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(54) Title: METHOD FOR MAKING TETRABENAZINE COMPOUNDS

(57) Abstract: A method of preparing a tetrabenazine compound (TBZ compound) having structure I comprising the steps of reacting a nucleophilic alkenyl species with aldehyde compound II and oxidizing the resultant allylic alcohol to provide enone III. The protecting group P^1 on the tetrahydroisoquinoline nitrogen is removed and the resultant deprotected intermediate is induced to undergo an amino cyclization reaction to provide a product TBZ compound having structure I. The method may be used to prepare either enantiomeric form of tetrabenazine; (+)-tetrabenazine or (-)-tetrabenazine. Alternatively the method may be adapted to provide a mixture enriched in one tetrabenazine enantiomer, a racemic mixture, or a diastereomeric mixture of tetrabenazine compounds. In addition, the present invention provides novel synthetic intermediate compositions which may be used to prepare either or both enantiomers of tetrabenazine, derivatives of tetrabenazine, and analogs of tetrabenazine.

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METHOD FOR MAKING TETRABENAZINE COMPOUNDS

BACKGROUND

[0001] This invention relates to tetrabenazine compounds (TBZ compounds) and methods for the preparation of said tetrabenazine compounds.

[0002] Since first reported on in 1957 (Pletscher, A. (1957) Release of 5-hydroxytryptamine by benzoquinolizine derivatives with sedative action, *Science 126*, 507), tetrabenazine and structurally related compounds have been widely investigated, and a number of TBZ compounds and derivatives of tetrabenazine have shown promise in the treatment of a variety of conditions affecting human health. For example, dihydrotetrabenazine has been identified as an agent for the treatment of schizophrenia and other psychoses (See for example WO 2007017654 A1), and tetrabenazine has shown promise as an agent in the treatment of Huntington's disease (Neurology (2006), 66(3), 366-372). Although most preparations used in biological studies of tetrabenazine and its derivatives have been carried out on racemates, in at least one instance the biological activity exhibited by enantiomers tested separately was highly differentiated (See Koeppe, R. A. et al. (1999) Assessment of extrastriatal vesicular monoamine transporter binding site density using stereoisomers of [11C]dihydrotetrabenazine, *J Cereb Blood Flow Metab 19*, 1376-1384).

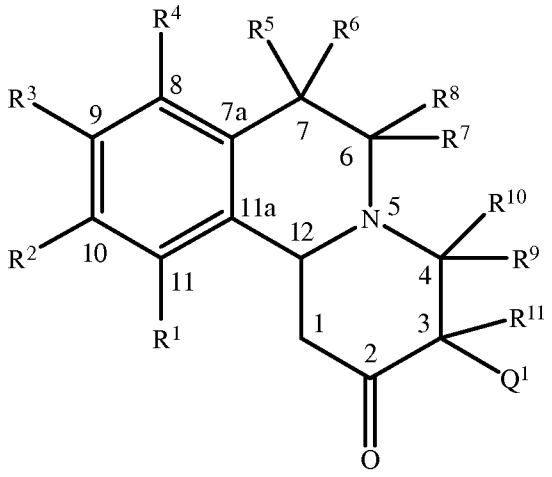
[0003] Notwithstanding, the availability of tetrabenazine and derivatives of tetrabenazine in racemic and enantiomerically enriched forms, there is a need for improved synthetic methods which provide either or both enantiomers of tetrabenazine, derivatives of tetrabenazine, and analogs of tetrabenazine. In addition, there is a need to provide novel synthetic intermediate compositions which may be used to prepare either or both enantiomers of tetrabenazine, derivatives of tetrabenazine, and analogs of tetrabenazine.

[0004] The present invention provides both a new and efficient synthetic methodology which may be used to prepare either or both enantiomers of tetrabenazine, derivatives of tetrabenazine and analogs of tetrabenazine. In addition the present invention provides novel synthetic intermediate compositions which may

be used to prepare either or both enantiomers of tetrabenazine, derivatives of tetrabenazine and analogs of tetrabenazine.

BRIEF DESCRIPTION

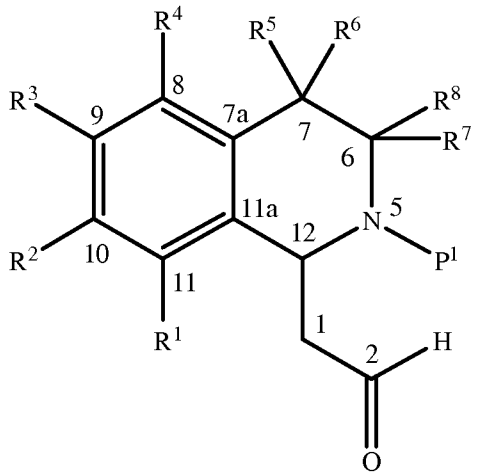
[0005] In one embodiment, the present invention provides a method of preparing a tetrabenazine (TBZ) compound having structure I,



I

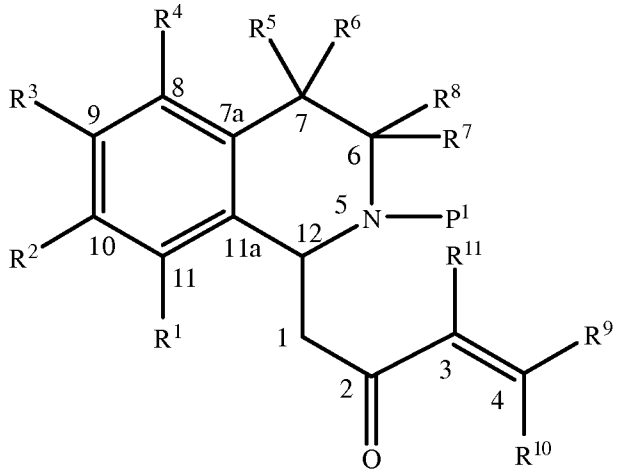
said method comprising:

(a) reacting a nucleophilic alkenyl species with aldehyde compound II



II

and oxidizing the resultant allylic alcohol to provide a first intermediate having structure III; and

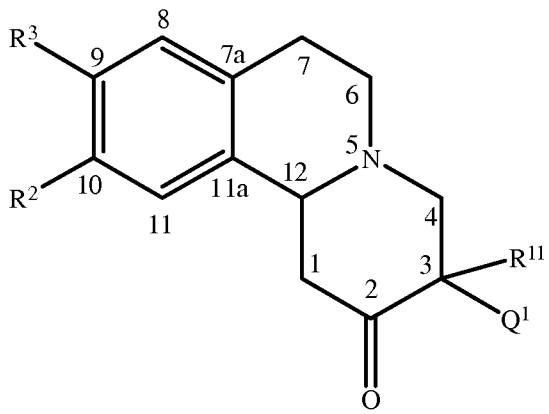


III

(b) removing protecting group P^1 and inducing an amino cyclization reaction to provide a product TBZ compound having structure I,

wherein with respect to structures I, II, and III; R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; P^1 is a protecting group, and Q^1 is hydrogen or an isotope thereof.

