=16.2Hz, 1H), 5.52 (d, J=16.2Hz, 1H), 7.85 (s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.49, 10.32, 21.89, 31.88, 54.08, 65.53, 67.22, 72.72, 114.79, 115.22, 146.01, 148.91, 158.50, 164.51, 173.53.

Nominal mass spectrum calculated m/z , found m/z .

STEP 12, Pathway B, Part 3. (12 CPT B-2 → 12 CPT)

This step is identical to, and the procedures used are the same as, **STEP 12**.

STEP 13, Pathway A, Part 2, path b-2. (12 CPT → 13 CPT)

12CPT (10.1g, 0.339mole), cesium carbonate (22.0g, 0.067mole), t-butyl acrylate (25mL, 0.169mole), and DMSO (150mL) were stirred at 47-50° for 19 hours. The mixture was cooled and 20mL of concd hydrochloric acid and 180mL of water were added. The mixture was extracted 4 times with a total of 500mL of a 4:1 (v/v) mixture of toluene and ethyl acetate. The combined extracts were washed three times with water and then evaporated to an oil. 200mL of toluene was added and the solution was concentrated to yield **13CPT** solvate, as the crystalline 1:1 toluene solvate (11.5g, 67%).

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.92 (t, J=7.4Hz, 3H), 1.50 (s, 9H), 1.71-1.79 (m, 2H), 2.28 (s, 3H), 4.59 (s, 2H), 5.16 (d, J=17.8Hz, 1H), 5.61 (d, J=17.8Hz, 1H), 6.94

(s, 1H), 7.0-7.2 (m, 5H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 7.64, 21.38, 28.20, 31.41, 49.27, 66.13, 72.50, 83.55, 97.80, 105.69, 118.59, 125.22, 128.14, 128.95, 137.78, 143.82, 149.48, 156.84, 159.26, 166.02, 173.60.

STEP 14. (13 CPT → 14 CPT)

The **13CPT**-toluene solvate (70.3g, 0.153mole) was dissolved in 1400mL toluene and 140mL trifluoroacetic acid and heated at 110° for 2 hours. The solution was cooled and concentrated under vacuum to about 350mL. Ethyl acetate (1L) was added and the mixture was cooled to -20°. Filtration yielded **14 CPT** as a light brown crystalline solid (37.92g, 93.4%).

^{1}H NMR (300.13 MHz, $CDCl_3$) δ 0.98 (t, J=7.5Hz, 3H), 1.80 (q, J=6.0Hz, 2H), 2.96 (m, 2H), 4.36 (t, J=6Hz, 2H), 5.24 (d, J=15Hz, 1H), 5.66 (d, J=15Hz, 1H), 7.27 (s, 1H).

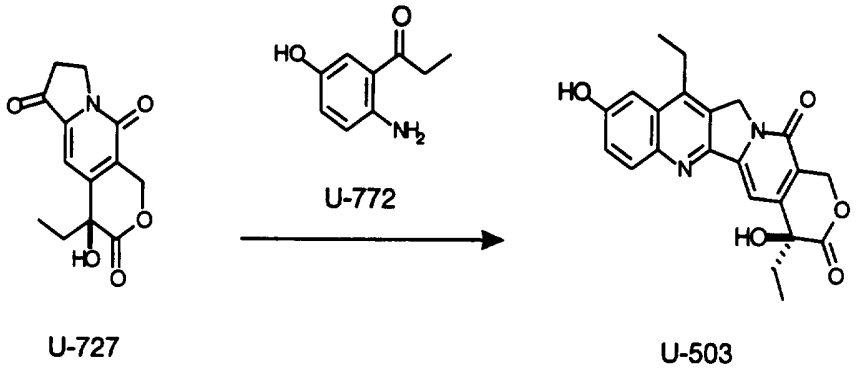
^{1}H NMR (300.13 MHz, DMSO-d_6) δ 0.80 (t, J=7.3Hz, 3H), 1.81 (m, 2H), 2.89 (t, J=6.3Hz, 2H), 4.13 (t, J=6.3Hz, 2H), 5.34 (d, J=17.1Hz, 1H), 5.41 (d, J=17.1Hz, 1H), 6.86 (s, 1H).

^{13}C NMR (75.47 MHz, DMSO-d_6) δ 7.52, 30.31, 33.71, 42.56, 65.20, 71.92, 98.49, 123.81, 140.19, 149.05, 156.97, 172.03, 197.93.

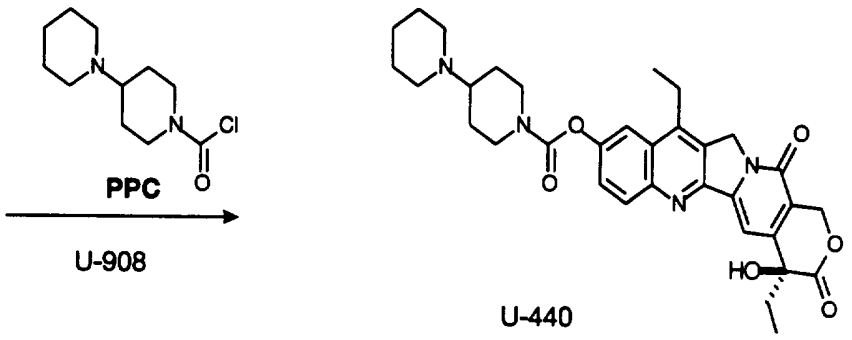
Nominal mass spectrum calculated m/z 263, found m/z 264 (m+1).

ADDITIONAL DISCLOSED REACTIONS

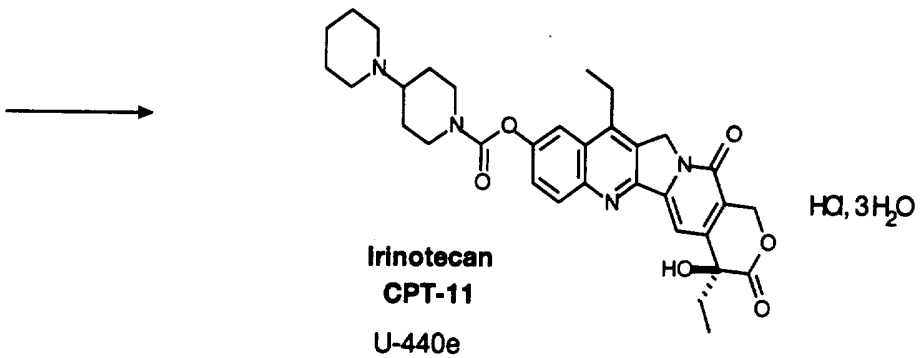
The following reactions, procedures and formula in the Chart below are also included with this invention.



U-727 U-503



U-440



Irinotecan
CPT-11
U-440e

The following references may be useful in understanding the ADDITIONAL DISCLOSED REACTIONS above. The preparation of **u-503** from natural camptothecin is described in US patent **4,473,692** (Sep 25, 1984), T. Miyasaka, S. Sawada, K. Nokata, M. Mutai. A related preparation of **U-440** from **U-503** is described in US patent **4,604,463**, (Aug 5, 1986), T. Miyasaka, S. Sawada, K. Nokata, E. Siguno, M. Mutai. The conversion of **U-440** into CPT-11 is described in: S. Sawada, S. Okajima, R. Aiyama, K. Nokata, T. Furuta, T. Yokohura, E. Siguno, K. Yamaguchi, T. Miyasaka, *Chem. Pharm. Bull*, 1991, Volume 39, pp. 1446-1454.

The reactions shown in the Additional Disclosed Reaction Chart above are described below.

Preparation of **U-503** and **U-440**

U-727 and **U-772** are reacted at 95° to 100° in a mixture of toluene and acetic acid for about 18-24 hours. The toluene and acetic are removed by distillation to yield **U-503** which is converted without purification into **U-440**.

The unpurified **U-503** is dissolved in pyridine and reacted at 20° to 25° with 4-piperidinopiperidinecarbamyl chloride dissolved in methylene chloride. The methylene chloride and pyridine are removed by distillation and the crude **U-440** is redissolved in methylene chloride and treated with saturated aqueous sodium bicarbonate solution. The **U-440** is then chromatographed on silica gel eluting with a mixture of methylene chloride and methanol, and isolated as a crystalline solid by crystallization from a mixture of methylene chloride and ethanol.

U-503. U-727 (1.05g, 4.0mmole), U-772 (0.62g, 3.8mmole), and p-toluenesulfonic acid monohydrate (0.02g) are mixed with toluene (10mL) and acetic acid (10mL) and heated for 18-24 hours at 95° to 100°. **U-503** gradually precipitates during the course of the reaction. When the reaction is complete the toluene and acetic acid are removed by distillation under reduced pressure to yield U-503 as a solid mass.

U-440. Pyridine (15mL) is added to the unpurified **U-503** and the mixture is stirred for 15 minutes at 20° to 25° to dissolve the U-503. A solution of 4-piperidinopiperidinecarbamyl chloride (1.32g, 5.7mmole) dissolved in methylene chloride (5mL) is added. The mixture is stirred at 20-25° for 2 hours to complete the reaction. The mixture is distilled to dryness under reduced pressure. Toluene (20mL) is added and the mixture is distilled to near dryness under reduced pressure.

The unpurified **U440** is dissolved in methylene chloride (25mL), saturated

aqueous sodium bicarbonate solution (5mL) is added, and the mixture is stirred at room temperature for 5 min. The phases are allowed to settle and the methylene chloride phase is removed. The aqueous phase is extracted with with methylene chloride (10mL). The methylene chloride phases are combined and distilled to yield crude solid **U-440**.

The crude solid **U-440** is dissolved in 95:5 methylene chloride-methanol (v/v, 10mL) and chromatographed on a column packed with 30g of 230-400 mesh silica, eluting with and 95:5 methylene chloride-methanol (v/v). The product containing fractions are combined and distilled to a volume of about 10mL under atmospheric pressure. Some product crystallization may occur at the end of the distillation. Ethanol (15mL) is added and the slurry is allowed to stand at -20° C for 24 hours. The product is filtered, washed with ethanol (10mL), and dried to yield 1.34g (62% chemical from 16CPT) of **U-140**.

PROCEDURES, REACTIONS AND COMPOUNDS OF CHART M-M and M-G

Chiral Reduction for Mappicine Synthesis and related compounds shown in **CHARTS M-G** and **M-M**. The precursors of these compounds are described by the early reactions of CHART G.

There are a number of reagents available for the reduction of ketones to produce chiral secondary alcohols. Aryl-alkyl ketones similar in structure to the intermediates shown in the mappicine CHARTS are particularly favorable substrates for chiral reduction. Among the reagents that are effective for this type of reduction are Noyori's binaphthol-lithium aluminum hydride complex[1], complexes of borane and chiral amino alcohols developed by Itsuno[2], borane reductions catalyzed by chiral oxazaborolidines[3], and complexes of lithium aluminum hydride and darvon alcohol[4].

Reaction products and intermediate from the above can then be reacted in obvious variants of the Friedlander type condensation to produce desired products such as those shown in the **CHARTS** below.

1. R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc*, 1979, 101, 3129; R. Noyori, U.S patent 4,284,581.

2. S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc. Chem. Comm.*, 1983, 469; S. Itsuno, M. Nakano, K. Miyazaki, H.Masuda, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc. Perkin* I, 1985, 2039.

3. E.J. Corey, R.K. Bakshi, S. Shibate, *J. Am. Chem. Soc.* 1987, 5551.

4. N. Cohen, R.J. Lopresti, C. Neukom, G. Saucey, *J. Org. Chem.* 1980, 45, 582.

The following is one specific example showing, in detail, the conditions for the reactions shown in **CHARTS M-G** and **M-M**.

5MM. 4CPT (10.0 g, 41.0 mmol) was dissolved in 500mL of heptane. The solution was cooled to 0°C and 24.4 mL of n-BuLi in hexanes (2.10M, 51.2 mmol) was added while maintaining reaction temperature at 0°C. The bright-orange slurry was stirred at 0°C for 1.75 h. Dimethyl sulfate (4.8 mL, 51.2 mmol) was added maintaining reaction temperature below 10°C. The reaction was stirred at 0°C for 2 h, and then treated with 1.5 mL of conc. NH_4OH before stirring an additional 1 h. Water (40mL) and EtOAc (75mL) were added. After 15 min, the phases were partitioned and the aqueous extracted from with 3 x 50 mL portions of EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated to a red oil. Purification by flash-chromatography (CH_2Cl_2) gave 5MM (6.97 g, 66%) as a clear, colorless oil: MS (EI) *m/z* 257, 259; MS (CI) *m/z* (-NH_3^+) 258, 260; ^{1}H NMR (300.14 MHz, $CDCl_3$) δ 7.08 (s, 1H), 4.05 - 4.01 (m, 2H), 3.97 (s, 3H), 3.80 - 3.75 (m, 2H), 2.28 (s, 3H), 1.93 (dd, J = 7.4, 14.9 Hz), 0.91 (t, J = 7.4 Hz); ^{13}C NMR (75.47 MHz) δ 162.9, 153.3, 144.9, 116.9, 114.4, 110.1, 64.5, 54.2, 31.5, 12.0, 7.4.

6MM. 5MM (12.0 g, 46 mmol) was dissolved in 25 mL of aqueous TFA (64% v/v) and heated to 40°C. After 4 h, the reaction mixture was cooled and quenched with 50 mL H_2O and 75 mL 2:1 (v/v) EtOAc:heptane. The phases were partitioned and the aqueous extracted from with 3 x 40 mL portions of 2:1 EtOAc:heptane. The organic extracts were combined and neutralized by washing with 200 mL of 9% (w/v) aqueous $NaHCO_3$. The phases were partitioned and the aqueous phase was extracted from with 3 x 50 mL portions of EtOAc. The organic phases were combined, dried (Na_2SO_4), filtered and concentrated to give 10g of a yellowish oil. The crude product was carried directly into the next reaction. A small portion was purified for characterization: MS (EI) *m/z* 213, 215; MS (CI) *m/z* (-NH_3^+) 214, 216; ^{1}H NMR (300.14 MHz, CDCl3) δ 6.88 (s, 1H), 3.99 (s, 3H), 2.82 (dd, J = 7.2, 14.5 Hz), 2.16 (s, 3H), 1.19 (t, J = 7.2 Hz); ^{13}C NMR (75.47 MHz) δ 204.2, 162.6, 150.5, 145.5, 116.3, 113.0, 54.4, 35.9, 11.8, 7.6.

6bMM. Crude 6MM (10g, approx 46 mmol) was dissolved in 100 mL of MeOH and cooled to 0°C. A freshly-prepared solution of 2.18 g of $NaBH_4$ (58 mmol) in 20 mL of 50% aqueous MeOH was added in all at once. After 20 min, the reaction was quenched with 50 mL aqueous HCl (1M, 50 mmol) and then diluted

with 100 mL CH_2Cl_2 and 10 mL of water. The phases were partitioned and the aqueous phase was extracted with 3 x 50 mL portions of CH_2Cl_2. The organic extracts were concentrated to a white solid. The solid material was recrystallized from hexane to give 7MM (8.54 g, 85% from 5MM) as long needles: mp = 97.0 - 97.5 °C; MS (EI) *m/z* 215, 217; MS (CI) *m/z* ($-NH_3^+$) 216, 218; ^1H NMR (300.14 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.85 - 4.81 (m, 1H), 3.95 (s, 3H), 2.08 (s, 3H), 1.76 - 1.63 (m, 2H), 0.98 (t, J = 7.4 Hz); ^{13}C NMR (75.47 MHz) δ 161.8, 155.6, 145.4, 115.0, 113.1, 71.0, 54.1, 30.4, 10.5, 9.8.

7MM 7MM (4.00 , 18.5 mmol) and sodium hydride (1.55g , 64.6 mmol) were stirred with 40mL of THF for 30 min. Benzyl bromide (2.3 mL, 18.9 mmol) was added and the mixture was stirred for 8 hours at room temperature. Saturatea ammonium chloride solution (10mL), 10 mL of water, and 20 mL CH_2Cl_2 were added. The phases were partitioned and the pH of the aqueous phase was adjusted with 1M HCl to neutrality before extracting with 3 x 20 mL portions of CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4), filtered and concentrated to a yellow oil. Flash chromatography over silica gel gave 8MM (5.09 g, 90%) as a clear oil: MS (EI) *m/z* 305, 307; MS (CI) *m/z* ($-NH_3^+$) 306, 308; ^1H NMR (300.14 MHz, $CDCl_3$) δ 7.38 - 7.32 (m, 5H), 7.07 (s, 1H), 4.53 - 4.46 (m, 2H), 4.26 (d, J = 11.7 Hz, 1H), 4.00 (s, 3H), 2.09 (s, 3H), 1.83 - 1.62 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz) δ 162.0, 154.0, 145.6, 137.9, 128.4, 127.8, 127.7, 116.3, 113.8, 78.0, 71.0, 54.2, 29.5, 10.5, 10.1.

8MM 8MM (4.00 g, 13.1 mmol), potassium acetate (1.92g, 19.6 mmol), palladium acetate (0.147g, 0.65 mmol), and DPPP (0.268g, 0.65 mmol), were stirred with 80 mL of DMF and 40 mL of n-propanol. The flask was purged with CO and then heated to 85°Cunder an atmospherre of CO. After 25 the mixture was cooled and purged with nitrogen. The solution was filtered over celite and the filtrate was concentrated and then partitioned between 80 mL of water and 160 mL MTBE. The aqueous phase was further extracted with 3 x 50 mL portions of MTBE. The organic extracts were combined, washed with 4 x 25 mL portions of water, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography using CH_2Cl_2 as eluent gave 9MM (4.14 g, 89%) as a clear, colorless oil: MS (EI) *m/z* 358; MS (CI) *m/z* ($-NH_3^+$) 358, 360; ^1H NMR (300.14 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.38 - 7.28 (m, 5H), 4.57 - 4.53 (m, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.36 - 4.32 (m, 2H), 4.25 (d, J = 11.6 Hz, 1H), 4.09 (s, 3H), 2.18 (s, 3H), 1.90 - 1.80 (m, 3H), 1.78 - 1.64 (m,

2H), 1.06 (t, J = 7.4 Hz), 0.97 (t, J = 7.4 Hz); ^{13}C NMR (75.47 MHz) δ 165.5, 162.3, 151.5, 142.8, 138.0, 128.3, 127.8, 127.7, 122.9, 116.5, 78.1, 70.9, 66.8, 53.8, 29.5, 22.0, 11.3, 10.4, 10.2.

9MM. A solution of sodium iodide (1.89 g , 12.6 mmol) and 8MM (3.00 g , 8.4 mmol) in 30 mL of CH_3CN was cooled to 0°C and trimethylsilyl chloride (1.6 mL, 12.6 mmol) was added. After 15 min. the reaction mixture was allowed to warm to room temperature. After 24 h the reaction was quenched by sequentially adding 4.2 mL of 6M HCl, 5.3 mL saturated sodium chloride solution, 10.6 mL H_2O, 0.4 mL 38% $Na_2S_2O_5$(aq) and 20 mL EtOAc. After stirring at room temperature for 30 min, the phases were separated and the aqueous phase extracted with 3 x 10 mL portions of EtOAc. The organic solutions were combined and washed with 7 mL of satd. $NaHCO_3$ and 0.25 mL of 38% aqueous sodium bisulfite. After stirring for 15 min, the phases were separated and the organic solution was washed with 2 x 10 mL of saturated aqueous sodium chloride solution. The solution was dried over Na_2SO_4, then filtered and concentrated to give 2.80 g (97%) of 9MM as a waxy yellow-white solid: MS (EI) *m/z* 343, 344; MS (CI) *m/z* (-NH_3^+) 344, 345; ^1H NMR (300.14 MHz, $CDCl_3$) δ 9.82 (broad s), 7.39 - 7.29 (m, 6H), 4.51 - 4.46 (m, 1H), 4.35 - 4.26 (m, 2H), 2.14 (s, 3H), 1.87 - 1.75 (m, 3H), 1.71 - 1.57 (m, 1H), 1.05 - 0.95 (m, 6H); ^{13}C NMR (75.47 MHz) δ 162.42, 161.28, 150.41, 137.63, 133.04, 130.54, 128.40, 127.87, 108.01, 77.76, 71.13, 67.95, 28.80, 21.84, 12.04, 10.29, 10.06.

10MM. A mixture of 9MM (3.22 g, 9.4 mmol), cesium carbonate (6.12 g , 18.8 mmol), t-butyl acrylate (13.5 mL, 92.3 mmol), and 50 mL of DMSO was heated to 65°C under a nitrogen atmosphere. After 3 hours the reaction mixture was cooled to 0°C and then slowly quenched with 60 mL of 0.5 M HCl, maintaining throughout an internal reaction temperature at or below 15°C. The mixture was diluted with 30 mL 1:4 EtOAc:toluene (v/v) and partitioned. The aqueous was extracted from with 2 x 30 mL portions of the above solvent. The organic extracts were combined and washed with 3 x 30 mL portions of water, dried over Na_2SO_4, filtered and concentrated to 4.57 g of yellow oil. Purification by column chromatography yields 3.28 g of 10MM as a foamy off-white solid (85%): MS (EI) *m/z* 411, 412; MS (CI) *m/z* (-NH_3^+) 412, 413; ^1H NMR (300.14 MHz, $CDCl_3$) δ 9.91 (br s), 7.39 - 7.29 (m, 5H), 6.91 (s, 1H), 4.67 (s, 2H), 4.52 - 4.48 (m, 2H), 4.26 (d, J = 11.8 Hz, 1H), 2.18 (s, 3H), 1.87 - 1.78 (m, 1H), 1.73 - 1.53 (m, 2H), 1.59 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz) δ 166.61, 160.77, 160.28, 150.69, 140.25, 137.89, 128.35,

127.77, 127.69, 126.63, 103.99, 99.13, 82.95, 78.02, 70.88, 49.08, 29.01, 28.25, 27.87, 11.84, 10.07.

11MM. A solution of 10MM (0.25g , 0.61 mmol), trifluoroacetic acid (0.45 mL), and toluene (18mL) was heated to 75°C. After 24 h, the solution was concentrated *via* rotary evaporation to a thick oil. The oil was diluted with 20 mL of toluene and concentrated to a thick oil. The oil was purified by flash chromatography (5% MeOH in CH_2Cl_2) to yield 0.138g of 11MM as a foamy yellow solid (73%): MS (EI) *m/z* ; MS (CI) *m/z* ($-NH_3^+$) ; ^1H NMR (300.14 MHz, $CDCl_3$) δ 7.27-7.18 (m, 5H), 7.04 (s, 1H), 4.43 - 4.38 (m, 2H), 4.23 - 4.13 (m, 3H), 2.80 (t, J = 6.9 Hz), 2.09 (s, 3H), 1.75 - 1.47 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz) δ 196.91, 161.48, 150.48, 137.67, 136.95, 132.94, 128.36, 127.71, 102.40, 77.77, 70.97, 41.92, 33.69, 28.90, 12.41, 9.98.

12MM. A solution of 11MM (0.135g, 0.43 mmol), N-Boc o-aminobenzaldehyde (0.14g, 0.63 mmol), p-toluenesulfonic acid (0.010g, 0.06 mmol) , glacial acetic acid (5mL), and toluene (25mL) was heated to 100°C. After 36 h the solution was concentrated under vacuum to dryness. The residue was dissolved in 25 mL of toluene and then concentrated to 0.333g of red-brown solids. The material was purified by flash chromatography (2% MeOH in CH_2Cl_2) to deliver 0.123g of 12MM as a foamy yellow solid (72%): MS (EI) *m/z* 396, 398; MS (CI) *m/z* ($-NH_3^+$) 397, 399; ^1H NMR (300.14 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7 Hz, 1H), 7.64 - 7.57 (m, 2H), 7.38 - 7.29 (m, 5H), 5.28 (s, 2H), 4.64 - 4.54 (m, 2H), 4.32 (d, J = 12 Hz, 1H), 2.25 (s, 3H), 1.99 - 1.67 (m, 1H), 1.02 (t, J = 7.3 Hz); ^{13}C NMR (75.47 MHz) δ 161.51, 153.51, 151.30, 148.78, 142.67, 138.12, 130.67, 130.12, 129.56, 128.64, 128.33, 127.98, 127.76, 127.60, 127.29, 126.87, 99.51, 78.18, 70.81, 49.91, 29.08, 11.99, 10.19.

CHARTS

Charts useful in the description of this invention are described briefly here and appear on the following pages. Detailed description is provided above. **CHART G** is a general description showing the generic structures involved in the reactions. After the production of the compound labeled 4G there are two quite different reaction pathways that may be pursued. One pathway continues with **CHART G** and eventually results in the production of camptothecin or related compounds. The other pathway, **CHART M-G**, eventually results in the production of mappicine or related compounds.

CHART CPT-11 is one species specific embodiment of **CHART G** that shows the specific reactions and intermediates resulting in the production of camptothecin. **CHART M-M** is one species specific embodiment of **CHART M** that shows the specific reactions and intermediates resulting in the production of mappicine.

Step 10 in **CHARTS G** and **CPT-11** show the resolution of enantiomers. Although only one enantiomer is shown, the other enantiomer could also be resolved using appropriate starting materials and making the necessary modifications that would be obvious to one of ordinary skill in the art. The procedures would then be applicable to whatever enantiomer or mixtures of enantiomers, was desired.

When only one asymmetric center is present, the procedures, with appropriate modifications as needed, may be used to produce either enantiomer. When two asymmetric centers are present, the sterochemistry of only one of the two centers may be shown. When there are two asymmetric centers in a molecule, the procedures herein will generally result in resolution of only one asymetric center, the second center will usually be unresolved. By making appropriate modifications to the procedures herein in combination with procedures available to one ordinarily skilled in the art, complete resolution of all four stereoisomers could be accomplished for the molecules having two asymmetric centers.

CHARTS M-G and G-G show one enantiomer, with a bold line showing orientation, however; the other enantiomer could just as well be made and isolated using procedures known to one ordinarily skilled in the art. The procedures would then be applicable to whatever enantiomer, or mixtures of enantiomers, was selected. The other enantiomers from **CHARTS M-G and G-G** are shown in some of the claims where the orientation is shown with either a bold or a dotted line.

Hydrogen atoms, and their connecting bonds, are not usually shown in the following CHARTS or in any of the formula used herein. Sometimes carbon atoms are only indicated by bonds and not by the letter "c."

The various charts follow.

CHART G p.1

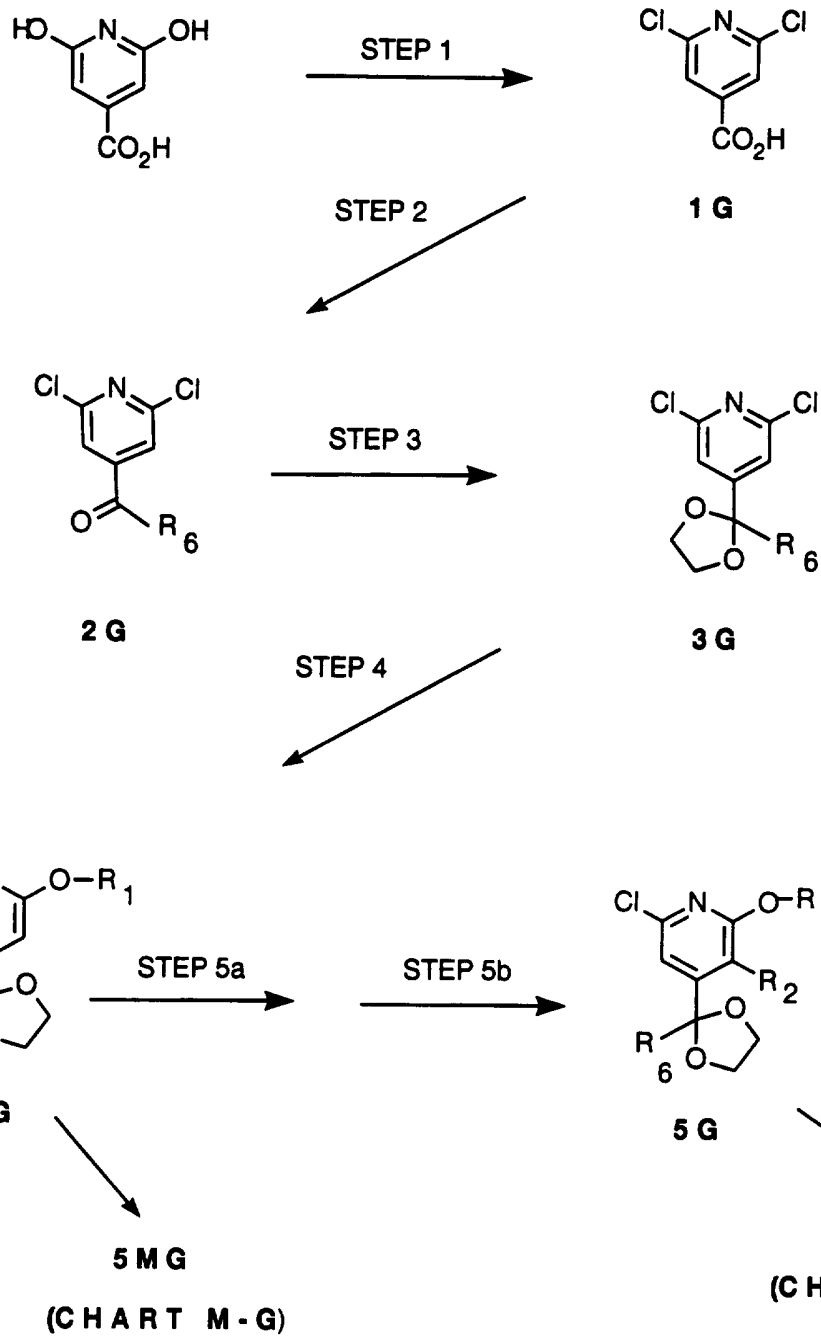
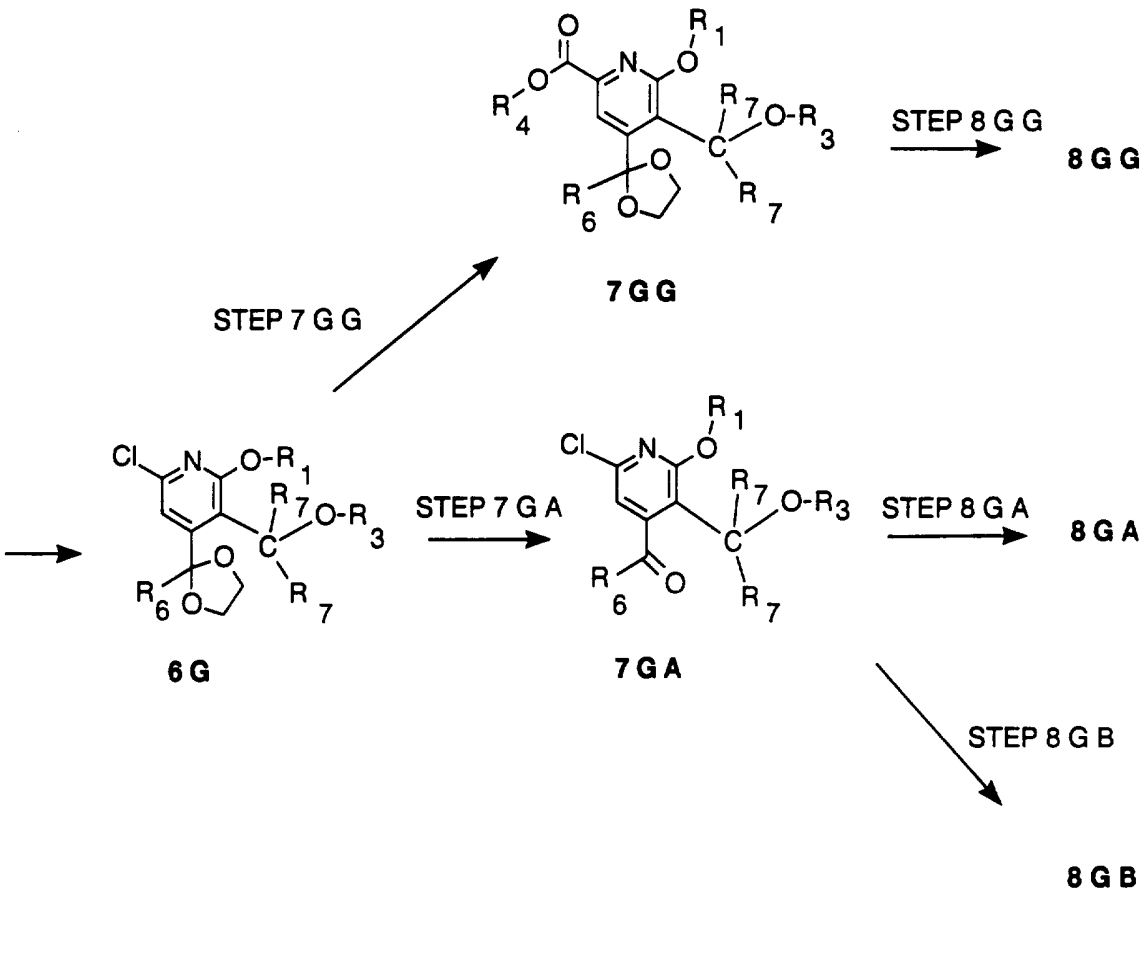

STEP 1
STEP 2
1 G
STEP 3
2 G
3 G
STEP 4
STEP 5a
STEP 5b
4 G
5 G
STEP 6
6 G
5 M G
(C H A R T M - G)
(C H A R T G p.2)

CHART G p.2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STEP 8 G G
8 G G
7 G G
STEP 7 G A
STEP 8 G A
8 G A
6 G
7 G A
STEP 8 G B
8 G B

CHART G p.3

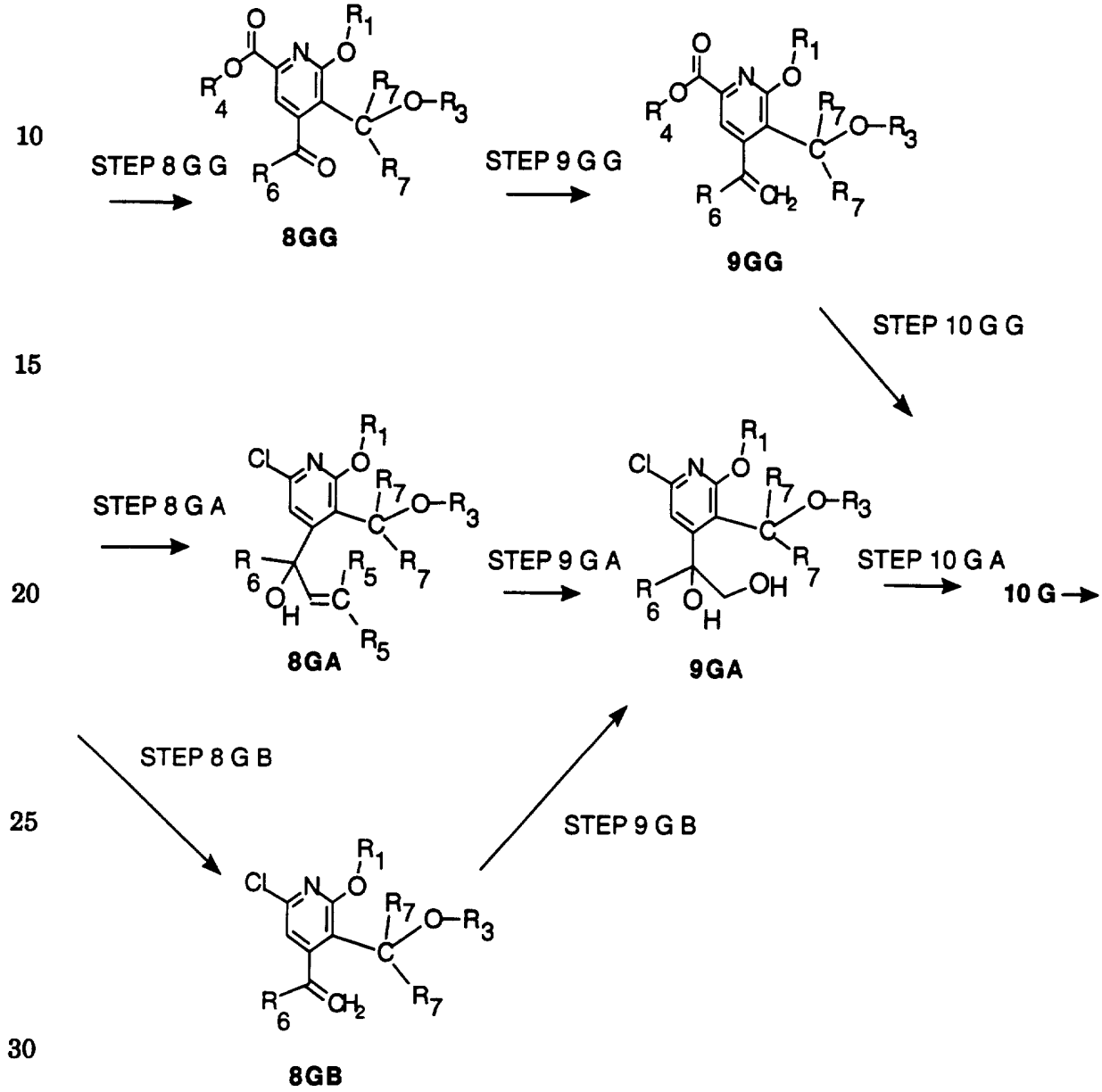

STEP 8 G G
8GG
STEP 9 G G
9GG
STEP 10 G G
STEP 8 G A
8GA
STEP 9 G A
9GA
STEP 10 G A
10 G
STEP 8 G B
8GB
STEP 9 G B

CHART G p.4

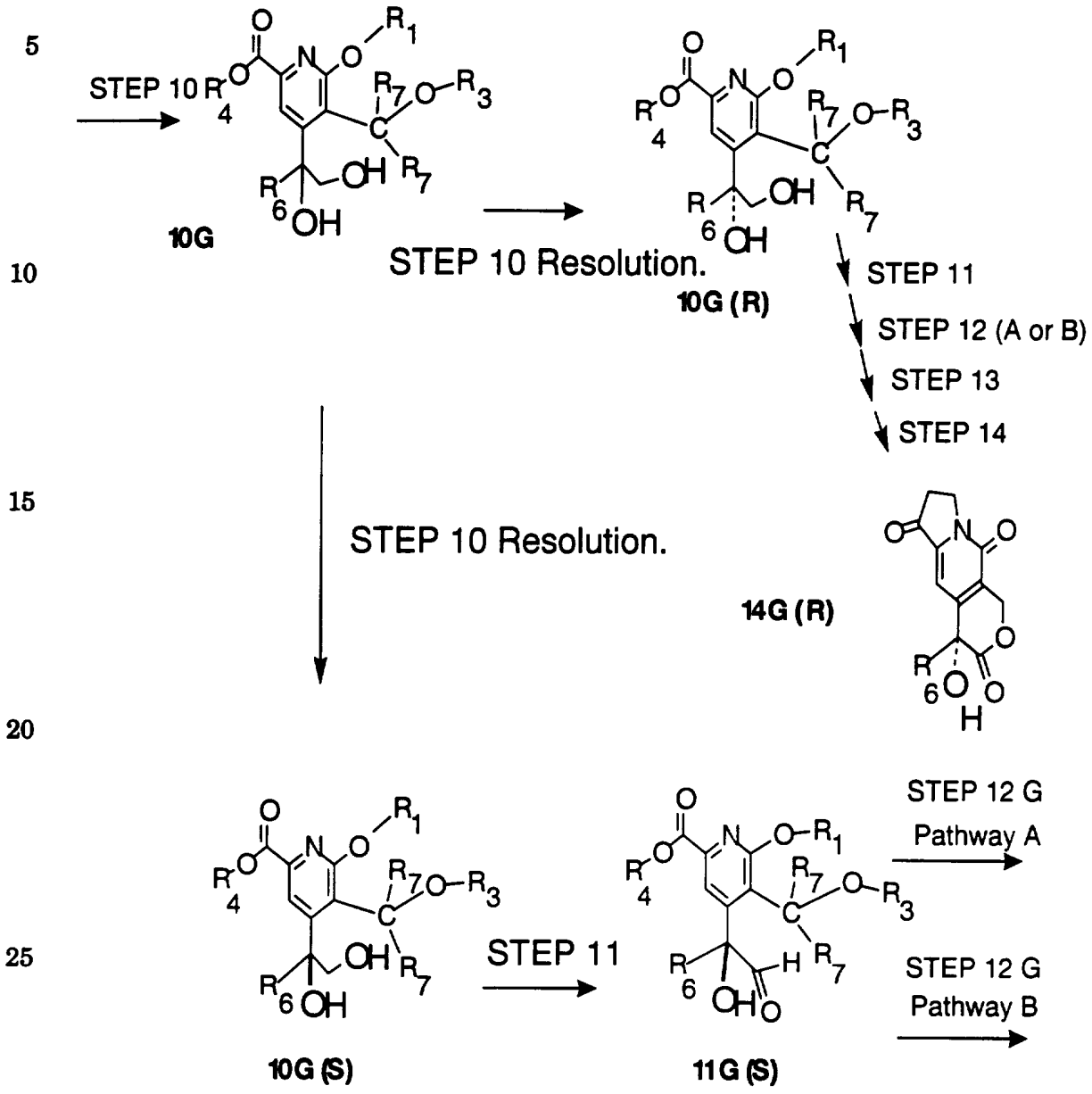

STEP 10
10G
STEP 10 Resolution.
10G (R)
STEP 11
STEP 12 (A or B)
STEP 13
STEP 14
STEP 10 Resolution.
14G (R)
10G (S)
STEP 11
11G (S)
STEP 12 G
Pathway A
STEP 12 G
Pathway B