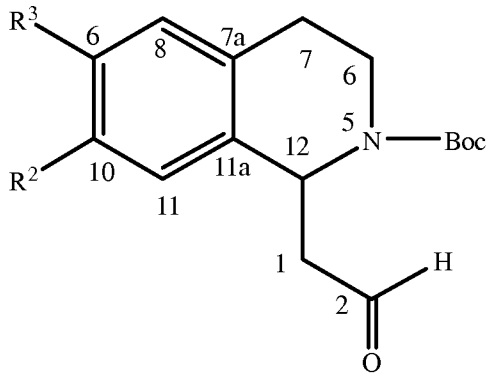
[0006] In another embodiment, the present invention provides a method of preparing a tetrabenazine (TBZ) compound having structure V,



V

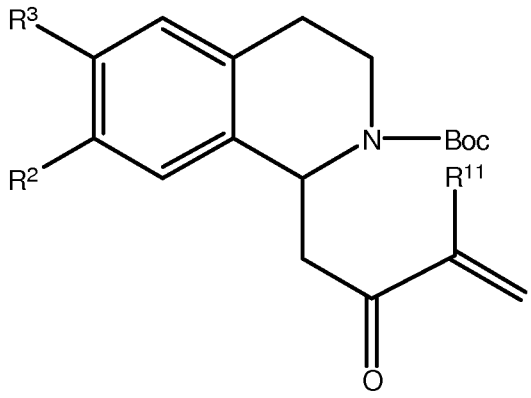
said method comprising:

(a) reacting a nucleophilic alkenyl species with aldehyde compound VI



VI

and oxidizing of the resultant allylic alcohol to provide a first intermediate having structure VII; and

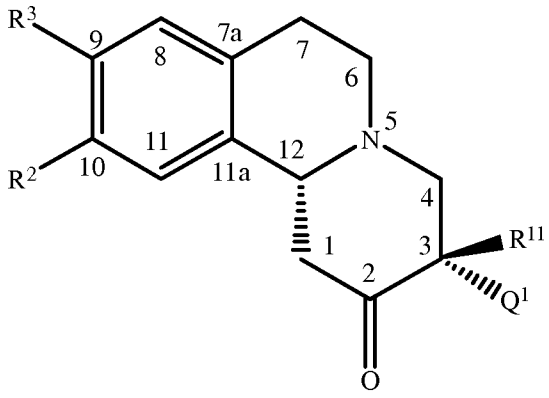


VII

(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure V,

wherein with respect to structures V, VI, and VII; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

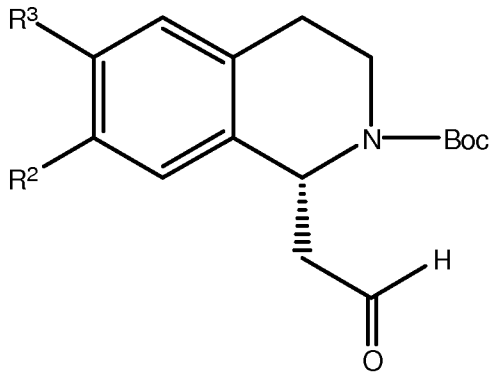
[0007] In yet another embodiment, the present invention provides a method of preparing an enantiomerically enriched tetrabenazine (TBZ) compound comprising at least 95 mole percent enantiomer VIII,



VIII

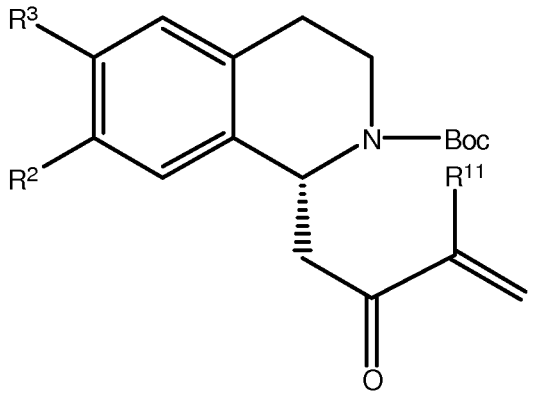
said method comprising:

(a) reacting a nucleophilic alkenyl species with an aldehyde compound comprising at least 95 mole percent enantiomer IX



IX

and oxidizing the resultant allylic alcohol to provide a first intermediate having structure X; and



X

(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure VIII,

wherein with respect to structures VIII, IX, and X; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

DETAILED DESCRIPTION

[0008] In the following specification and the claims, which follow, reference will be made to a number of terms, which shall be defined to have the following meanings.

[0009] The singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise.

[0010] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event occurs and instances where it does not.

[0011] As used herein, the term "solvent" can refer to a single solvent or a mixture of solvents.

[0012] Approximating language, as used herein throughout the specification and claims, may be applied to modify any quantitative representation that could permissibly vary without resulting in a change in the basic function to which it is related. Accordingly, a value modified by a term or terms, such as "about", is not to be limited to the precise value specified. In some instances, the approximating language may correspond to the precision of an instrument for measuring the value.

[0013] As used herein, the term "aromatic radical" refers to an array of atoms having a valence of at least one comprising at least one aromatic group. The array of atoms having a valence of at least one comprising at least one aromatic group may include heteroatoms such as nitrogen, sulfur, selenium, silicon and oxygen, or may be composed exclusively of carbon and hydrogen. As used herein, the term "aromatic radical" includes but is not limited to phenyl, pyridyl, furanyl, thienyl, naphthyl, phenylene, and biphenyl radicals. As noted, the aromatic radical contains at least one aromatic group. The aromatic group is invariably a cyclic structure having 4n+2 "delocalized" electrons where "n" is an integer equal to 1 or greater, as illustrated by phenyl groups (n = 1), thienyl groups (n = 1), furanyl groups (n = 1), naphthyl groups (n = 2), azulenyl groups (n = 2), anthraceneyl groups (n = 3) and the like. The aromatic radical may also include nonaromatic components. For example, a benzyl group is an aromatic radical which comprises a phenyl ring (the aromatic group) and a methylene group (the nonaromatic component). Similarly a tetrahydronaphthyl radical is an aromatic radical comprising an aromatic group (C_6H_3) fused to a nonaromatic component $-(CH_2)_4-$. For convenience, the term "aromatic radical" is defined herein to encompass a wide range of functional groups such as alkyl groups, alkenyl groups, alkynyl groups, haloalkyl groups, haloaromatic groups, conjugated dienyl groups, alcohol groups, ether groups, aldehyde groups, ketone groups, carboxylic acid groups, acyl groups (for example carboxylic acid derivatives such as esters and amides), amine groups, nitro groups, and the like. For example, the 4-methylphenyl radical is a C_7 aromatic radical comprising a methyl group, the methyl group being a functional group which is an alkyl group. Similarly, the 2-nitrophenyl group is a C_6 aromatic radical comprising a nitro group, the nitro group being a functional group. Aromatic radicals include halogenated aromatic radicals such as 4-trifluoromethylphenyl, hexafluoroisopropylidenebis(4-phen-1-yloxy) (i.e., $-OPhC(CF_3)_2PhO-$), 4-