CHART G p.5

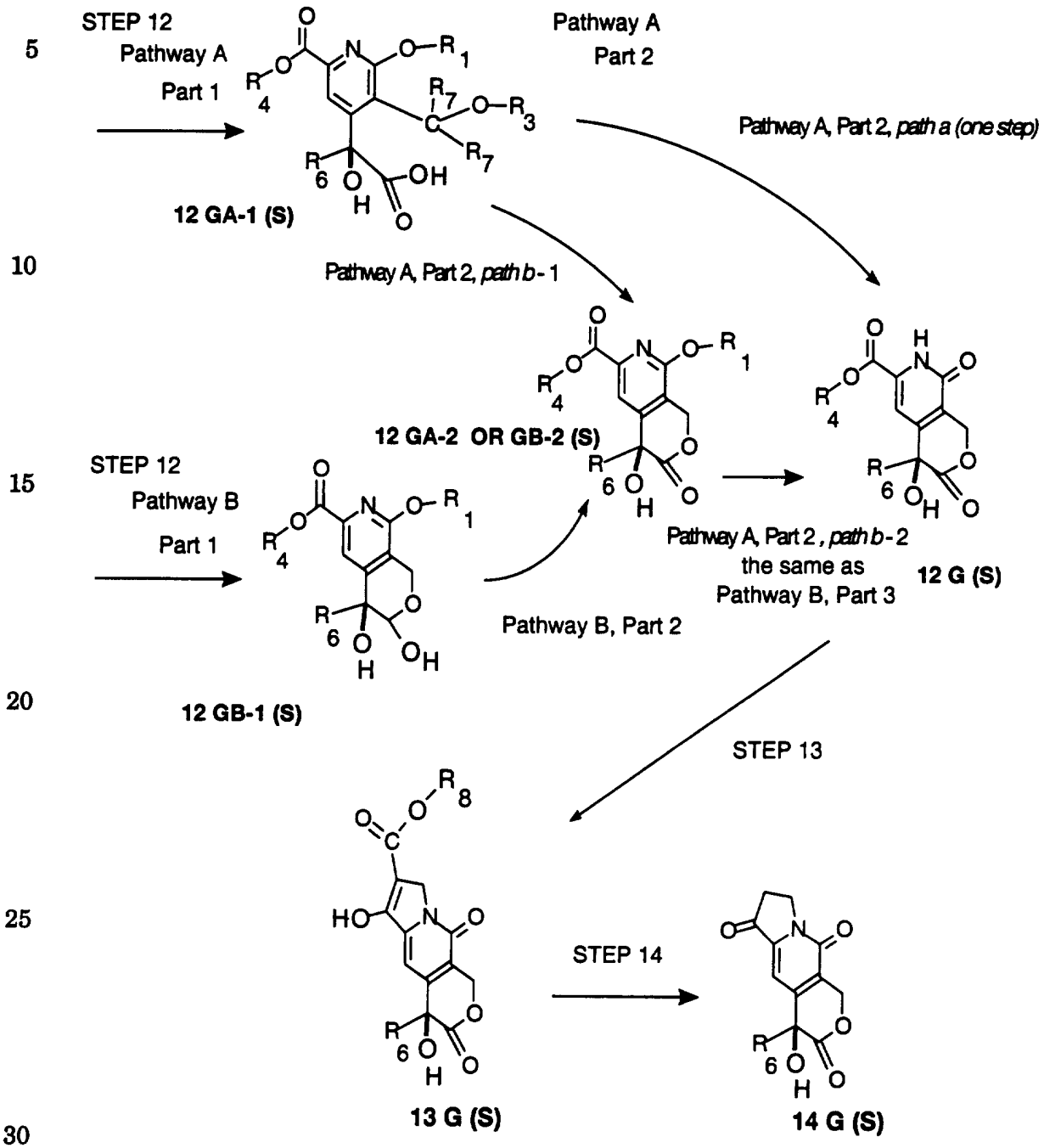

STEP 12
Pathway A
Part 1
12 GA-1 (S)
Pathway A
Part 2
Pathway A, Part 2, path a (one step)
Pathway A, Part 2, path b-1
12 GA-2 OR GB-2 (S)
STEP 12
Pathway B
Part 1
12 GB-1 (S)
Pathway B, Part 2
Pathway A, Part 2, path b-2
the same as
Pathway B, Part 3
12 G (S)
STEP 13
13 G (S)
STEP 14
14 G (S)

CHART CPT p.1

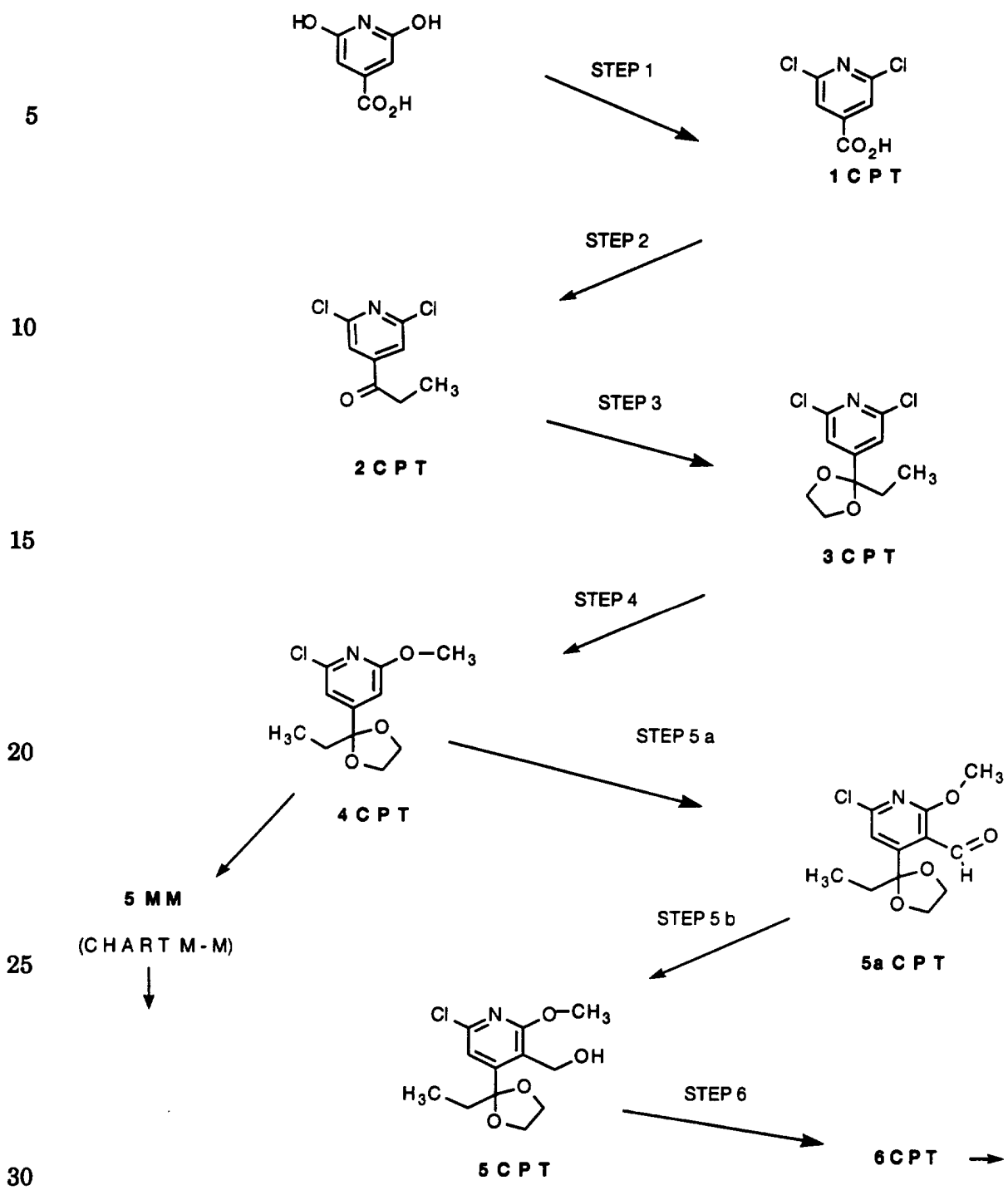

STEP 1
1 C P T
STEP 2
2 C P T
STEP 3
3 C P T
STEP 4
4 C P T
STEP 5 a
5a C P T
STEP 5 b
5 C P T
STEP 6
6CPT
5 MM
(CHART M-M)

CHART CPT p.2

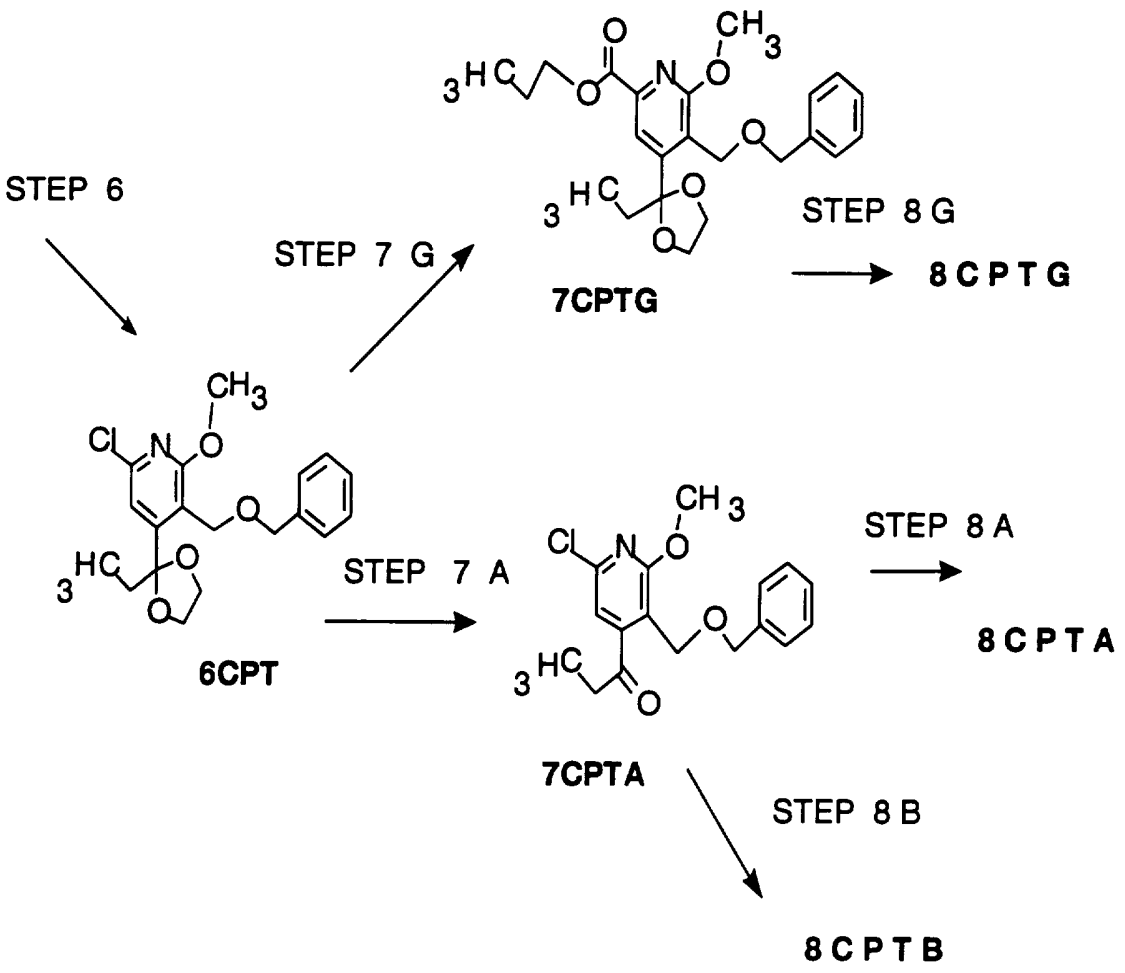

STEP 6
STEP 7 G
STEP 8 G
7CPTG
8 C P T G
6CPT
STEP 7 A
STEP 8 A
8 C P T A
7CPTA
STEP 8 B
8 C P T B

CHART CPT p.3

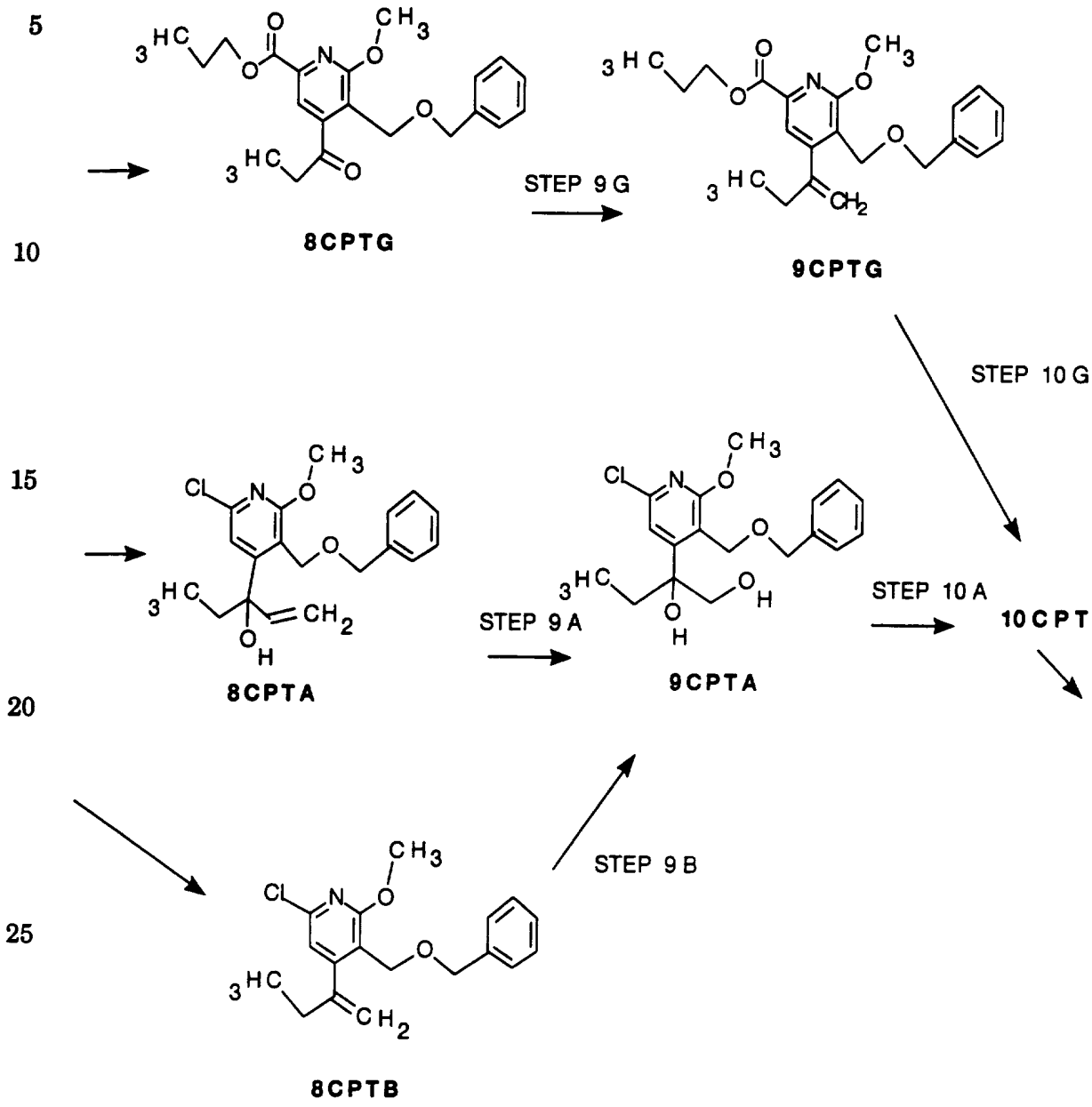

8CPTG
STEP 9G
9CPTG
STEP 10G
8CPTA
STEP 9A
9CPTA
STEP 10A
10CPT
STEP 9B
8CPTB

CHART CPT p.4

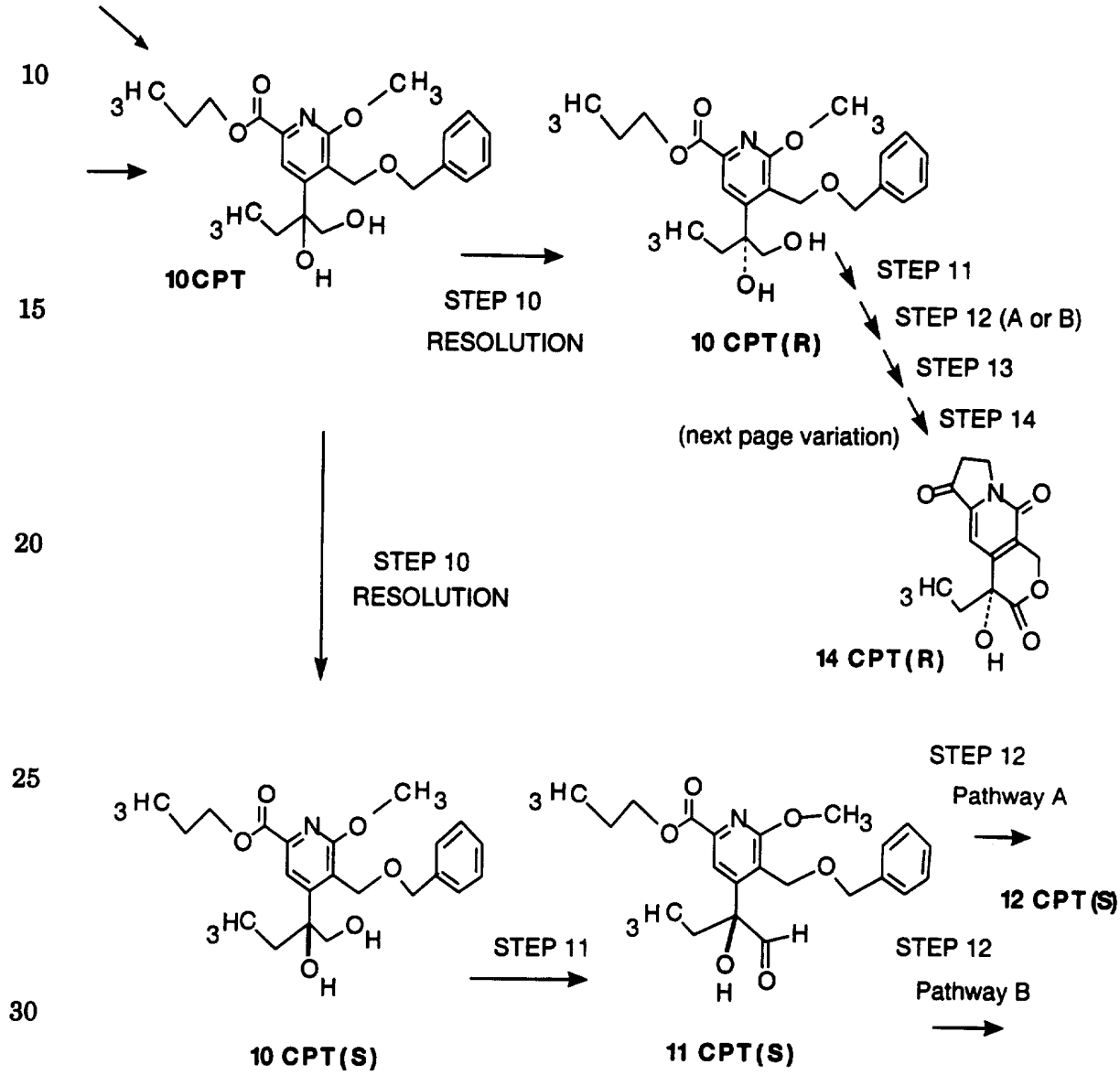

10CPT
STEP 10
RESOLUTION
10 CPT(R)
STEP 11
STEP 12 (A or B)
STEP 13
STEP 14
(next page variation)
14 CPT(R)
STEP 10
RESOLUTION
10 CPT(S)
STEP 11
11 CPT(S)
STEP 12
Pathway A
12 CPT(S)
STEP 12
Pathway B

CHART CPT p.5

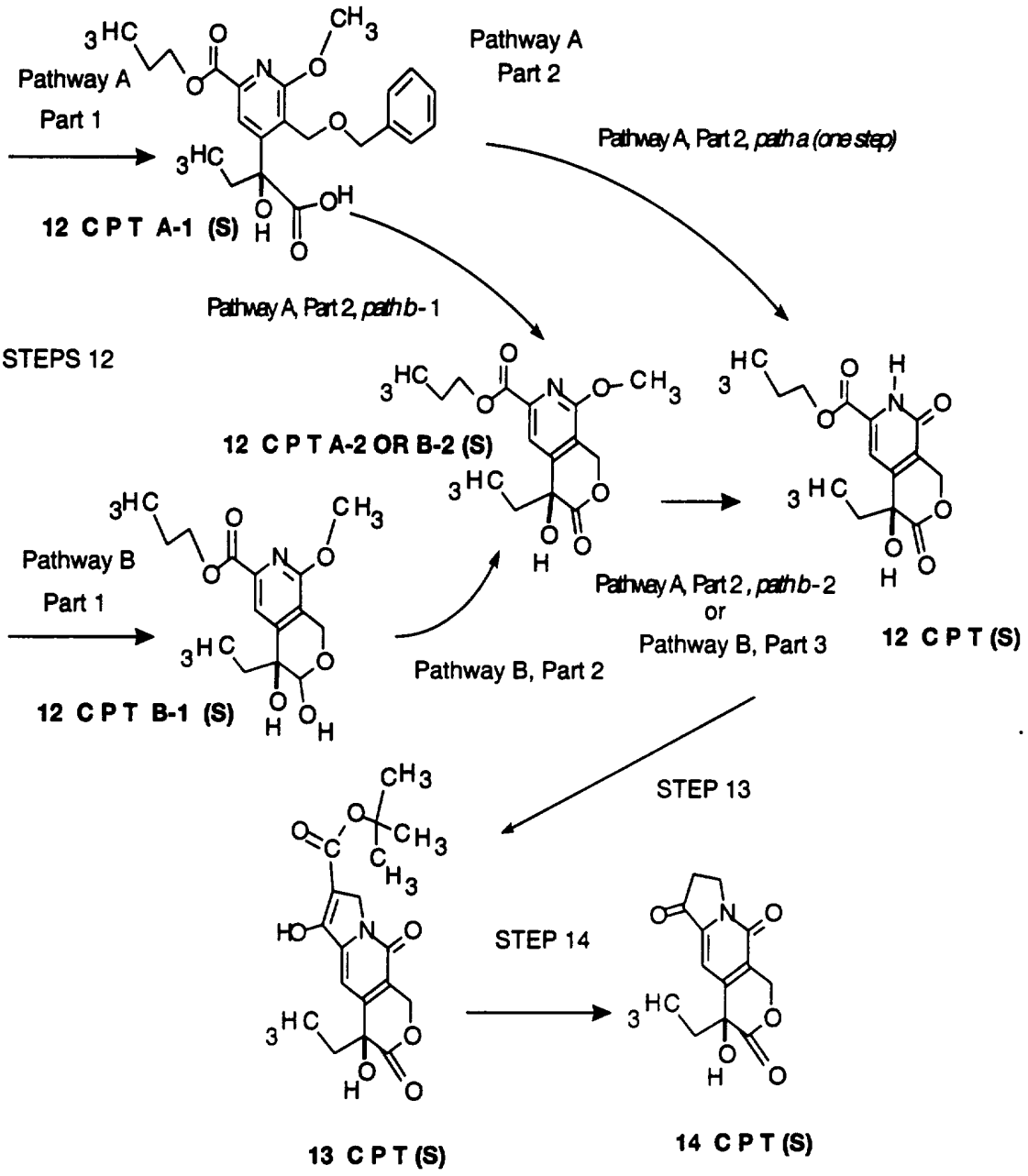

Pathway A
Part 1
12 C P T A-1 (S)
Pathway A
Part 2
Pathway A, Part 2, path a (one step)
Pathway A, Part 2, path b-1
STEPS 12
12 C P T A-2 OR B-2 (S)
Pathway B
Part 1
12 C P T B-1 (S)
Pathway B, Part 2
Pathway A, Part 2, path b-2
or
Pathway B, Part 3
12 C P T (S)
STEP 13
STEP 14
13 C P T (S)
14 C P T (S)

CHART M-G p.1

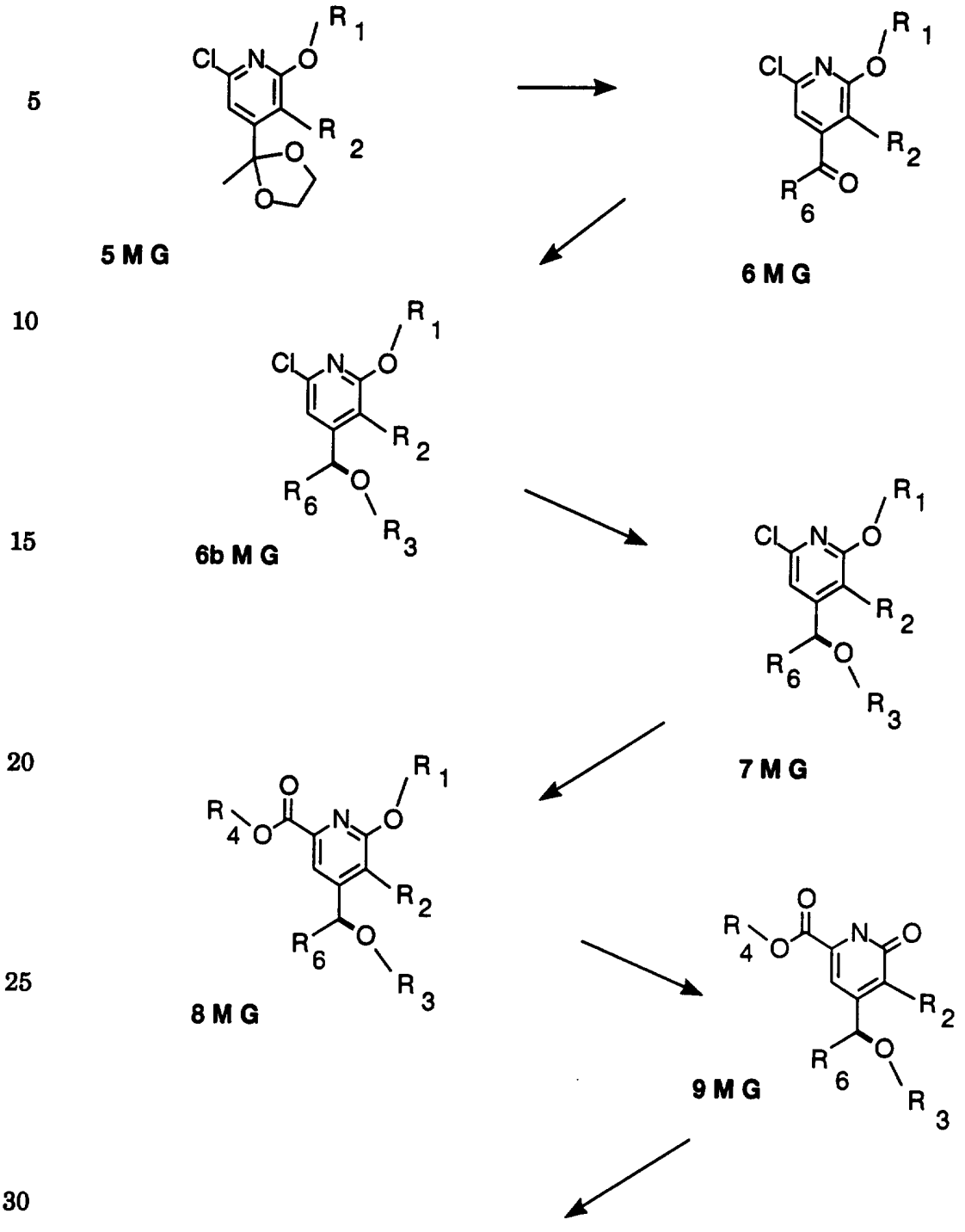


CHART M-G p.2

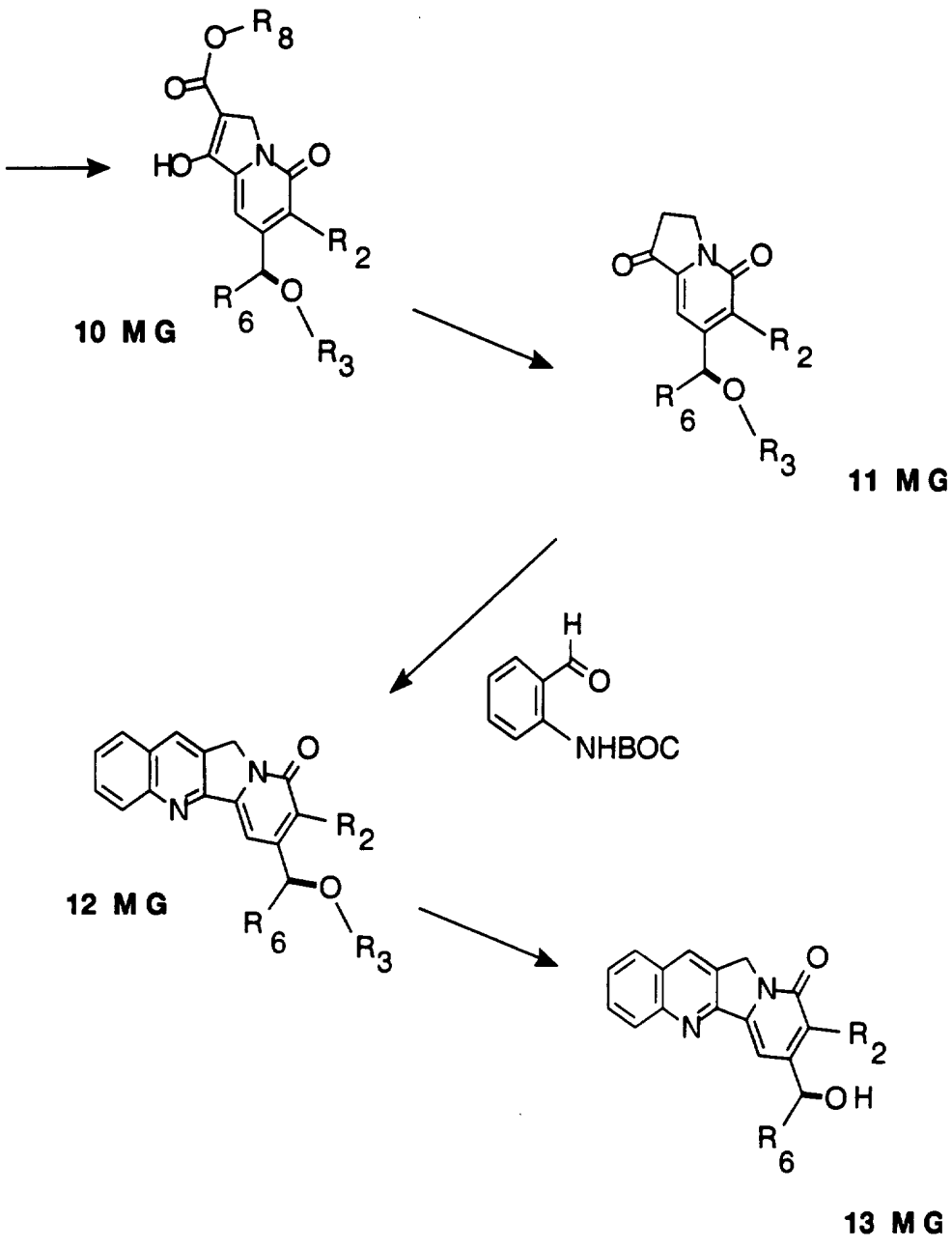


CHART M-M p.1

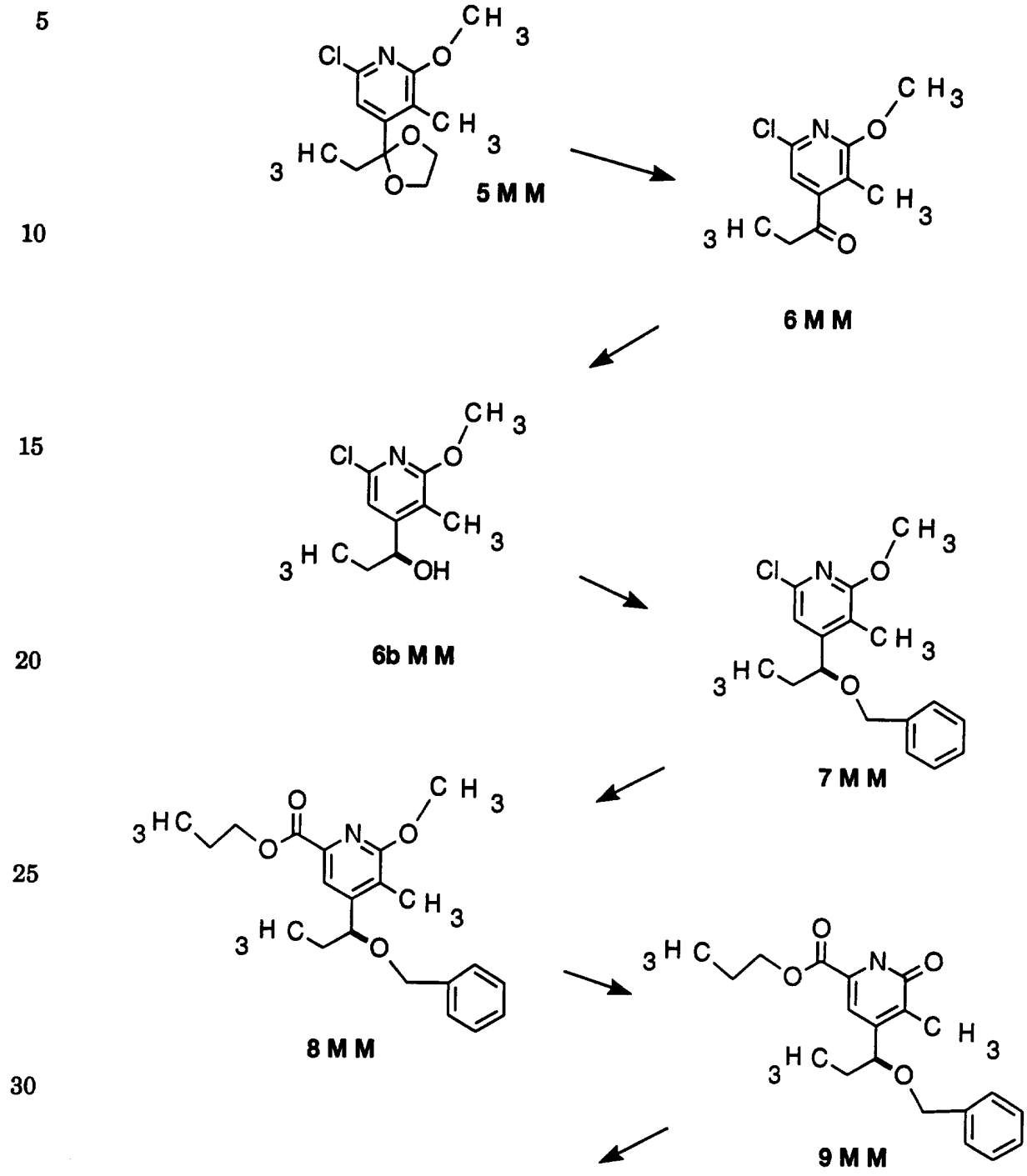
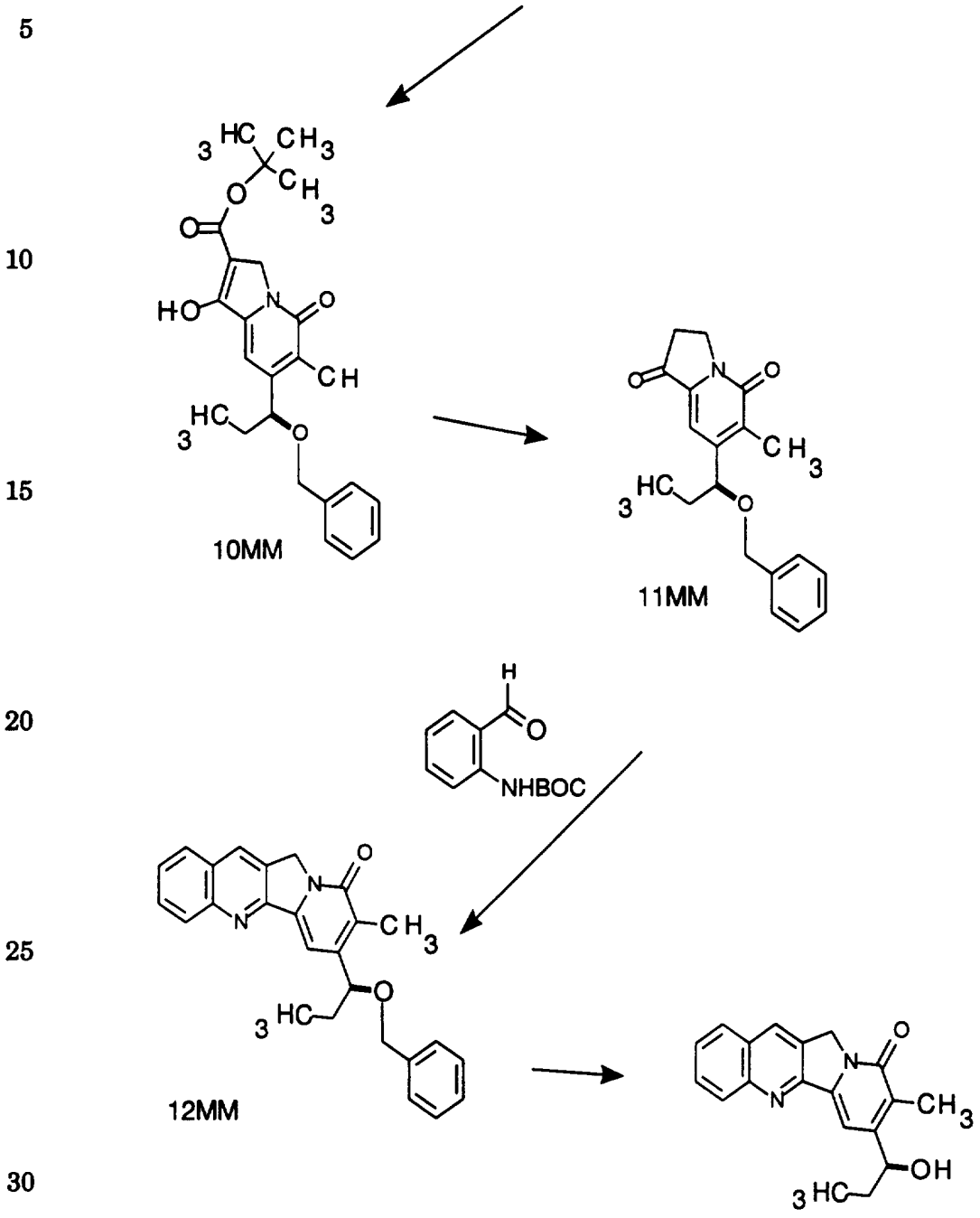


CHART M-M p.2



CLAIMS

1. A compound selected from the compounds described and labeled in the specification as **2G, 3G, 4G, 5G, 6G, 6MG, 6bMG, 7GG, 7GA, 7MG, 8GG, 8GA, 8GB, 8MG, 9GG, 9GA, 9MG, 10G, 10G(S), 10G(R), 10MG, 11G, 11G(S), 11G(R), 11MG, 12GA-1, 12GA-1(S), 12GA-1(R), 12GA-2, 12GA-2(S), 12GA-2(R), 12GB-1, 12GB-1(S), 12GB-1(R), 12GB-2, 12GB-2(S), 12GB-2(R), 12G, 12G(S), 12G(R), 12MG, 13G, 13G(S), 13G(R) or 13MG.**

where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H,

a) any optionally substituted alkyl, including C_{1-8} alkyl, alkylaryl, including C_{1-8}alkyl-aryl, C_{1-8}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

b) -C(O)-R_3, or

c) -$C(R_7)_2$-O-R_3 where each R_7 is independent of the other;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_5 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, or two R_5 groups may be combined to form cyclopentane or cyclohexane, or substituted derivatives thereof;

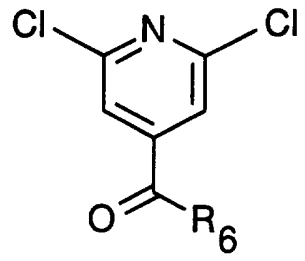
where R_6 is optionally substituted C_{1-8} alkyl, lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl,

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

where R_8 is optionally substituted C_{1-8} alkyl, including lower alkyl, including t-butyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl.