chloromethylphen-1-yl, 3-trifluorovinyl-2-thienyl, 3-trichloromethylphen-1-yl (i.e., 3-CCl_3Ph-), 4-(3-bromoprop-1-yl)phen-1-yl (i.e., 4-$BrCH_2CH_2CH_2$Ph-), and the like. Further examples of aromatic radicals include 4-allyloxyphen-1-oxy, 4-aminophen-1-yl (i.e., 4-H_2NPh-), 3-aminocarbonylphen-1-yl (i.e., NH_2COPh-), 4-benzoylphen-1-yl, dicyanomethylidenebis(4-phen-1-yloxy) (i.e., -OPhC$(CN)_2$PhO-), 3-methylphen-1-yl, methylenebis(4-phen-1-yloxy) (i.e., –OPhCH_2PhO-), 2-ethylphen-1-yl, phenylethenyl, 3-formyl-2-thienyl, 2-hexyl-5-furanyl, hexamethylene-1,6-bis(4-phen-1-yloxy) (i.e., –OPh$(CH_2)_6$PhO-), 4-hydroxymethylphen-1-yl (i.e., 4-$HOCH_2$Ph-), 4-mercaptomethylphen-1-yl (i.e., 4-$HSCH_2$Ph-), 4-methylthiophen-1-yl (i.e., 4-CH_3SPh-), 3-methoxyphen-1-yl, 2-methoxycarbonylphen-1-yloxy (e.g., methyl salicyl), 2-nitromethylphen-1-yl (i.e., 2-NO_2CH_2Ph), 3-trimethylsilylphen-1-yl, 4-t-butyldimethylsilylphenl-1-yl, 4-vinylphen-1-yl, vinylidenebis(phenyl), and the like. The term "a C_3 – C_{10} aromatic radical" includes aromatic radicals containing at least three but no more than 10 carbon atoms. The aromatic radical 1-imidazolyl ($C_3H_2N_2$-) represents a C_3 aromatic radical. The benzyl radical (C_7H_7-) represents a C_7 aromatic radical.

[0014] As used herein the term "cycloaliphatic radical" refers to a radical having a valence of at least one, and comprising an array of atoms which is cyclic but which is not aromatic. As defined herein a "cycloaliphatic radical" does not contain an aromatic group. A "cycloaliphatic radical" may comprise one or more noncyclic components. For example, a cyclohexylmethyl group ($C_6H_{11}CH_2$-) is a cycloaliphatic radical which comprises a cyclohexyl ring (the array of atoms which is cyclic but which is not aromatic) and a methylene group (the noncyclic component). The cycloaliphatic radical may include heteroatoms such as nitrogen, sulfur, selenium, silicon and oxygen, or may be composed exclusively of carbon and hydrogen. For convenience, the term "cycloaliphatic radical" is defined herein to encompass a wide range of functional groups such as alkyl groups, alkenyl groups, alkynyl groups, haloalkyl groups, conjugated dienyl groups, alcohol groups, ether groups, aldehyde groups, ketone groups, carboxylic acid groups, acyl groups (for example carboxylic acid derivatives such as esters and amides), amine groups, nitro groups, and the like. For example, the 4-methylcyclopent-1-yl radical is a C_6 cycloaliphatic radical comprising a methyl group, the methyl group being a functional group which is an

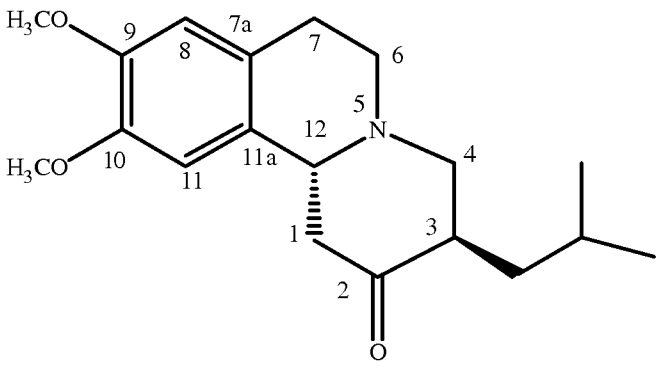
alkyl group. Similarly, the 2-nitrocyclobut-1-yl radical is a C_4 cycloaliphatic radical comprising a nitro group, the nitro group being a functional group. A cycloaliphatic radical may comprise one or more halogen atoms which may be the same or different. Halogen atoms include, for example; fluorine, chlorine, bromine, and iodine. Cycloaliphatic radicals comprising one or more halogen atoms include 2-trifluoromethylcyclohex-1-yl, 4-bromodifluoromethylcyclooct-1-yl, 2-chlorodifluoromethylcyclohex-1-yl, hexafluoroisopropylidene-2,2-bis (cyclohex-4-yl) (i.e., $-C_6H_{10}C(CF_3)_2$ C_6H_{10}-), 2-chloromethylcyclohex-1-yl, 3-difluoromethylenecyclohex-1-yl, 4-trichloromethylcyclohex-1-yloxy, 4-bromodichloromethylcyclohex-1-ylthio, 2-bromoethylcyclopent-1-yl, 2-bromopropylcyclohex-1-yloxy (e.g., $CH_3CHBrCH_2C_6H_{10}O$-), and the like. Further examples of cycloaliphatic radicals include 4-allyloxycyclohex-1-yl, 4-aminocyclohex-1-yl (i.e., $H_2NC_6H_{10}$-), 4-aminocarbonylcyclopent-1-yl (i.e., $NH_2COC_5H_8$-), 4-acetyloxycyclohex-1-yl, 2,2-dicyanoisopropylidenebis(cyclohex-4-yloxy) (i.e., $-OC_6H_{10}C(CN)_2C_6H_{10}O$-), 3-methylcyclohex-1-yl, methylenebis(cyclohex-4-yloxy) (i.e., $-OC_6H_{10}CH_2C_6H_{10}O$-), 1-ethylcyclobut-1-yl, cyclopropylethenyl, 3-formyl-2-terahydrofuranyl, 2-hexyl-5-tetrahydrofuranyl, hexamethylene-1,6-bis(cyclohex-4-yloxy) (i.e., $-O$ $C_6H_{10}(CH_2)_6C_6H_{10}O$-), 4-hydroxymethylcyclohex-1-yl (i.e., 4-$HOCH_2C_6H_{10}$-), 4-mercaptomethylcyclohex-1-yl (i.e., 4-$HSCH_2C_6H_{10}$-), 4-methylthiocyclohex-1-yl (i.e., 4-$CH_3SC_6H_{10}$-), 4-methoxycyclohex-1-yl, 2-methoxycarbonylcyclohex-1-yloxy (2-$CH_3OCOC_6H_{10}O$-), 4-nitromethylcyclohex-1-yl (i.e., $NO_2CH_2C_6H_{10}$-), 3-trimethylsilylcyclohex-1-yl, 2-t-butyldimethylsilylcyclopent-1-yl, 4-trimethoxysilylethylcyclohex-1-yl (e.g., $(CH_3O)_3SiCH_2CH_2C_6H_{10}$-), 4-vinylcyclohexen-1-yl, vinylidenebis(cyclohexyl), and the like. The term "a $C_3 - C_{10}$ cycloaliphatic radical" includes cycloaliphatic radicals containing at least three but no more than 10 carbon atoms. The cycloaliphatic radical 2-tetrahydrofuranyl (C_4H_7O-) represents a C_4 cycloaliphatic radical. The cyclohexylmethyl radical ($C_6H_{11}CH_2$-) represents a C_7 cycloaliphatic radical.