2. A compound of claim 1, represented by the formula shown below,

Formula 2G



where R_6 is optionally substituted C_{1-8} alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

3. A compound of claim 2,

where R_6 is lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, including benzyl or substituted lower alkyl-substituted C_6-aryl.

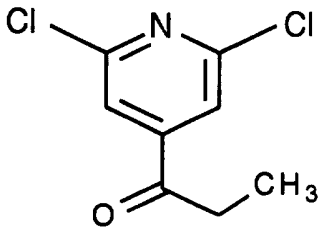
4. A compound of claim 3,

where R_6 is C_{1-4} alkyl, including ethyl, or C_6aryl.

5. A compound of claim 4,

where R_6 is C_{1-2} alkyl.

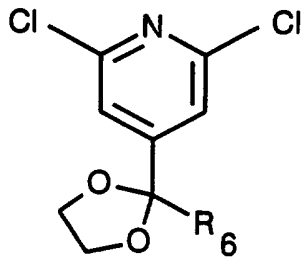
6. A compound of claim 5, represented by the formula shown below,



2CPT

7. A compound of claim 1, represented by the formula shown below,

Formula 3G



where R_6 is optionally substituted C_{1-8} alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

8. A compound of claim 7,

where R_6 is optionally substituted lower alkyl, including ethyl, aryl, substituted aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

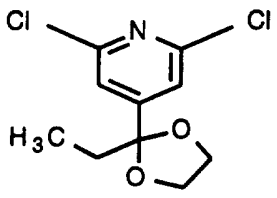
9. A compound of claim 8,

where R_6 is lower alkyl, including ethyl, or C_6 aryl.

10. A compound of claim 9,

where R_6 is C_{1-3} alkyl.

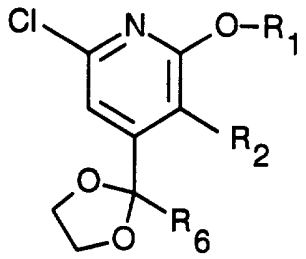
11. A compound of claim 10, shown by formula 4CPT, below,



3 C P T

12. A compound of claim 1, represented by the formula shown below,

Formula 4G and 5G



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H,

a) any optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl, alkylaryl, C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, including substituted benzyl and unsubstituted benzyl;

b) -C(O)-R_3, or

c) -$C(R_7)_2$-O-R_3 where each R_7 is independent of the other;

where R_6 is lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

13. A compound of claim 1,

where R_1 is any optionally substituted lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_2 is H, any optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

b) -C(O)-R_3, or

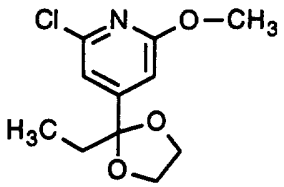
c) -$C(R_7)_2$-O-R_3 where each R_7 is independent of the other; and where R3 and R7 are any optionally substituted alkyl, including C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl; or

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

14. A compound of claim 13,
where R_1 is any lower alkyl, C_{3-6} cycloalkyl;
where R_2 is H, C_{1-3} alkyl; or
where R_6 is lower alkyl, including ethyl, or C_6aryl.

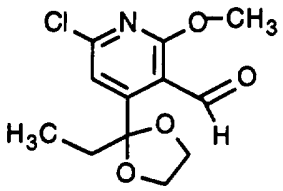
15. A compound of claim 13,
where R_1 is C_{1-3} alkyl;
where R_2 is H, methyl, ethyl; or
where R_6 is C_{1-3} alkyl.

16. A compound of claim 13, shown by formula 4CPT, below,



4 C P T

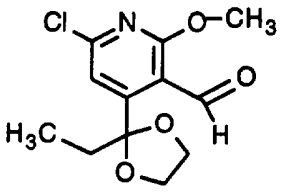
17. A compound of claim 13, shown by formula 5aCPT, below,



5a C P T

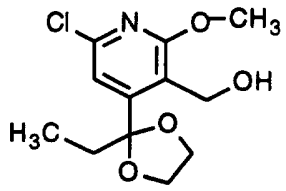
18. The bisulfite adduct of a compound of claim 13, shown by formula 5aCPT, below,

(bisulfite adduct)



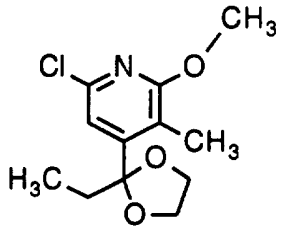
5a C P T

19. A compound of claim 13, shown by formula 5CPT, below,



5 C P T

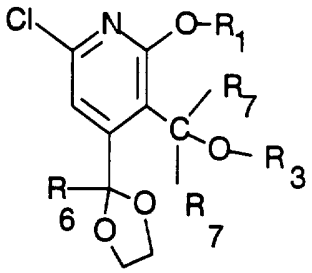
20. A compound of claim 13, shown by formula 5MM, below,



5 M M

21. A compound of claim 1, represented by the formula shown below,

Formula 6G



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl; or

where R_7 is independently H, lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

22. A compound of claim 21,

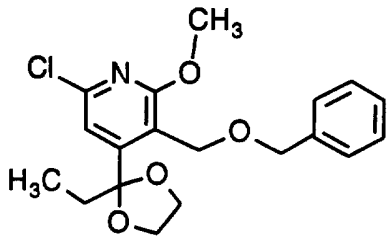
where R_1 is any lower alkyl,

where R_7 is independently H, or lower alkyl;

where R_3 is lower alkyl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or

where R_6 is lower alkyl.

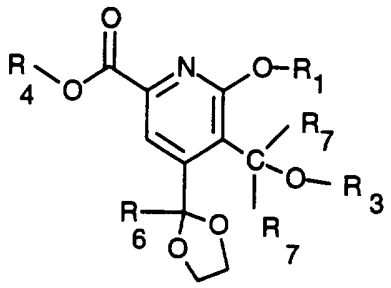
23. A compound of claim 22 represented by formula 6CPT, below,



6 C P T

24. A compound of claim 1, represented by the formula shown below,

Formula 7GG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10}

cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is any C_{1-6} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl; or

where R_7 is independently H, lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

25. A compound of claim 24

where R_1 is optionally substituted lower alkyl;

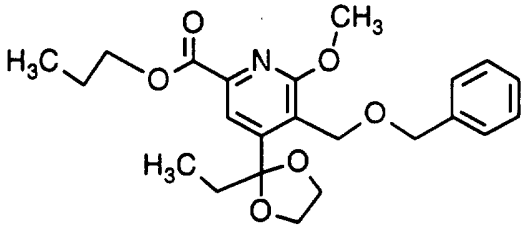
where R_3 is optionally substituted lower alkyl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, lower alkyl, C_{3-6}cycloalkyl;

where R_6 is H, or lower alkyl; or

where R_7 is independently H, or lower alkyl.

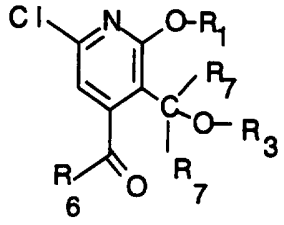
26. A compound of claim 25 represented by formula 7CPTG below,



7 C P T G

27. A compound of claim 1, represented by the formula shown below,

Formula 7GA



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl; or

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

28. A compound of claim 24,

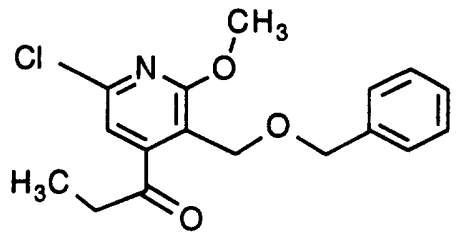
where R_1 is any optionally substituted lower alkyl,

where R_3 is H, optionally substituted lower alkyl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-4} alkyl; or

where R_7 is independently H, or optionally substituted C_{1-4} alkyl.

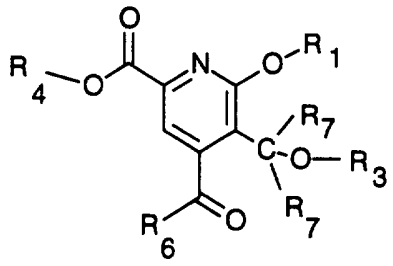
29. A compound of claim 25, represented by formula below,



7 C P T A

30. A compound represented by the formula shown below,

formula 8GG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

31. A compound of claim 30,

where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted lower alkyl, cycloalkyl, aryl, substituted aryl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_7 is independently H, optionally substituted lower alkyl.

32. A compound of claim 31,

where R_1 is any lower alkyl, C_{3-6} cycloalkyl;

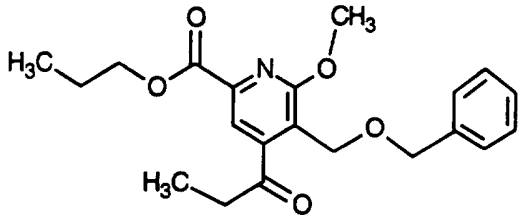
where R_3 is benzyl or substituted benzyl;

where R_4 is H, lower alkyl;

where R_6 is lower alkyl, including ethyl, or aryl; or

where R_7 is H, C_{1-3} alkyl.

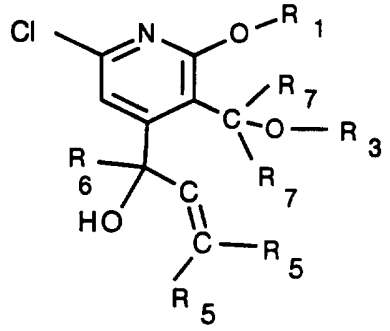
33. A compound of claim 32, represented by the formula below,



8CPTG

34. A compound of claim 1, represented by the formula shown below,

Formula 8GA



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_5 is, independently; H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, or two R_5 groups may be combined to form cyclopentane or cyclohexane, or substituted derivatives thereof;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

35. A compound of claim 34,

where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl; or

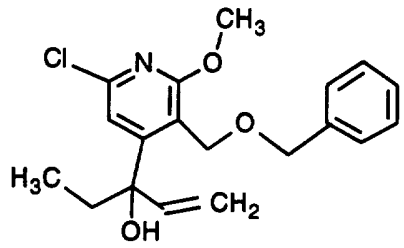
where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl,

substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

36. A compound of claim 35,
where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl;
where R_3 is benzyl or substituted benzyl; or
where R_6 is optionally substituted lower alkyl, including ethyl, or aryl.

37. A compound of claim 36,
where R_1 is C_{1-3} alkyl;
where R_3 is benzyl or substituted benzyl; or
where R_6 is C_{1-3} alkyl, including ethyl, or aryl.

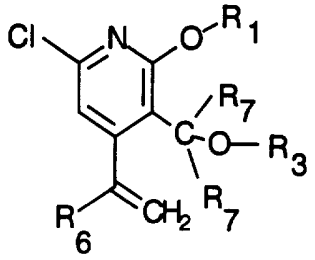
38. A compound of claim 37, represented by formula 8CPTA, below,



8 C P T A

39. A compound of claim 1, represented by the formula shown below,

formula 8GB



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl; or

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R_7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

40. A compound of claim 39

where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

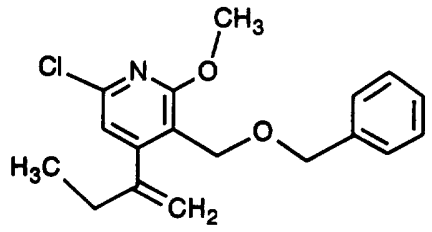
where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_7 is independently H, optionally substituted lower alkyl.

41. A compound of claim 40,
where R_1 is any lower alkyl, C_{3-6} cycloalkyl;
where R_3 is benzyl or substituted benzyl;
where R_6 is lower alkyl, including ethyl, or C_6aryl; or
where R_7 is H.

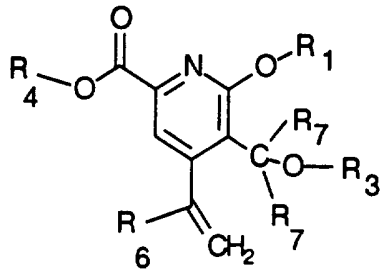
42. A compound of claim 41, represented by formula 8CPTB, below,



8 C P T B

43. A compound of claim 1, represented by the formula shown below,

formula 9GG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including, C_{1-6} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

44. A compound of claim 43

where R_1 is any optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted lower alkyl, cycloalkyl, aryl, substituted aryl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_7 is independently H, lower alkyl.

45. A compound of claim 44,

where R_1 is any lower alkyl, C_{3-6} cycloalkyl;

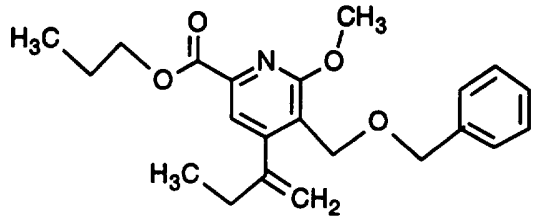
where R_3 is benzyl or substituted benzyl;

where R_4 is H, lower alkyl;

where R_6 is lower alkyl, including ethyl, or aryl; or

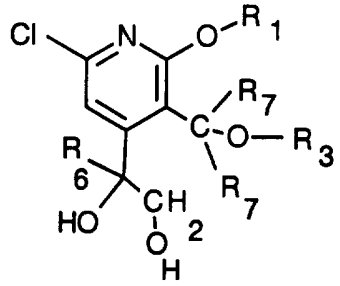
where R_7 is H.

46. A compound of claim 45, represented by the formula below,



9CPTG

47. A compound of claim 1, represented by the formula shown below,



Formula 9GA

where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

48. A compound of claim 47,

where R_1 is any optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

49. A compound of claim 48,

where R_1 is any lower alkyl, C_{3-6} cycloalkyl;

where R_3 is benzyl or substituted benzyl; or

where R_6 is lower alkyl, including ethyl, or aryl.

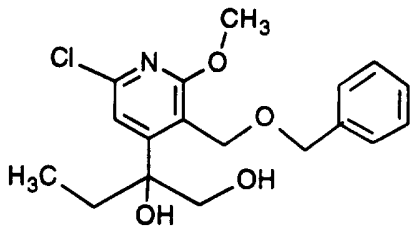
50. A compound of claim 49,

where R_1 is C_{1-3} alkyl;

where R_3 is benzyl or substituted benzyl; or

where R_6 is C_{1-3} alkyl.

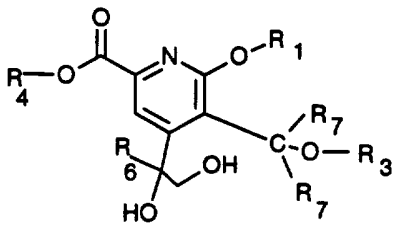
51. A compound of claim 50, represented by formula 9CPTA, below,



9CPTA

52. A compound of claim 1, represented by the formula shown below,

Formula 10G



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including C_{1-6} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted C_{1-8} alkyl, including lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

53. A compound of claim 52,

where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-6} alkyl, including lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, C_6aryl, substituted C_6aryl, C_3alkylC_6aryl, or substituted C_3alkylC_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl, or

where R_7 is independently H, optionally substituted lower alkyl, aryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

54. A compound of claim 53,

where R_1 is any lower alkyl, C_{3-6} cycloalkyl;

where R_3 is benzyl or substituted benzyl;

where R_4 is any C_{1-4} alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl; or

where R_6 is lower alkyl, including ethyl, or aryl; or

where R_7 is independently H, lower alkyl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

55. A compound of claim 54,

where R_1 is C_{1-3} alkyl;

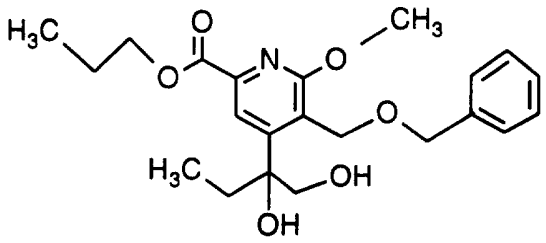
where R_3 is benzyl or substituted benzyl;

where R_4 is any C_{1-4} alkyl;

where R_6 is C_{1-3} alkyl; or

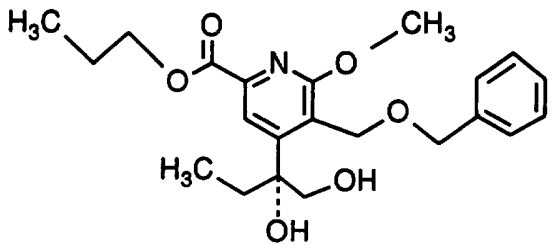
where R_7 is H.

56. A compound of claim 55, represented by formula 10 CPT, below,



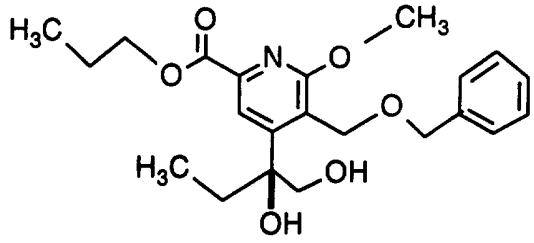
10 C P T

57. A compound of claim 56, represented by formula 10 CPT(R), below,



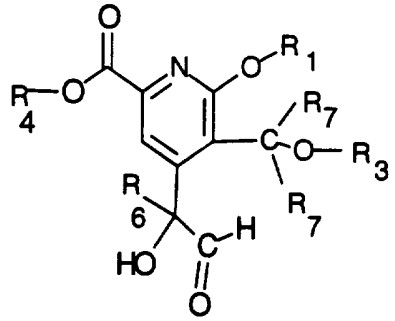
10 C P T (R)

58. A compound of claim 57, represented by formula 10 CPT(S), below,



10 C P T (S)

59. A compound of claim 1, represented by the formula shown below,



Formula 11G

where R_1 is optionally substituted C_{1-8} alkyl, lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, lower lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including

benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, lower alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted C_{1-8} alkyl, lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

60. A compound of claim 59,

where R_1 is any optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-6} alkyl, including lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, C_6aryl, substituted C_6aryl, C_3alkylC_6aryl, or substituted C_3alkylC_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_7 is independently H, or lower alkyl.

61. A compound of claim 60,

where R_1 is lower alkyl, C_{3-6} cycloalkyl;

where R_3 is benzyl or substituted benzyl;

where R_4 is H, C_{1-4} alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl;

where R_6 is lower alkyl; or

where R_7 is independently H.

62. A compound of claim 61,

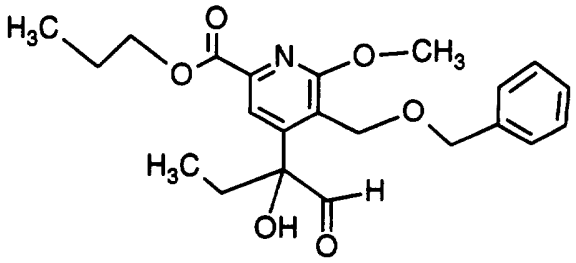
where R_1 is C_{1-3} alkyl;

where R_3 is benzyl or substituted benzyl;

where R_4 is C_{1-4} alkyl;

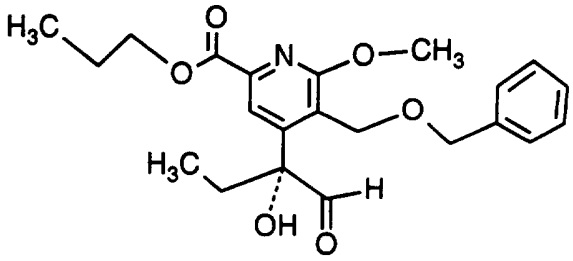
where R_6 is ethyl.

63. A compound of claim 62, represented by formula 11 CPT, below,



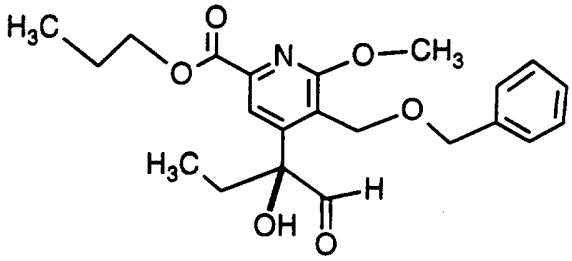
11 C P T

64. A compound of claim 63, represented by formula 11 CPT(R), below, formula 11 CPT, below,



11 C P T(R)

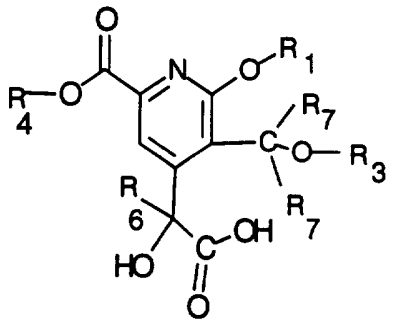
65. A compound of claim 64, represented by formula 11 CPT(S), below,



11 C P T (S)

66. A compound of claim 1, represented by the formula shown below,

Formula 12GA-1



where R_1 is optionally substituted C_{1-8} alkyl, lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_3 is optionally substituted C_{1-8} alkyl, lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, lower alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl;

where R_7 is independently H, optionally substituted C_{1-8} alkyl, lower alkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, or two R7 groups may be combined to form cyclopentane or cyclohexane or substituted derivatives thereof.

67. A compound of claim 66,

where R_1 is any optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-4} alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl;

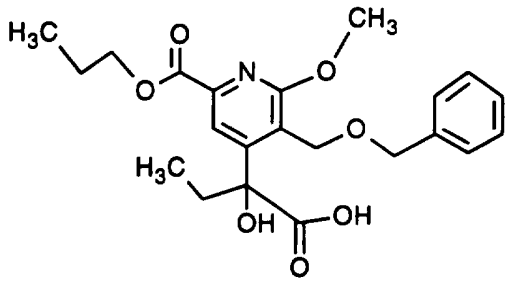
where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_7 is independently H, or optionally substituted C_{1-6} alkyl.

68. A compound of claim 67,
where R_1 is any lower alkyl, C_{3-6} cycloalkyl;
where R_3 is benzyl or substituted benzyl;
where R_4 is H, C_{1-4} alkyl;
where R_6 is lower alkyl, including ethyl, or aryl; or
where R_7 is independently H, C_{1-3} alkyl.

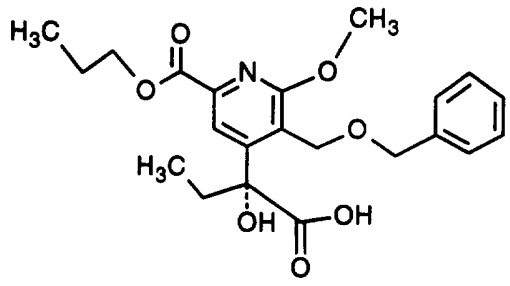
69. A compound of claim 68,
where R_1 is C_{1-3} alkyl;
where R_3 is benzyl or substituted benzyl; or
where R_6 is C_{1-3} alkyl; or
where R_7 is H.

70. A compound of claim 69, represented by formula 12 CPTA-1, below,



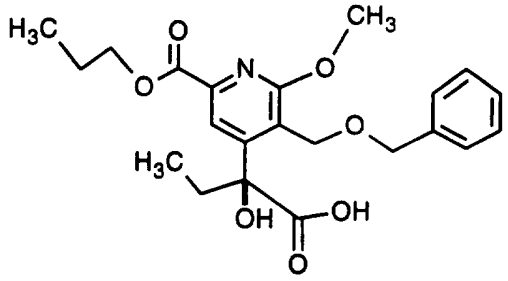
12 C P T A-1

71. A compound of claim 70, represented by formula 12 CPTA-1(R), below,



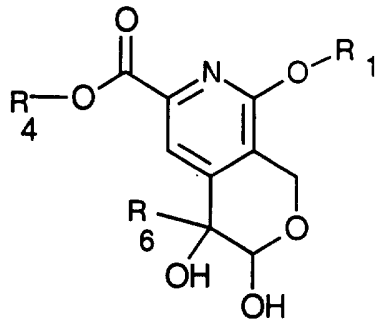
12 C P T A-1 (R)

72. A compound of claim 71, represented by formula 12 CPTA-1(S), below,



12 C P T A-1 (S)

73. A compound of claim 1, represented by the formula shown below,



12GB-1

where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10}

cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

74. A compound of claim 73,

where R_1 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_4 is H, optionally substituted lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

75. A compound of claim 74,

where R_1 is C_{1-4} alkyl, C_{3-6} cycloalkyl;

where R_4 is C_{1-4} lower alkyl, C_{3-6} cycloalkyl; or

where R_6 is C_{1-4} alkyl, including ethyl, or aryl.

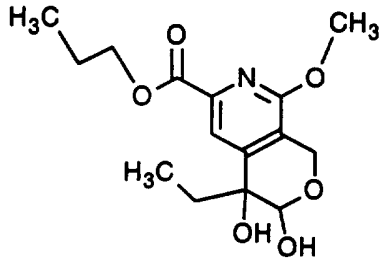
76. A compound of claim 75,

where R_1 is C_{1-3} alkyl;

where R_4 is C_{1-3} alkyl; or

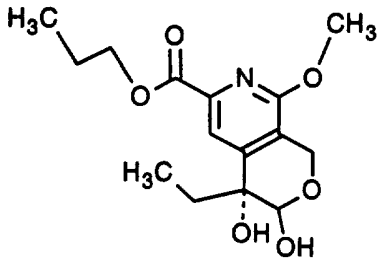
where R_6 is C_{1-3} alkyl.

77. A compound of claim 76, represented by formula 12 CPTB-1, below,



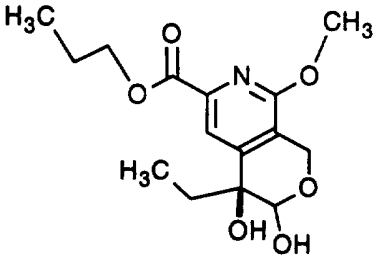
12 CPT B-1

78. A compound of claim 77, represented by formula 12 CPTB-1(R), below,



12 C P T B-1 (R)

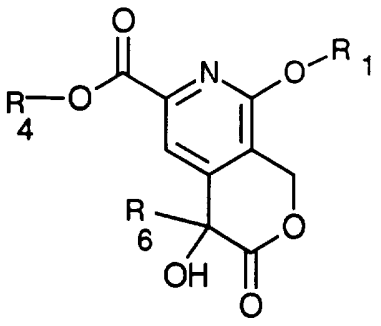
79. A compound of claim 78, represented by formula 12 CPTB-1(S), below,



12 C P T B-1 (S)

80. A compound of claim 1, represented by the formula shown below,

Formula 12GA-2 or
Formula 12GB-2



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including optionally substituted C_{1-6} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

81. A compound of claim 80,

where R_1 is any lower alkyl, C_{3-6} cycloalkyl, lower alkyl-C_{3-6} cycloalkyl, alkenyl, aryl, or substituted aryl, or benzyl;

where R_4 is H, lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl; or

where R_6 is lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

82. A compound of claim 81,

where R_1 is C_{1-4} alkyl, C_{3-6} cycloalkyl;

where R_4 is H, C_{1-4} alkyl, C_{3-6} cycloalkyl; or

where R_6 is C_{1-4} alkyl, including ethyl, or aryl.

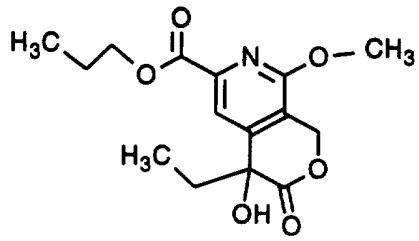
83. A compound of claim 82,

where R_1 is C_{1-3} alkyl;

where R_3 is benzyl or substituted benzyl; or

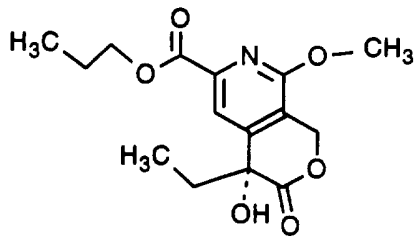
where R_6 is C_{1-3} alkyl.

84. A compound of claim 83, represented by formula 12CPTA-2, or 12CPTB-2 below,



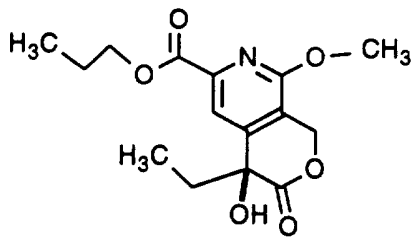
12 CPTA-2

85. A compound of claim 84, represented by formula 12CPTA-2(R), or 12CPTB-2(R) below,



12 CPTA-2(R)

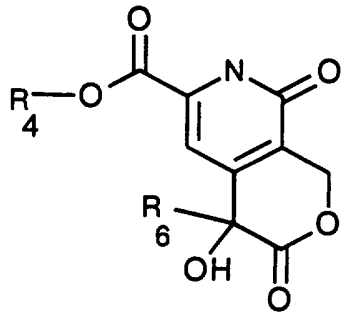
86. A compound of claim 85, represented by formula 12CPTA-2(S), or 12CPTB-2 below,



12 CPTA-2(s)

87. A compound of claim 1, represented by the formula shown below,

Formula 12G



where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

88. A compound of claim 87,

where R_3 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl.

89. A compound of claim 88,

where R_1 is C_{1-4} alkyl, C_{3-6} cycloalkyl;

where R_4 is C_{1-4} alkyl, C_{3-6} cycloalkyl; or

where R_6 is C_{1-4} alkyl, including ethyl, or aryl.

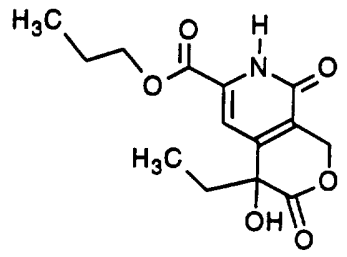
90. A compound of claim 89,

where R_1 is C_{1-3} alkyl;

where R_4 is C_{1-3} alkyl; or

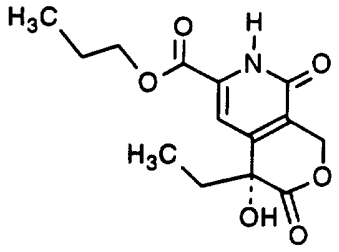
where R_6 is C_{1-3} alkyl.

91. A compound of claim 90, represented by formula 12CPT, below,



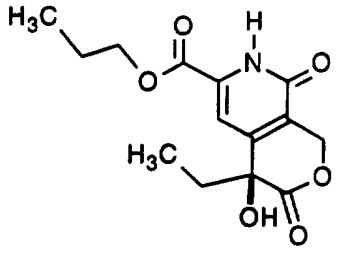
12 CPT

92. A compound of claim 91, represented by formula 12CPT(R), below,



12 CPT (R)

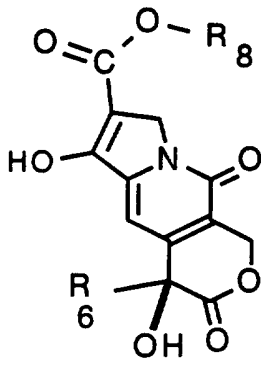
93. A compound of claim 92, represented by formula 12CPT(S), below,



12 CPT (S)

94. A compound of claim 1, represented by the formula shown below,

Formula 13G



13 G

where R_6 is optionally substituted C_{1-8} alkyl, including C_{1-6} alkyl, including ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl; or

where R_8 is optionally substituted C_{1-8} alkyl, including C_{1-6} alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or substituted derivatives thereof.

95. A compound of claim 94,

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6-aryl, substituted lower alkyl-C_6-aryl, or benzyl; or

where R_8 is optionally substituted lower alkyl, C_{3-6} cycloalkyl, alkenyl, aryl, substituted aryl, and C_{1-6} alkyl-C_{1-6} aryl, or substituted C_{1-6} alkyl-C_{1-6} aryl, including benzyl and substituted benzyl.

96. A compound of claim 95,

where R_6 is lower alkyl, including ethyl, or C_{1-6}aryl or

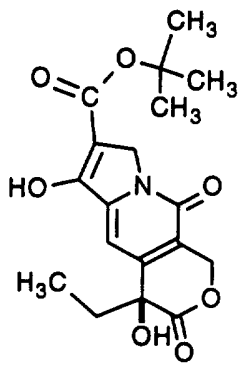
where R_8 is lower alkyl, including ethyl, or C_{1-6}aryl.

97. A compound of claim 96,

where R_6 is butyl or

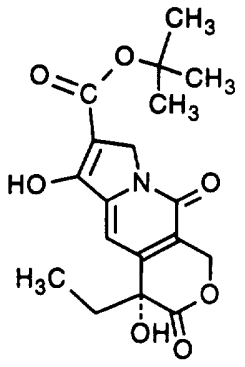
where R_8 is lower alkyl, including ethyl, or C_{1-6}aryl.

98. A compound of claim 97, represented by formula 13CPT, below,



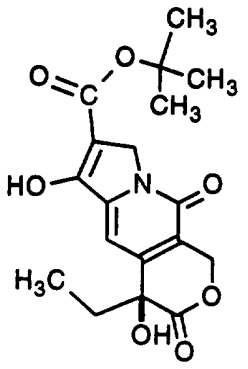
13 C P T

99. A compound of claim 98, represented by formula 13CPT(R), below,



13 C P T (R)

100. A compound of claim 99, represented by formula 13CPT(S), below,

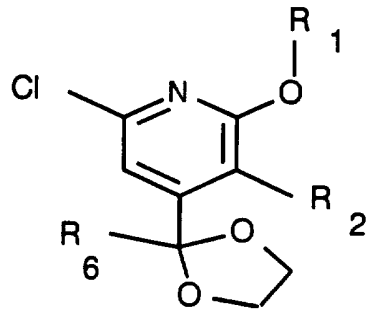


13 C P T (S)

101. The toluene solvate of the compounds in claims 94-100.

102. A compound of claim 1, represented by the formula shown below,

Formula 5MG



where R_1 is optionally substituted C_{1-8} alkyl, including C_{1-6} alkyl, lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted C_{1-8} alkyl, including, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

103. A compound of claim 102,

where R_1 is optionally substituted lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted lower alkyl; or

where R_6 is optionally substituted lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, including benzyl and substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

104. A compound of claim 103,

where R_1 is any lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, alkylaryl, or substituted lower alkyC_6aryl, including benzyl and substituted benzyl;

where R_2 is C_{1-6}alkyl; or

where R_6 is lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, including benzyl, substituted benzyl.

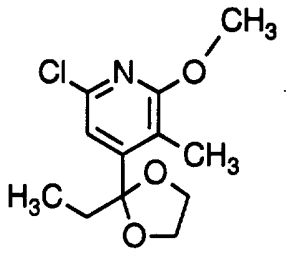
105. A compound of claim 104,

where R_1 is C_{1-3} alkyl;

where R_2 is C_{1-3} alkyl; or

where R_6 is C_{1-3} alkyl, including ethyl.

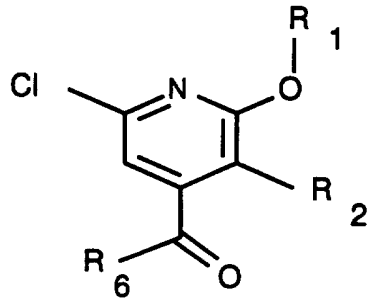
106. A compound of claim 105 represented by formula 5MM, below,



5 M M

107. A compound of claim 1, represented by the formula shown below,

Formula 6MG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted C_{1-8} alkyl, including, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

108. A compound of claim 107,

where R_1 is optionally substituted lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is optionally substituted alkyl, including C_{1-6}alkyl, benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

109. A compound of claim 108,

where R_1 is any lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

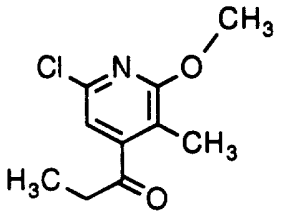
where R_2 is C_{1-4} alkyl;

where R_6 is lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl,

substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

110. A compound of claim 109,
where R_1 is C_{1-3} alkyl;
where R_2 is C_{1-3} alkyl; or
where R_6 is C_{1-3} alkyl, including ethyl.

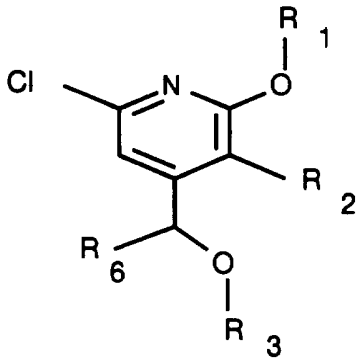
111. A compound of claim 110 represented by formula 6MM, below,



6 M M

112. A compound of claim 1, represented by the formula shown below,

Formula 7MG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

113. A compound of claim 112,

where R_1 is any lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_2 is H, C_{1-6} alkyl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is any lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl.

114. A compound of claim 113,

where R_1 is any lower alkyl, C_{3-7} cycloalkyl,

where R_2 is C_{1-4} alkyl;

where R_3 is H, lower alkyl, lower alkyl-C_{3-7} cycloalkyl;

where R_6 is lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

115. A compound of claim 114,

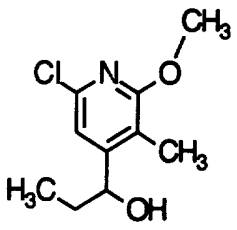
where R_1 is C_{1-3} alkyl;

where R_2 is C_{1-3} alkyl;

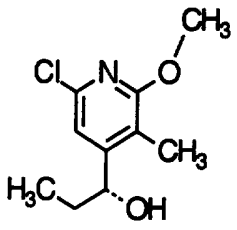
where R_3 is H; or

where R_6 is C_{1-3} alkyl, including ethyl.