[0015] As used herein the term "aliphatic radical" refers to an organic radical having a valence of at least one consisting of a linear or branched array of atoms which is not cyclic. Aliphatic radicals are defined to comprise at least one carbon atom. The array of atoms comprising the aliphatic radical may include heteroatoms

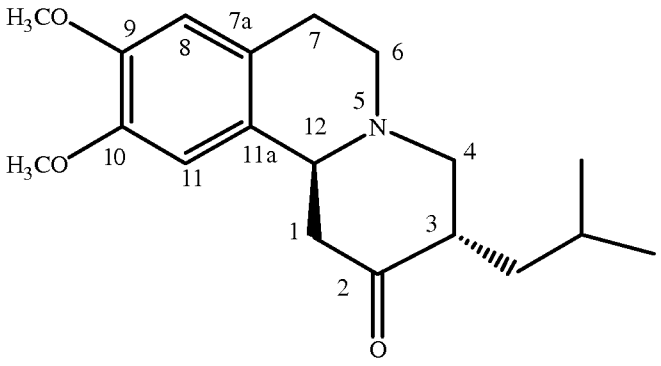
such as nitrogen, sulfur, silicon, selenium and oxygen or may be composed exclusively of carbon and hydrogen. For convenience, the term "aliphatic radical" is defined herein to encompass, as part of the "linear or branched array of atoms which is not cyclic" a wide range of functional groups such as alkyl groups, alkenyl groups, alkynyl groups, haloalkyl groups , conjugated dienyl groups, alcohol groups, ether groups, aldehyde groups, ketone groups, carboxylic acid groups, acyl groups (for example carboxylic acid derivatives such as esters and amides), amine groups, nitro groups, and the like. For example, the 4-methylpent-1-yl radical is a C_6 aliphatic radical comprising a methyl group, the methyl group being a functional group which is an alkyl group. Similarly, the 4-nitrobut-1-yl group is a C_4 aliphatic radical comprising a nitro group, the nitro group being a functional group. An aliphatic radical may be a haloalkyl group which comprises one or more halogen atoms which may be the same or different. Halogen atoms include, for example; fluorine, chlorine, bromine, and iodine. Aliphatic radicals comprising one or more halogen atoms include the alkyl halides trifluoromethyl, bromodifluoromethyl, chlorodifluoromethyl, hexafluoroisopropylidene, chloromethyl, difluorovinylidene, trichloromethyl, bromodichloromethyl, bromoethyl, 2-bromotrimethylene (e.g., $-CH_2CHBrCH_2-$), and the like. Further examples of aliphatic radicals include allyl, aminocarbonyl (i.e., $-CONH_2$), carbonyl, 2,2-dicyanoisopropylidene (i.e., $-CH_2C(CN)_2CH_2-$), methyl (i.e., $-CH_3$), methylene (i.e., $-CH_2-$), ethyl, ethylene, formyl (i.e.,-CHO), hexyl, hexamethylene, hydroxymethyl (i.e.,$-CH_2OH$), mercaptomethyl (i.e., $-CH_2SH$), methylthio (i.e., $-SCH_3$), methylthiomethyl (i.e., $-CH_2SCH_3$), methoxy, methoxycarbonyl (i.e., CH_3OCO-) , nitromethyl (i.e., $-CH_2NO_2$), thiocarbonyl, trimethylsilyl (i.e., $(CH_3)_3Si-$), t-butyldimethylsilyl, 3-trimethyoxysilylpropyl (i.e., $(CH_3O)_3SiCH_2CH_2CH_2-$), vinyl, vinylidene, and the like. By way of further example, a $C_1 - C_{10}$ aliphatic radical contains at least one but no more than 10 carbon atoms. A methyl group (i.e., CH_3-) is an example of a C_1 aliphatic radical. A decyl group (i.e., $CH_3(CH_2)_9-$) is an example of a C_{10} aliphatic radical.

[0016] As noted, in one embodiment the present invention provides a method of preparing a TBZ compound having structure I. TBZ compounds are defined herein to include tetrabenazine, derivatives of tetrabenazine, and analogs of tetrabenazine. The terms "tetrabenazine compound" and "TBZ compounds" are used

interchangeably and have the same meaning. Tetrabenazine itself is a man-made, biologically active compound, and the term "tetrabenazine" is defined herein to be either a racemic mixture of enantiomers XVII and XVIII, or an enantiomerically enriched mixture of enantiomers XVII and XVIII, or a single enantiomer XVII or XVIII. It will be clear from context which form of tetrabenzine is meant. The tetrabenazine compound having structure XVII is at times herein referred to as (+)-tetrabenazine. The tetrabenazine compound having structure XVIII is at times herein referred to as (-)-tetrabenazine. For convenience and clarity, the numbering system shown in structures I, XVII, XVIII and elsewhere has been adopted and is used throughout this application to specify the ring positions (RP) of the TBZ compounds discussed herein as well as the synthetic intermediates used in the method of the present invention.