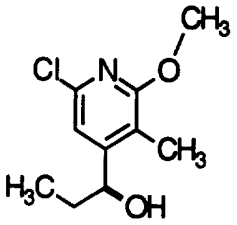
116. A compound of claim 115 represented by formulas 6bMM, below,



6b M M

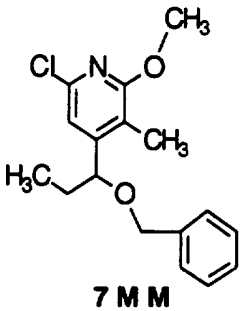


6b M M

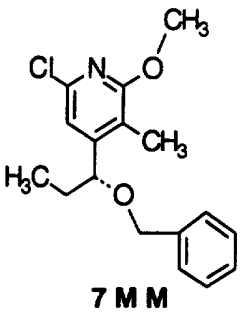


6b M M

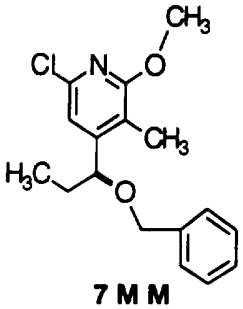
117. A compound of claim 114 represented by formulas 7MM, below,



7 M M



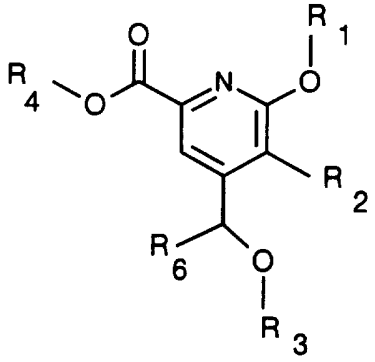
7 M M



7 M M

118. A compound of claim 1, represented by the formula shown below,

Formula 8MG



where R_1 is optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl,

alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

119. A compound of claim 118,

where R_1 is optionally substituted C_{1-8} alkyl, including C_{1-6} alkyl, lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_2 is H, optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, including substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl.

120. A compound of claim 119,

where R_1 is optionally susbtituted lower alkyl, C_{3-7} cycloalkyl,

where R_2 is H, C_{1-6}alkyl, substituted benzyl and unsubstituted benzyl;

where R_3 is H any optionally substituted lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally susbtituted lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally susbtituted lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

121. A compound of claim 120,

where R_1 is C_{1-3} alkyl;

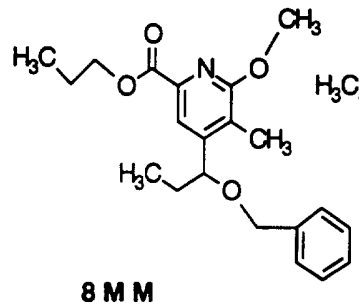
where R_2 is is C_{1-3} alkyl;

where R_3 is H, lower alkyl-C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl; or

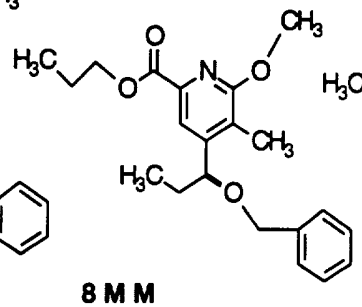
where R_4 is C_{1-3} alkyl; or

where R_6 is C_{1-3} alkyl, including ethyl.

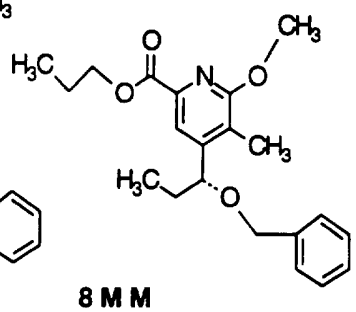
122. A compound of claim 121 represented by formulas 8MM, below,



8 M M



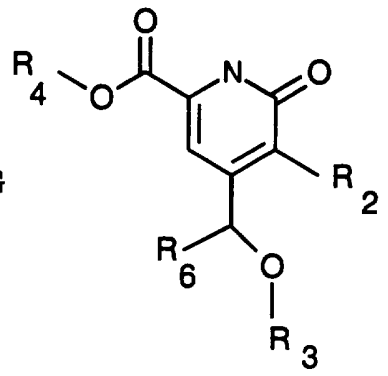
8 M M



8 M M

123. A compound of claim 1, represented by the formula shown below,

Formula 9MG



where R_2 is H, optionally substituted C_{1-8}alkyl, including C_{1-6}alkyl, alkylaryl, including C_{1-8}alkyl-aryl, C_{1-8}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8}alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted C_{1-8}alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted C_{1-8}alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

124. A compound of claim 123,

where R_2 is H, optionally substitutedC_{1-6}alkyl, C_{1-6}alkyl-C_6aryl,including substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl.

125. A compound of claim 124,

where R_2 is H, optionally substituted C_{1-4} alkyl;

where R_3 is H, optionally substituted lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_4 is H, optionally substituted lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

126. A compound of claim 125,

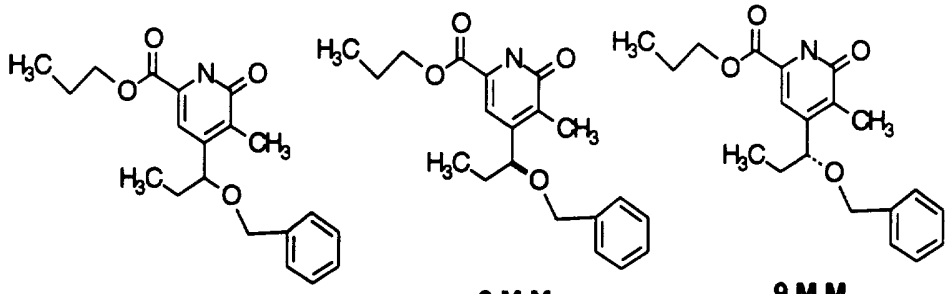
where R_2 is H or C_{1-3} alkyl;

where R_3 is H, any lower alkyl-C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl; or

where R_4 is H, C_{1-3} alkyl; or

where R_6 is C_{1-3} alkyl, including ethyl.

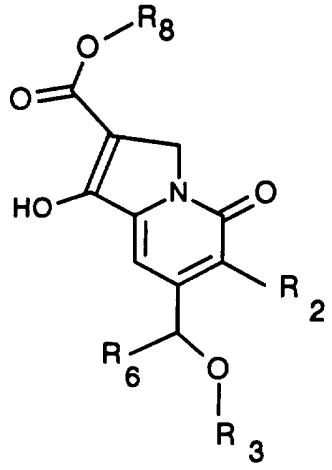
127. A compound of claim 126 represented by formulas 9MM, below,



9MM 9MM 9MM

128. A compound of claim 1, represented by the formula shown below,

Formula 10MG



where R_2 is H or optionally substituted C_{1-8} alkyl, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8} alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted C_{1-8} alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

where R_8 is optionally substituted C_{1-8} alkyl, including lower alkyl, including t-butyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, alkenyl, aryl, substituted aryl, alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl.

129. A compound of claim 128,

where R_2 is optionally substituted C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, including substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is optionally substituted lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted

benzyl; or

where R_8 is any lower alkyl, including t-butyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl.

130. A compound of claim 129,

where R_2 is H or C_{1-4} alkyl;

where R_3 is H, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

where R_6 is lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl; or

where R_8 is any lower alkyl, including t-butyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl.

131. A compound of claim 130,

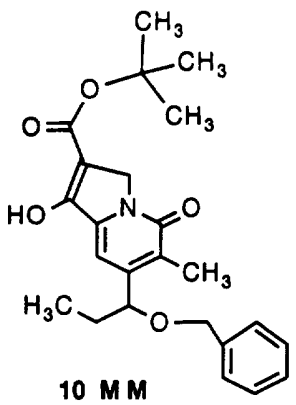
where R_2 is is C_{1-3} alkyl;

where R_3 is H, lower alkyl-C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl;

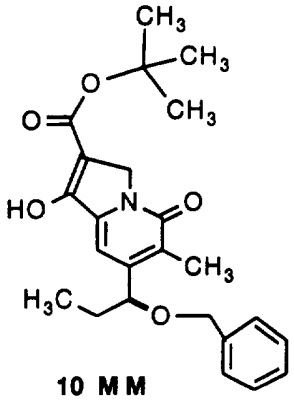
where R_6 is C_{1-3} alkyl, including ethyl or

where R_8 is any lower alkyl, including t-butyl.

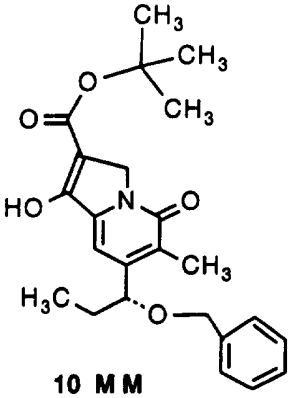
132. A compound of claim 131 represented by formulas 10MM, below,



10 M M



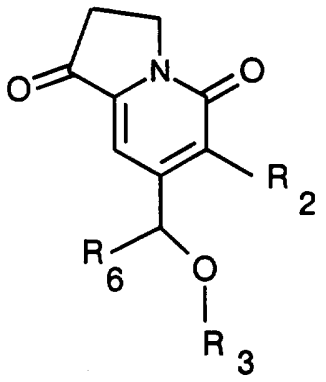
10 M M



10 M M

133. A compound of claim 1, represented by the formula shown below,

Formula 11MG



where R_2 is H, optionally substituted C_{1-8}alkyl, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;;

where R_3 is H, optionally substituted C_{1-8}alkyl, including $_{1-6}$ alkyl, including lower alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted C_{1-8}alkyl, including ower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

134. A compound of claim 133,

where R_2 is H, optionally substituted C_{1-8}alkyl, including C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, including substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8}alkyl, including lower alkyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted C_{1-8}alkyl, including lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl.

135. A compound of claim 134,

where R_2 is C_{1-4} alkyl;

where R_3 is H, optionally substituted lower alkyl, lower alkyl-C_{3-7}

cycloalkyl, C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl; or

where R_6 is lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

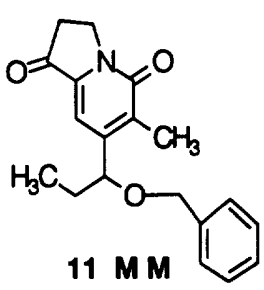
136. A compound of claim 135,

where R_2 is is C_{1-3} alkyl;

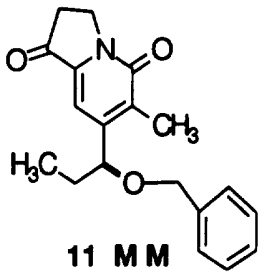
where R_3 is any benzyl and substituted benzyl;

where R_6 is C_{1-3} alkyl, including ethyl.

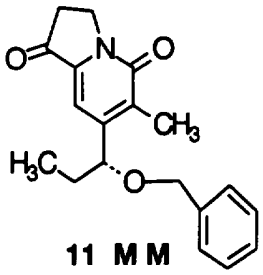
137. A compound of claim 136 represented by formulas 11MM, below,



11 MM



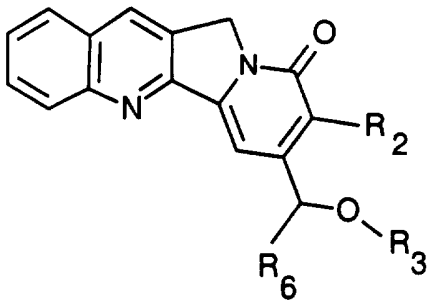
11 MM



11 MM

138. A compound of claim 1, represented by the formula shown below,

Formula 12MG



where R_2 is H, optionally substituted C_{1-8}alkyl, including C_{1-6}alkyl, alkylaryl, including C_{1-6}alkyl-aryl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-8}alkyl, including C_{1-6} alkyl, cycloalkyl, alkenyl, aryl, substituted aryl, and alkylaryl, or substituted alkylaryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted C_{1-8}alkyl, including lower alkyl, ethyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, benzyl, substituted benzyl, C_{3-10} cycloalkyl, lower alkyl-C_{3-10} cycloalkyl, heteroaryl, or substituted heteroaryl.

139. A compound of claim 138,

where R_2 is H or optionally substituted C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, substituted benzyl and unsubstituted benzyl;

where R_3 is H, optionally substituted C_{1-6} alkyl, including lower alkyl, cycloalkyl, C_6aryl, substituted C_6aryl, and C_{1-6}alkylC_6aryl, or substituted C_{1-6}alkylC_6aryl, including benzyl and substituted benzyl; or

where R_6 is any lower alkyl, including ethyl, C_{3-7} cycloalkyl, lower alkyl-C_{3-7} cycloalkyl, alkenyl, C_6aryl, substituted C_6aryl, lower alkyl-C_6aryl, or substituted lower alkyl C_6aryl, including benzyl and substituted benzyl.

140. A compound of claim 139,

where R_2 is H, C_{1-6} alkyl;

where R_3 is H, optionally substituted C_{1-6}alkyl, C_{1-6}alkyl-C_6aryl, including benzyl and substituted benzyl; or

where R_6 is optionally substituted lower alkyl, ethyl, C_6aryl, substituted C_6aryl, lower alkyl C_6aryl, substituted lower alkyl C_6aryl, benzyl, substituted benzyl.

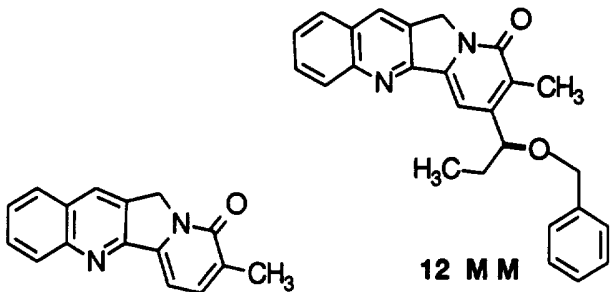
141. A compound of claim 140,

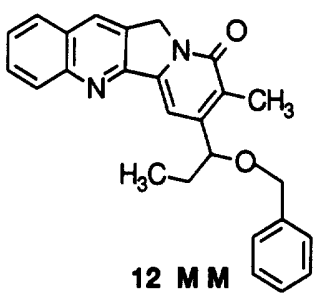
where R_2 is is C_{1-3} alkyl;

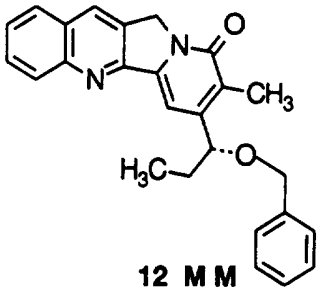
where R_3 is substituted benzyl and substituted benzyl;

where R_6 is C_{1-3} alkyl, including ethyl.

142. A compound of claim 141 represented by formulas 12MM, below,







143. The process of making the compounds described in claim 2, see formula 2G, by either, 1) mixing 2,6-dichloroisonicotinic acid with a nucleophile that is either a Grignard Reagent or an alkyllithium and an ethereal solvent followed by exposing the reaction products to dilute acid or 2) by converting 2,6-dichloroisonicotinic acid into the acid chloride followed by conversion into the Weinreb amide followed by mixing with a nucleophile that is either a Grignard Reagent or an alkyllithium and an ethereal solvent followed by exposing the reaction products to dilute acid.

144. The process of claim 143, where the reactants are maintained at a temperature of about -30° to about +10°.

145. The process of claim 144, where the compound produced is described in claim 6, see formula 2CPT.

146. The process of claim 143, for producing the compounds in claim 7, see formula 3G, by beginning with the product of claim 140, see formula 2G, and mixing that product with an alcohol or diol in the presence of trimethylchlorosilane.

147. The process of claim 146, where the alcohol or diol is ethylene glycol.

148. The process of claim 146, where the compound produced is represented by

formula 3CPT as described in claim 11.

149. The process of claim 146, where the the alcohol or diol is ethylene glycol and the temperature is maintained between about 0^{o} to about $+60^{o}$.

150. The process of claim 146, for producing the compounds in claim 12, formula 4G, where R_2 is H, by beginning with the product of claim 143, formula 3G, and mixing that product with a sodium or potassium alkoxide in a solvent.

151. The process of claim 150, where the reactants are maintained at a temperature between about 20^{o} and about about 80^{o}.

152. The process of claim 150, for producing the compounds in claim 12, formula 5G, by beginning with the product of claim 147, formula 4G, where R_2 is H, and mixing that product with a solvent and an alkyllithium base or aryllithium base to form the pyridyl anion which is then mixed with an electrophile, the product of which is then mixed with an acid and then the end product is isolated.

153. The process of claim 152, where the solvent is selected from diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane or hydrocarbons such as toluene, hexane, heptane, cyclohexane, or isooctane, or mixtures of any of these.

154. The process of claim 152, where the alkyllithium is selected from methyllithium, n-butyllithium, sec-butyllithium or t-butyllithium, or mixtures of any of these.

155. The process of claim 152, where the electrophile is a formamide including dimethylformamide, N-formylpiperidine, or N formylmorpholine or N-methylformanilide or similar formamides or mixtures of any of these.

156. The process of claim 152, where the reactants are maintained at a temperature between about -40^{o} and about $+50^{o}$.

157. The process of claim 156, where the reactants are maintained at a temperature between about -5^{o} and about $+5^{o}$.

158. The process of claim 156, where the product is isolated with a dilute acid.

159. The process of claim 158, where the dilute acid is selected from a moderate to strong acids such as hydrochloric acid, acetic acid, or sulfuric acid, or mixtures of any of these.

160. The process of claim 158, where sodium bisulfite is mixed with the producet of claim 155 and the compound produced is the bisulfite adduct.

161. The process of claim 159, where the compound produced is represented by formula 5aCPT.

162. The process of claim 160, where 5aCPT bisulfite adduct is further mixed with acid or base to produce the compound represented by formula 5aCPT.

163. The process of claim 150, for producing the compounds in claim 12, formula 4G or 5G, by beginning with the product of claim 147, formula 4G, where R_2 is H, or the product of claim 149, formula 5G, and mixing that product with a reducing agent.

164. The process of claim 163, where the reducing agent is a hydride.

165. The process of claim 164, where the hydride is sodium borohydride.

166. The process of claim 163, where the reactants are mixed in an alcohol or under two-phase conditions.

167. The process of claim 166, where the alcohol is methanol or 2-propanol or the two phase condition is water and an organic phase.

168. The process of claim 167, where the organic phase is heptane, methylene chloride or methyl t-butyl ether, or mixtures of these solvents.

169. The process of claim 163, where the compound produced is represented by formula 5CPT as described in claim 17.

170. The process of claim 163, where the compound produced is represented by formula 5MM as described in claim 20.

171. The process of claim 163, for producing the compounds in claim 21, formula 6G, by beginning with the product of claim 163, formula 5G, and a) mixing that product with a base and an alkylating agent in a solvent or b) mixing that product under phase transfer conditions using water and an organic solvent.

172. The process of claim 171, where the base is a hydride such as sodium hydride or potassium hydride, or an alkoxide base such as potassium t-butoxide or mixtures of these bases.

173. The process of claim 172, where the base is potassium t-butoxide.

174. The process of claim 172, where the solvent is selected from an ethereal solvent such as tetrahydrofuran (THF), methyl t-butyl ether (MTBE) or 1,2-dimethoxyethane or an alcohol such as t-butanol.

175. The process of claim 174, where the solvent is THF or MTBE and the temperature is between about 20^{o} and about 40^{o}.

176. The process of claim 171, where the organic solvent is selected from methylene chloride, or a hydrocarbon such as hexane, heptane, or toluene and where the base is selected from a hydroxide such as sodium or potassium hydroxide, or a carbonate such as sodium or potassium carbonate.

177. The process of claim 171, where the compound produced is represented by formula 6CPT as described in claim 23.

178. The process of claim 171, for producing the compounds in claim 24, formula 7G, or 7GG by beginning with the product of claim 169, formula 6G, and mixing that product with carbon monoxide and an alcohol in the presence of a soluble palladium II salt, a phosphine ligand and a base in a polar aprotic solvent.

179. The process of claim 178, where the soluble palladium II salt is selected from

palladium acetate.

180. The process of claim 179, where the phosphine ligand is selected from 1,3-bisdiphenylphosphinopropane.

181. The process of claim 180, where the base is selected from sodium or potassium acetate, sodium or potassium carbonate, triethylamine, or tri n-butylamine.

182. The process of claim 181, where the polar aprotic solvent is selected from dimethyl formamide or acetonitrile.

183. The process of claim 182, where the compound produced is represented by formula 7CPTG as described in claim 26.

184. The process of claim 178, for producing the compounds in claim 27, formula 7GA, by beginning with the product of claim 178, formula 6G, and then removing the ketal by a) mixing that product with water in the presence of a strong acid or by b) using an exchange reaction to remove the ketal.

185. The process of claim 184, where the process temperature is between about 15° to about 80°.

186. The process of claim 185, where the concentration of the acid is between about 50 and 90%.

187. The process of claim 186, where the strong acid is trifluoroacetic acid.

188. The process of claim 187, where the compound produced is represented by formula 7CPTA as described in claim 29.

189. The process of claim 184, where the exchange reaction procedes with a ketone that is catalyzed by a strong acid or on an acidic ion exchange resin.

190. The process of claim 189, where the ketone is acetone or 2-butanone or where

the acidic ion exchange resin is a resin such as amberlyst A-15 resin.

191. The process of claim 190, where the compound produced is represented by formula 7CPTA as described in claim 29.

192. The process of claim 184, for producing the compounds in claim 30, formula 8GG, by beginning with the product of claim 178, formula 7G, or 7GG, and then removing the ketal by a) mixing that product with water in the presence of a strong acid or by b) using an exchange reaction to remove the ketal.

193. The process of claim 192, where the process temperature is between about 15^{o} to about 80^{o}.

194. The process of claim 193, where the concentration of the acid is between about 50 and 90%.

195. The process of claim 194, where the strong acid is trifluoroacetic acid.

196. The process of claim 195, where the compound produced is represented by formula 8CPTG as described in claim 33.

197. The process of claim 192, where the exchange reaction procedes with a ketone that is catalyzed by a strong acid or on an acidic ion exchange resin.

198. The process of claim 197, where the ketone is acetone or 2-butanone or where the acidic ion exchange resin is a resin such as amberlyst A-15 resin.

199. The process of claim 198, where the compound produced is represented by formula 8CPTG as described in claim 33.

200. The process of claim 184, or claim 192 for producing the compounds in claim 34, formula 8GA, by beginning with the product of claim 184 or claim 192, formula 7GA , and dissolving that product in a solvent mixing it with vinyllithium or a vinylmagnesium halide.

201. The process of claim 200, where the solvent is selected from ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, or MTBE, either alone or as mixtures, or as mixtures with hydrocarbons such as toluene, heptane, or cyclohexane.

202. The process of claim 201, where the process temperature is between about -78° and about 25°.

203. The process of claim 202, where the product is isolated after reaction with a dilute acid.

204. The process of claim 203, where the dilute acid is hydrochloric, sulfuric, or acetic acids.

205. The process of claim 204, where the compound produced is represented by formula 8CPTA as described in claim 38.

206. The process of claim 184, for producing the compounds in claim 39, formula 8GB, by beginning with the product of claim 184, formula 7GA, and mixing that product in a ylide solution and solvent as a Wittig reaction.

207. The process of claim 206, where the ylide solution is prepared from a methyl triphenylphosphonium salt, and a strong base, in a solvent.

208. The process of claim 207, where the solvent is as diethyl ether, terahydrofuran, 1,2-dimethoxyethane, or DMF.

209. The process of claim 208, where the strong base is selected from n-butyllithium, potassium t-butoxide, or potassium bis trimethylsilylamide.

210. The process of claim 209, where the methyl triphenylphosphonium salt is the bromide salt, the base is potassium bis trimethylsilylamide, the solvent is DMF.

211. The process of claim 210, where the process temperature is between about -5° and about 25° and the reaction is run for anytime from about 5 minutes to about 2

hours.

212. The process of claim 211, where the compound produced is represented by formula 8CPTB as described in claim 42.

213. The process of claim 192, for producing the compounds in claim 43, formula 9GG, by beginning with the product of claim 192, formula 8GG, and mixing that product in a ylide solution and solvent as a Wittig reaction.

214. The process of claim 213, where the ylide solution is prepared from a methyl triphenylphosphonium salt, and a strong base, in a solvent.

215. The process of claim 214, where the solvent is as diethyl ether, terahydrofuran, 1,2-dimethoxyethane, or DMF.

216. The process of claim 215, where the strong base is selected from n-butyllithium, potassium t-butoxide, or potassium bis trimethylsilylamide.

217. The process of claim 216, where the methyl triphenylphosphonium salt is the bromide salt, the base is potassium bis trimethylsilylamide, the solvent is DMF.

218. The process of claim 217, where the process temperature is between about -5° and about 25° and the reaction is run for anytime from about 5 minutes to about 2 hours.

219. The process of claim 218, where the compound produced is represented by formula 9CPTG as described in claim 46.

220. The process of claim 200, for producing the compounds in claim 47, formula 9GA, by beginning with the product of claim 200, formula 8GA, and mixing that product with a solvent and ozone to produce an intermediate that is reduced either directly or through an intermediate to 9GA.

221. The process of claim 200, where the solvents are selected from chlorinated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, 1,2-

dichloroethane, or other multiply chlorinated ethane or ethylene derivatives, either alone, as mixture, or as mixtures with alcohols such as methanol.

222. The process of claim 221, where the process is at a temperature from about -78° to about -25°.

223. The process of claim 222, where the reducing agent is sodium borohydride.

224. The process of claim 223, where the solvent is selected from a mixture of methylene chloride and methanol, and where the temperature is from about -78° to about -40° for the initial reaction with ozone, and a temperature of about 0° to 25° for the reduction of the intermediate.

225. The process of claim 224, where the compound produced is represented by formula 9CPTA as described in claim 51.

226. The process of claim 213, for producing the compounds in claim 52, formula 10GG, by beginning with the product of claim 213, formula 9GG, and converting the diol by osmylation under standard conditions.

227. The process of claim 226, where the process temperature is from about 15° to about 50°.

228. The process of claim 227, where the compound produced is represented by formula 10CPT as described in claim 56.

229. The process of claim 213, for producing the compounds in claim 52, formula 10GG, by beginning with the product of claim 213, formula 9GG, and converting the diol by osmylation under standard conditions.

230. The process of claim 229, where the process temperature is from about 15° to about 50°.

231. The process of claim 229, where the compound produced is represented by formula 10CPT as described in claim 56.

232. The process of claim 220, for producing the compounds in claim 52, formula 10GG, by beginning with the product of claim 220, formula 9GA, and mixing that product with carbon monoxide and an alcohol in the presence of a soluble palladium II salt, a phosphine ligand and a base in a polar aprotic solvent.

233. The process of claim 232, where the soluble palladium II salt is selected from palladium acetate.

234. The process of claim 233, where the phosphine ligand is selected from 1,3-bisdiphenylphosphinopropane.

235. The process of claim 234, where the base is selected from sodium or potassium acetate, sodium or potassium carbonate, triethylamine, or tri n-butylamine.

236. The process of claim 235, where the polar aprotic solvent is selected from dimethyl formamide or acetonitrile.

237. The process of claim 236, where the compound produced is represented by formula 10CPT as described in claim 56.

238. The process of resolving the compounds described in claim 52, formula 10G, by treating the racemic diol with an acetylating reagent.

239. The process of claim 238, where the acetylating reagent is selected from vinyl acetate, isopropenyl acetate, acetic anhydride or ethyl acetate in an organic solvent with an appropriate lipase.

240. The process of claim 239, where the organic solvent is ether, or hexane and the lipase is *Pseudomonas*.

241. The process of claim 239, where the lipase is *Pseudomonas cepaica*.

242. The process of claim 238, where the lipase is *Pseudomonas cepaica* and the process is conducted between 25^0 to 45^0 at a substrate concentration of 15-40

mg/mL. and the resolved compounds are represented by formula 10CPT(R) or 10CPT(S), as described in claims 57 and 58.

243. The process of making the compounds described in claim 59, see formula 11G, by oxidizing the compounds described in claim 52, see formula 10G, to the hydroxy aldehyde under either a) Swern type conditions or b) a two phase system comprising water and an aprotic solvent.

244. The process of claim 243, where the Swern type conditions are DMSO, oxalyl chloride and triethylamine in an aprotic solvent and the temperature ranges from about -78° to about 25°.

245. The process of claim 244, where the aprotic solvent is methylene chloride.

246. The process of claim 243, where the two phase system comprising water and an aprotic solvent is a sodium hypochlorite solution catalyzed by TEMPO or a substituted TEMPO such as 4-acetoxy-TEMPO and where the other phase is methylene chloride.

247. The process of claim 246, where the process temperature is between about -5° and about +25° and the time allowed for reaction may be anytime from about 30 minutes to about 2 hours.

248. The process of claim 247, for producing the compounds in claim 63, formula 11CPT, 11CPT(R) as described in claim 64, or 11CPT(S) as described in claim 65.

249. The process of claim 243, for producing the compounds in claim 66, formula 12GA-1, by oxidizing the product of claim 243, formula 11G.

250. The process of claim 247, where the temperature is about 10° or 20° and the reaction time is about an hour.

251. The process of claim 247, where the oxidizing agent is sodium chlorite.

252. The process of claim 249, to produce the compound described in claim 70,

formula 12 CPTA-1, claim 71, formula 12 CPTA-1(R), or claim 72, formula 12 CPTA-1(S).

253. The process of claim 243, for producing the compounds in claim 73, formula 12GB-1, by removing the leaving group from the product of claim 243, formula 11G.

254. The process of claim 253, where the leaving group is removed by hydrogenation over a catalyst.

255. The process of claim 254, where the catalyst is palladium.

256. The process of claim 253, where the compound produced is represented by formula 12CPTB-1 as described in claim 77, formula 12CPTB-1(R) as described in claim 78, or formula 12CPTB-1(S) as described in claim 78.

257. The process of claim 249, for producing the compounds in claim 80, formula 12GA-2 or 12GB-2, by removing the leaving group from the product of claim 249, formula 12GA-1.

258. The process of claim 257, where the leaving group is removed by hydrogenation over a catalyst.

259. The process of claim 258, where the catalyst is palladium.

260. The process of claim 257, where the compound produced is represented by formula 12CPTA(B)-2 described by claim 84, formula 12CPTA(B)-2(R) described by claim 85, or formula 12CPTA(B)-2(S) described by claim 86.

261. The process of claim 253, for producing the compounds in claim 80, formula 12GA-2 or 12GB-2, by oxidizing the lactol from the product of claim 253, formula 12GB-1.

262. The process of claim 261, where the lactol is oxidized under a) Swern type conditions, or b) a two phase system comprising water and an aprotic solvent.

263. The process of claim 262, where the Swern type conditions are DMSO, oxalyl chloride and triethylamine in an aprotic solvent and the temperature ranges from about -78° to about 25°.

264. The process of claim 263, where the aprotic solvent is methylene chloride.

265. The process of claim 261, where the compouds produced are represented by formula 12CPTA(B)-2 described by claim 84, formula 12CPTA(B)-2(R) described by claim 85, or formula 12CPTA(B)-2(S) described by claim 86.

266. The process of claim 249, for producing the compounds in claim 87, formula 12G, by removal of the leaving group from the product of claim 249, formula12GA-1, by mixing the compound with trimethylsilyl iodide.

267. The process of claim 266, where the trimethylsilyl is either preformed or generated in sutu from trimethylsilyl chloride and sodium iodide in methylene chloride or acetonitrile and the process temperature is between about 15° and 50° for any length of time between 12 and 48 hours.

268. The process of claim 266, where the compouds produced are represented by formula 12CPTA described by claim 91, formula 12CPT(R) described by claim 92, or formula 12CPT(S) described by claim 93.

269. The process of claim 257, for producing the compounds in claim 87, formula 12G, by removal of the leaving group from the product of claim 257, formula 12GA-2 or 12GB-2, by mixing the compound with trimethylsilyl iodide.

270. The process of claim 269, where the trimethylsilyl is either preformed or generated in sutu from trimethylsilyl chloride and sodium iodide in methylene chloride or acetonitrile and the process temperature is between about 15° and 50° for any length of time between 12 and 48 hours.

271. The process of claim 270, where the compouds produced are represented by formula 12CPTA described by claim 91, formula 12CPT(R) described by claim 92, or formula 12CPT(S) described by claim 93.

272. The process of making the compounds described in claim 94, formula 13G, by mixing the compounds described in claim 87, see formula 12G, with an acrylate ester in the presence of a base.

273. The process of claim 272, where the acrylate ester is methyl, ethyl, or t-butyl acrylate.

274. The process of claim 273, where the base is potassium hydride, sodium hydride, potassium t-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, or a tertiary amine, including diisopropylethyl amine, in a polar aprotic solvent such as dimethyl sulfoxide, DMF, or acetonitrile.

275. The process of claim 272, where the acrylate ester is t-butyl acrylate and where the base is cesium carbonate in DMSO and the temperature is between about 20° and 100° preferably about 50° and where the compounds produced are represented by formula 13CPT described by claim 98, formula 13CPT(R) described by claim 99, or formula 13CPT(S) described by claim 100.

276. The process of claim 272 for producing the compounds described by formula 14G, where the variables are defined above, where the ketoester is converted into the compounds described by formula 14G by mixing 13G with a strong acid.

277. The process of claim 276, where a solvent such as toluene is added to the acid, ketoester mixture.

278. The process of claim 277, where the solvent is toluene and the acid is trifluoroacetic acid.

279. The process of claim 152, where the electrophile is a methylating agent including dimethyl sulfate, methyl iodide, methylbromide, or methyltriflate.

280. The process of claim 279, where the reactants are maintained at a temperature between about -40° and about $+50^{\circ}$.

281. The process of claim 279, where the reactants are maintained at a temperature between about -5° and about +5°.

282. The process of claim 279, where the product is isolated with a dilute acid.

283. The process of claim 279, where the methylating agent is dimethyl sulfate and where the dilute acid is selected from a moderate to strong acids such as hydrochloric acid, acetic acid, or sulfuric acid, or mixtures of any of these acids.

284. The process of claim 279, where the compound produced is represented by formula 5MM.

285. The process of making the compounds described in claim 107, formula 6MG, by deketalizing the compounds described in claim 102, formula 5MG.

286. The process of claim 285, where deketalizing step is under acidic conditions.

287. The process of claim 286, where the product of the process is the compound described in claim 111, formula 6MM.

288. The process of claim 287, where the product of the process of claim 285, formula 6MG, is reduced to produce the compounds described in claim 112, formula 7MG, where R_3 is H.

289. The process of claim 288, where the compounds produced are described in claim 116, formula 6bMM, racemate or either isomer.

290. The process of claim 285, for producing the compounds in claim 112, formula 7MG, where R_3 is not H, by beginning with the product of claim 285, formula 7MG, where R_3 is H, and mixing that product with a base and an alkylating agent in a solvent.

291. The process of claim 290, where the compounds produced are described in claim 117, formula 7MM, racemate or either isomer.

292. The process of claim 290 where the base is a hydride such as sodium hydride or potassium hydride, or an alkoxide base such as potassium t-butoxide or mixtures of these bases and the alkylating agent is an alkyl halide.

293. The process of claim 292, where the base is potassium t-butoxide and the alkylating agent is benzyl bromide.

294. The process of claim 290, for producing the compounds in claim 118, formula 8MG, by beginning with the product of claim 284, formula 7MG, and mixing that product with carbon monoxide and an alcohol in the presence of a soluble palladium II salt, a phosphine ligand and a base in a polar aprotic solvent.

295. The process of claim 294, where the soluble palladium II salt is selected from palladium acetate.

296. The process of claim 294, where the phosphine ligand is selected from 1,3-bisdiphenylphosphinopropane.

297. The process of claim 294, where the base is selected from sodium or potassium acetate, sodium or potassium carbonate, triethylamine, or tri n-butylamine.

298. The process of claim 297, where the polar aprotic solvent is selected from dimethyl formamide or acetonitrile.

299. The process of claim 294, where the compound produced from that process is described by claim 122, formula 8MM, either isomer or the racemate.

300. The process of claim 294, for producing the compounds in claim 123, formula 9MG, by removal of the leaving group from the product of claim 294, formula 8MG, and mixing the compound with trimethylsilyl iodide.

301. The process of claim 300, where the trimethylsilyl is either preformed or generated *in situ* from trimethylsilyl chloride and sodium iodide in methylene chloride or acetonitrile.

302. The process of claim 300 where the process temperature is between about 15° and 50° for any length of time between 12 and 48 hours.

303. The process of claim 300, where the compounds produced are described by claim 127, formula 9MM.

304. The process of claim 300, for producing the compounds in claim 128, formula 10MG, by mixing the compounds produced in claim 300, formula 9MG, with an acrylate ester in the presence of a base in a polar aprotic solvent.

305. The process of claim 304, where the acrylate ester is methyl, ethyl, or t-butyl acrylate.

306. The process of claim 304, where the base is potassium hydride, sodium hydride, potassium t-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, or a tertiary amines, including diisopropylethyl amine in a polar aprotic solvent such as dimethyl sulfoxide, DMF, or acetonitrile.

307. The process of claim 304, where the compounds produced are represented by the compounds described in claim 137, formula 10MM, racemate and both isomers.

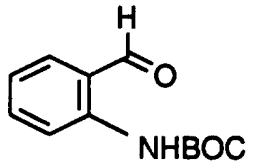
308. The process of claim 304, for producing the compounds in claim 133, formula 11MG, by mixing the compounds produced in claim 304, formula 10MG, with a strong acid.

309. The process of claim 308, where the strong acid is trifluoroacetic acid.

310. The process of claim 308, where the compounds produced are represented by the compounds described in claim 137, formula 11MM, racemate and both isomers.

311. The process of claim 308, for producing the compounds in claim 138, formula 12MG, by starting with the product of claim 308, formula 11MM, and using the process of the Friedlander type condensation reaction with obvious intermediates to create obvious products comprising the appropriately modified formula 12MG and the appropriately modified obvious intermediate.

312. The process of claim 311, where the appropriately modified obvious intermediate used in the Friedlander type condensation reaction is the compound shown below,



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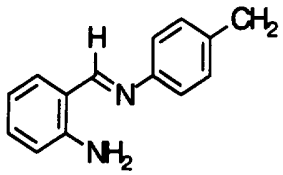
313. The process of claim 311, where the appropriately modified obvious intermediate used in the Friedlander type condensation reaction is the compound shown below,



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314. The process of claims 312 or 313, where the compounds produced are represented by the compounds described by formula 12 MM, racemate and both isomers.

315. The process of claim 311, for producing the compounds of formula 13MG by starting with the product of claim 311 and removing the leaving group.

316. The process of claim 315, where the leaving group is removed by mixing the product of claim 311 with hydrogen over a catalyst.

317. The process of claim 316, where the catalyst is palladium.

318. The process of claim 317, where the compound produced from the reaction is mappicine.

319. The novel compounds described in the specification.

320. The novel processes described in the disclosure.

321. Any of claims 1-142 made independently.

322. Any of claims 142 - 318 made independently.

323. Any of claims 142 - 318 in any combination of two or more consecutive reactions.

324. The invention as herein described.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 96/04163

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/22 C07D471/14 C07D471/04 C07D491/14 C07D491/04
A61K31/435 C07D213/61 C07D213/64 C07D213/79 C07D405/04

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 6 C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 29310 (SMITHKLINE BEECHAM CORP ;FORTUNAK JOSEPH M (US); KITTERINGHAM JOHN) 22 December 1994 see the whole document ---	1-324
A	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1990, LETCHWORTH GB, pages 27-31, XP002010690 A. EJIMA ET AL.: "Antitumour agents. Part 2. Asymmetric synthesis of (S)-Camptothecin" cited in the application see the whole document ---	1-324
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* 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 document 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

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1996	19.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bosma, P

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INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 96/04163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 053 512 (WANI MANSUKH C ET AL) 1 October 1991 cited in the application see the whole document -----	1-324

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 96/04163

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9429310	22-12-94	US-A-	5405963	11-04-95
		AU-B-	7056994	03-01-95
		EP-A-	0705262	10-04-96
		US-A-	5541329	30-07-96
		US-A-	5468859	21-11-95
		ZA-A-	9404090	21-02-95
US-A-5053512	01-10-91	US-A-	5401747	28-03-95
		US-A-	5180722	19-01-93
		US-A-	5244903	14-09-93
		US-A-	5340817	23-08-94
		US-A-	5364858	15-11-94
		US-A-	5122606	16-06-92