XVII



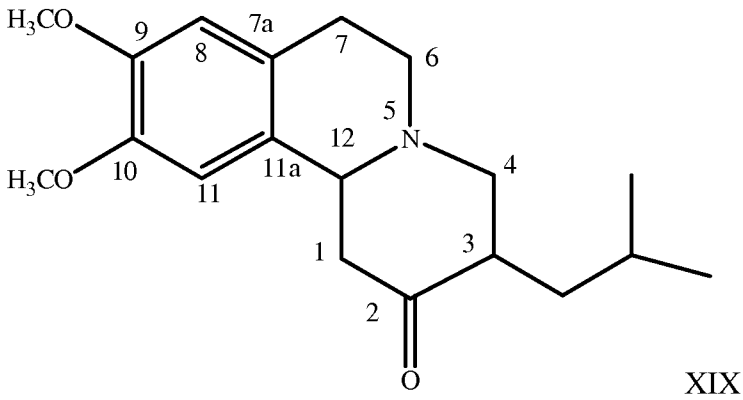
XVIII

[0017] The terms "derivatives of tetrabenazine", and "analogs of tetrabenazine" refer to TBZ compounds which are related to but are not identical to tetrabenazine. A derivative of tetrabenazine is a TBZ compound is derived from tetrabenazine (i.e., is made from tetrabenazine). An analog of tetrabenazine is a TBZ compound which is sufficiently related structurally to fall within the scope of generic structure I but is not identical to tetrabenazine itself. As with tetrabenazine itself, derivatives of tetrabenazine and analogs of tetrabenazine may be racemic, enantiomerically enriched mixtures of enantiomers, single enantiomers, or comprise a mixture of diastereomers. In one embodiment, the present invention provides a tetrabenazine compound having structure XVII in which ring positions 3 and 12 each possess the R configuration.

[0018] The tetrabenazine compounds produced by the method of the present invention may be "optically active", i.e. display an optical rotation measurable on a polarimeter. Alternatively, the tetrabenazene compounds produced by the method of the present invention may be "optically inactive", i.e. do not display an optical rotation measurable on a polarimeter. In various embodiments, the method of the present invention provides tetrabenazine compounds (TBZ compounds) having the same absolute stereochemistry shown in structure XVII, i.e. R configuration at ring positions 3 and 12. In various other embodiments, the method of the present invention provides tetrabenazine compounds having absolute stereochemistry opposite that shown in structure XVII, i.e. S configuration at ring positions 3 and 12.

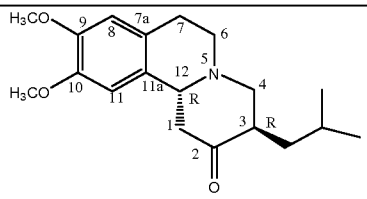
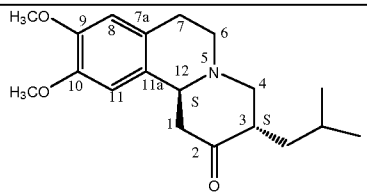
[0019] In general, and throughout this disclosure, where no absolute or relative stereochemistry is shown for a structure, the structure is intended to encompass all possible absolute and relative stereochemical configurations. Thus, structure XIX depicts a tetrabenazine compound in which no absolute or relative stereochemistry is shown. As such, structure XIX is intended to represent a genus of tetrabenazine compounds which includes tetrabenazine having the R configuration at ring positions 3 and 12, a tetrabenazine compound having the opposite (S configuration) absolute stereochemistry at ring positions 3 and 12, racemic tetrabenazine containing a 1:1 mixture of enantiomer XVII and its 3-S/12-S enantiomer XVIII, and diastereomeric mixtures of tetrabenazine compounds, e.g. a

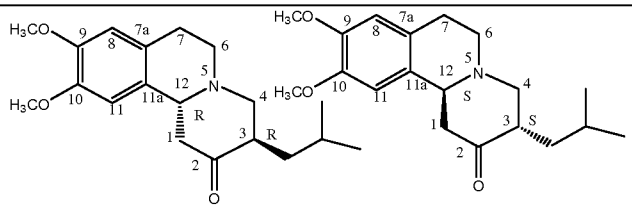
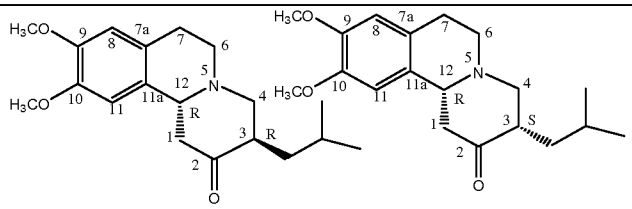
mixture of tetrabenzine enantiomer XVII and a tetrabenazine compound having the same absolute (R configuration) stereochemistry at ring position-12 as enantiomer XVII, but possessing the S configuration at ring position-3. Representative tetrabenazine compounds encompassed by generic formula XIX are illustrated in Table 1. Those having ordinary skill in the art will appreciate that the individual compounds shown in Tables 1, 5, and 8 herein are illustrative of TBZ compounds falling within the scope of generic structure I.



XIX

Table 1 Exemplary Tetrabenazine Compounds Encompassed By Generic Formula XIX

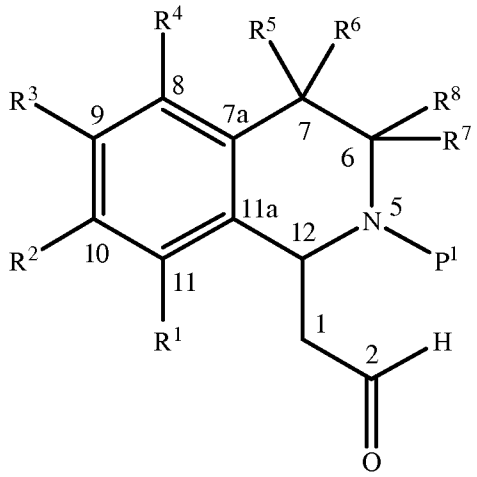
Entry	Name	Ring Position* Stereo-chemistry		Structure
		RP-3	RP-12	
1a	Single "R,R" enantiomer of tetrabenazine	R	R	
1b	Single "S,S" enantiomer of tetrabenazine	S	S	

1c	Tetrabenazine racemic mixture	R/S	R/S	
1d	Tetrabenazine & tetrabenazine compound in diastereomeric mixture	R	R/S	

* RP-3 = Ring position-3, RP-12 = Ring position-12

[0020] The examples given in Table 1 are merely illustrative of tetrabenazine compounds generally, and should not be construed to limit the scope of the invention. Entry 1d depicts a diastereomeric mixture comprising tetrabenazine XVII and a diastereomer having the same absolute stereochemistry at ring position-12 (R configuration) but having the opposite absolute stereochemistry at ring position-3 (S configuration). As will be appreciated by those skilled in the art, a tetrabenazine compound comprising racemic tetrabenazine and diastereomers associated with each of the enantiomers of the racemate are also possible.

[0021] As noted, in one embodiment, the method of the present invention comprises reacting a nucleophilic alkenyl species with an aldehyde compound having structure II

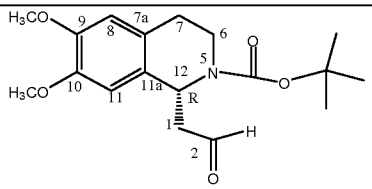
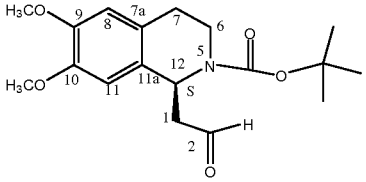
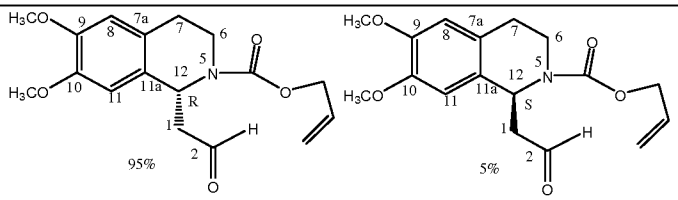
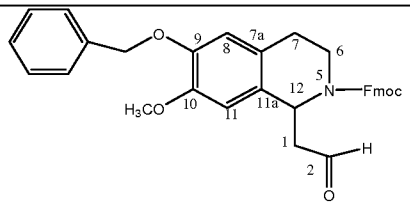


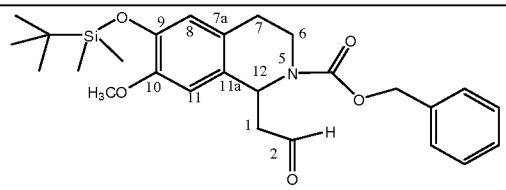
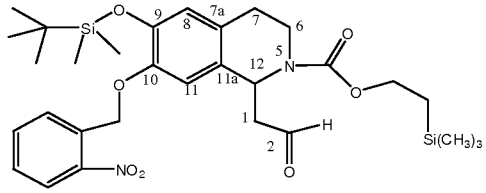
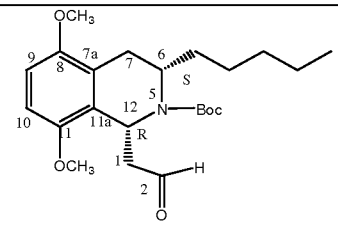
II

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^5-R^8 are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and P^1 is a protecting group.

[0022] Representative aldehyde compounds encompassed by generic formula II are illustrated in Table 2. The preparation of the aldehyde compound featured in Entry 2a of Table 2 is described in the experimental section of this disclosure. In general, the class of aldehyde compounds represented by structure II may be prepared by art recognized methods, for example using the methodology depicted in Scheme 1.

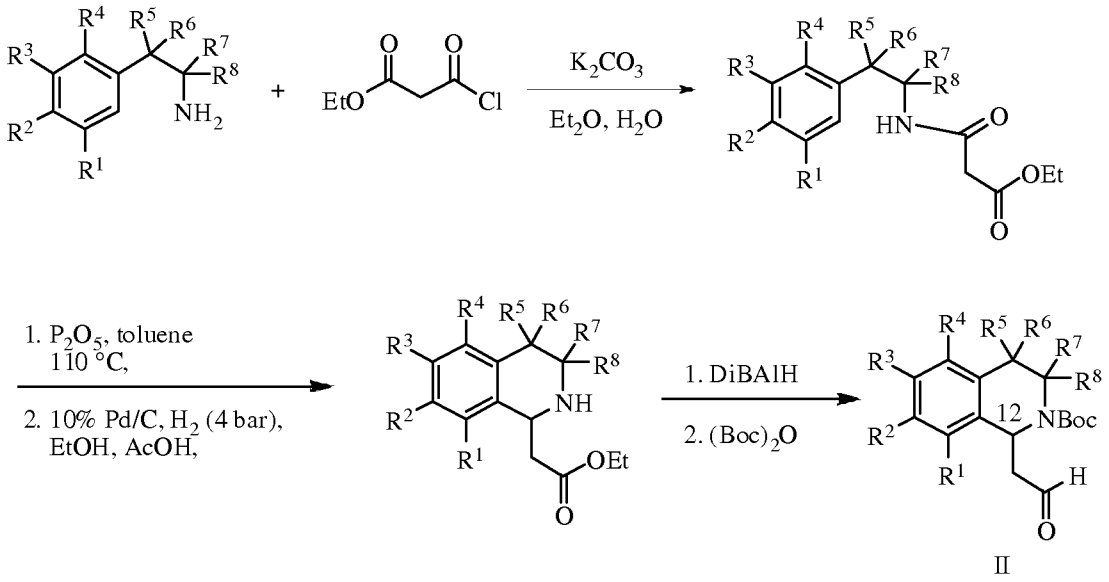
Table 2 Aldehyde Compounds Encompassed By Generic Structure II

Entry	Compound Type	Ring Position* Stereo-chemistry	Structure
2a	Single "R" enantiomer, "Boc" protecting group P^1	RP-12 "R"	
2b	Single "S" enantiomer, "Boc" protecting group P^1	RP-12 "S"	
2c	Enantiomerically enriched mixture of "R" and "S" enantiomers, "alloc" protecting group P^1	RP-12 "R/S"	
2d	Racemic mixture of "R" and "S" enantiomers; "Fmoc" protecting group P^1	RP-12 "R/S"	

2e	Racemic mixture of "R" and "S" enantiomers; "Cbz" protecting group P^1	RP-12 "R/S"	
2f	Racemic mixture of "R" and "S" enantiomers; "Teoc" protecting group P^1	RP-12 "R/S"	
2g	Single "R,S" enantiomer, "Boc" protecting group P^1	RP-12 "R", RP-6 "S"	

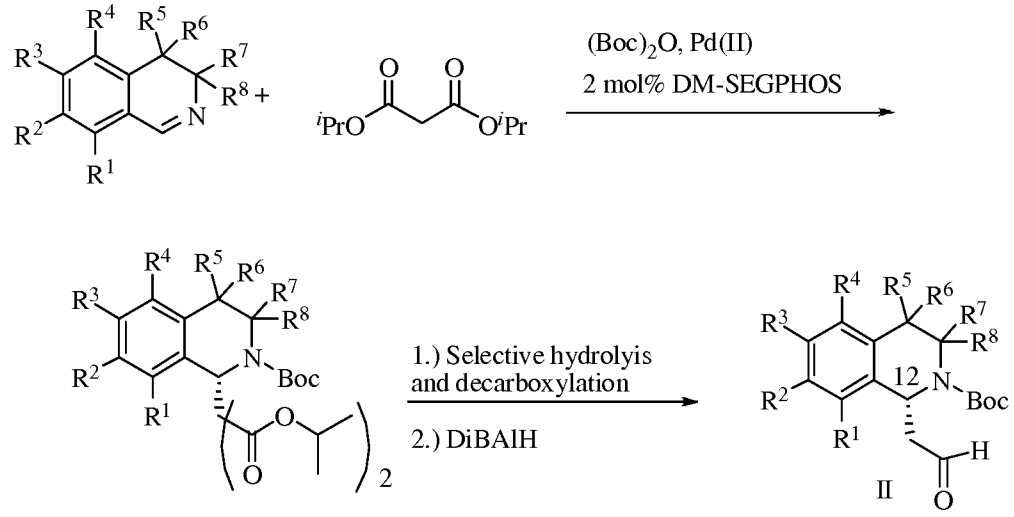
RP-12 = Ring position-12, RP-6 = Ring position-6

In Scheme 1 the groups R^1 - R^8 are defined as in generic structure II. DiBAlH represents the reductant diisobutyl aluminum hydride, and $(Boc)_2O$ represents di-*tert*-butyl dicarbonate (Boc anhydride). Thus, a phenethyl amine may be reacted with a malonate ester mono acid chloride to provide an amide which undergoes cyclization to a dihydroisoquinoline in the presence of phosphorous pentoxide (P_2O_5). Catalytic reduction of the intermediate dihydroisoquinoline affords the tetrahydroisoquinoline ester which is reduced to the corresponding aldehyde compound with diisobutylaluminium hydride. Treatment of the tetrahydroquinoline aldehyde with $(Boc)_2O$ affords aldehyde compound II wherein protecting group P^1 is a Boc group.



Scheme 1

[0023] Aldehyde compounds II may also be prepared from intermediates prepared using methodology described by Sasamoto et al. (Journal of the American Chemical Society 128, 14010-14011, 2006). Sasamoto et al. disclose the preparation



Scheme 2

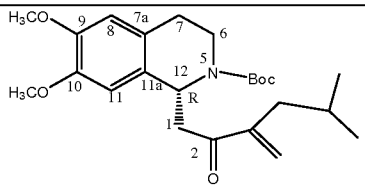
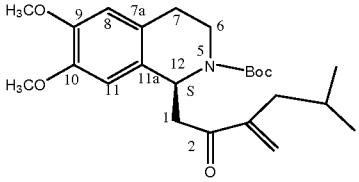
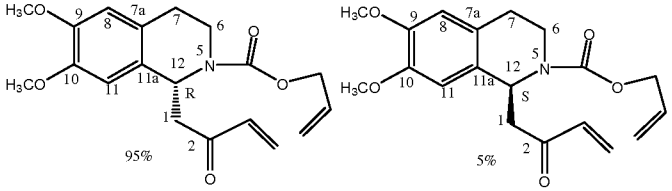
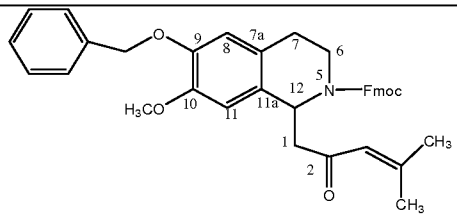
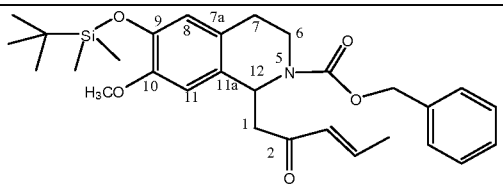
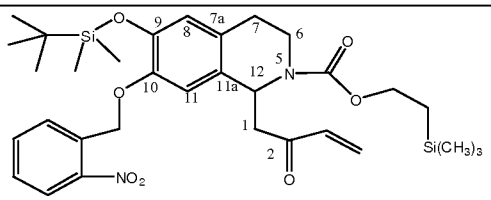
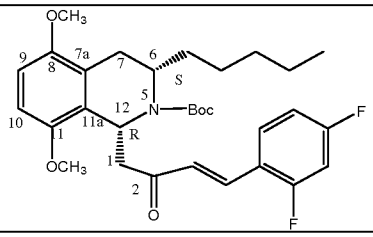
of enantiomerically enriched tetrahydroquinoline malonate compounds which may be converted to aldehyde compound II by selective hydrolysis of one of the ester moieties and decarboxylation followed by reduction of the resultant tetrahydroisoquinoline monoester to aldehyde compound II as depicted in Scheme 2.

One of ordinary skill in the art will appreciate that the 2 mole percent DM-SEGPHOS represents a chiral catalyst responsible for the enantiomeric enrichment of the product aldehyde, and further that the use DM-SEGPHOS of opposite chirality as the chiral catalyst will afford a product aldehyde II enantiomerically enriched in the "S" enantiomer (aldehyde compound II having the S configuration at ring position-12. Suitable chiral catalysts include those disclosed by Sasamoto et al. (Journal of the American Chemical Society 128, 14010-14011, 2006), for example (S)-Binap, (R)-Binap, (S)-DM-Binap, (R)-DM-Binap, (S)-DM-SEGPHOS, (R)-DM-SEGPHOS. Typically use of a catalyst consisting of a ligand possessing a single, for example "S", configuration produces stereochemically enriched malonate adducts of the opposite "R" configuration and *vice versa*. In addition to the use of a chiral catalyst to generate aldehyde compounds II enriched in a single configuration at ring position-12, there are available a wide variety of methods for the separation of racemic aldehyde II into its constituent enantiomers. For example, racemic aldehyde compound II may be separated into its constituent enantiomers by high performance liquid chromatography (hplc) on a chiral hplc column. Other methods include conversion of the racemic TBZ compound into an adduct of the TBZ compound comprising a mixture of diastereomers separable by fractional crystallization. For example a racemic TBZ compound having structure I is first reacted with (-)-tartaric acid to form an adduct (ammonium tartarate salt) of the racemic TBZ compound comprising a mixture of diastereomers separable by fractional crystallization.

[0024] Those skilled in the art will appreciate that aldehyde compound shown in Scheme 1 is a mixture of "R" and "S" configurations at ring position 12, and that the aldehyde compound depicted in Scheme 2 represents a compound having the "R" configuration at ring position-12, and that both compounds fall within the scope of the genus defined by structure II.

[0025] In one embodiment, the product of the reaction of a nucleophilic alkenyl species with aldehyde compound II is an allylic alcohol which is oxidized to provide a first intermediate having structure III. Representative first intermediate compounds encompassed by generic structure III are illustrated in Table 3.

Table 3 First Intermediate Compounds Having Structure III

Entry	Compound Type	Ring Position* Stereo-chemistry	Structure
3a	Single "R" enantiomer, "Boc" protecting group P^1	RP-12 "R"	
3b	Single "S" enantiomer, "Boc" protecting group P^1	RP-12 "S"	
3c	Enantiomerically enriched mixture of "R" and "S" enantiomers, "alloc" protecting group P^1	RP-12 "R/S"	
3d	Racemic mixture of "R" and "S" enantiomers; "Fmoc" protecting group P^1	RP-12 "R/S"	
3e	Racemic mixture of "R" and "S" enantiomers; "Cbz" protecting group P^1	RP-12 "R/S"	
3f	Racemic mixture of "R" and "S" enantiomers; "Teoc" protecting group P^1	RP-12 "R/S"	
3g	Single "R,S" enantiomer, "Boc" protecting group P^1	RP-12 "R", RP-6 "S"	

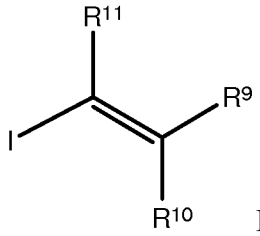
RP-12 = Ring position-12, RP-6 = Ring position-6

[0026] As will be appreciated by one of ordinary skill in the art the allylic alcohol resulting from the addition of the nucleophilic alkenyl species to aldehyde compound II may be oxidized to provide the first intermediate using one or more of a variety of oxidizing reagents. In one embodiment, the allylic alcohol is oxidized using an oxidizing reagent (oxidant) selected from the group consisting of manganese oxide, Dess-Martin Reagent, pyridinium chlorochromate, Cornforth Reagent (pyridinium dichromate), chlorosulfonium choride, Jones Reagent (chromic acid), Swern Oxidation reagent (DMSO-oxalyl chloride), Moffatt Oxidation reagent (DCC, DMSO under acidic conditions), von Doering Oxidation reagent (pyridine-SO_3), Corey-Kim Oxidation reagent (N-bromosuccinimide-dimethyl sulfide), Oppenhauer Oxidation reagent (acetone-aluminum isopropoxide), tetrapropylammonium peruthinate (TPAP), catalytic TEMPO oxidation in the presence of sodium hypochlorite solution. In one embodiment, the allylic alcohol is oxidized to the first intermediate using the Dess-Martin reagent.

[0027] There is no particular limitation on the nucleophilic alkenyl species other than that it react with aldehyde compound II to afford an allylic alcohol which upon oxidation affords first intermediate III. In one embodiment, the nucleophilic alkenyl species is a vinyl anion, for example vinyl lithium or vinyl magnesium bromide. In certain embodiments the nucleophilic alkenyl species is generated *in situ* from an alkenyl halide. For example, nucleophilic alkenyl species may generated *in situ* and induced to add to the carbonyl group of aldehyde compound II using Nozaki-Hiyama-Kishi ("NHK") reaction chemistry, nickel catalyzed formation of a nucleophilic organochromium reagent from, for example, an alkenyl halide. NHK reaction chemistry, is well suited for use within the context of the present invention and has been reviewed by Fürstner in *Chem. Rev.* **1999,** *99,* 991-1045 which review article is incorporated herein by reference in its entirety. Thus, in one embodiment the nucleophilic alkenyl species is generated using NHK reaction chemistry. Under such conditions the nucleophilic alkenyl species may be said to be prepared in the course of an NHK coupling reaction. In an alternate embodiment, the nucleophilic

alkenyl species is derived from an alkenyl halide via metal halide exchange, for example lithiation, or Grignard reagent formation.

[0028] In one embodiment, the nucleophilic alkenyl species is derived from an alkenyl iodide having structure IV

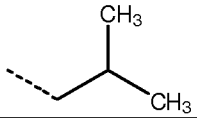
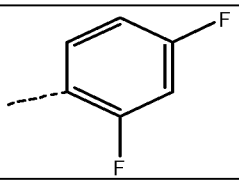


IV

wherein R^9-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical. Alkenyl iodides having structure IV are suitable for use in Nozaki-Hiyama-Kishi ("NHK") reactions.

[0029] Representative alkenyl iodides having structure IV encompassed by generic structure IV are illustrated in Table 4.

Table 4 Alkenyl Iodides Having Structure IV

Entry	R^9	R^{10}	R^{11}
4a	H	H	
4b	H	H	H
4c	CH_3	CH_3	H
4d	CH_3	H	H
4e		H	H

[0030] In various embodiments of the present invention the protecting group P^1 of the first intermediate III is removed and thereafter an amino cyclization reaction

is caused to occur (induced) thereby providing a product TBZ compound having structure I. In one embodiment, the amino cyclization reaction occurs spontaneously during the deprotection step under acidic conditions. In alternate embodiment, the amino cyclization reaction occurs spontaneously during the deprotection step under basic conditions.

[0031] In one embodiment, the protecting group P^1 is removed in a separate step following isolation and purification of first intermediate III. In alternate embodiment, the protecting group P^1 is removed as part of the oxidation step. Protecting groups P^1 are illustrated in Tables 2 and 3 and elsewhere in this disclosure. Suitable protecting groups P^1 include Boc, Fmoc, Cbz, Alloc, Teoc, benzyl, and *t*-butyl groups. As is evident from the foregoing listing, in one embodiment, the protecting group P^1 comprises a carbonyl group. In one embodiment, the protecting group P^1 is selected from the group consisting of Boc, Fmoc, Cbz, Alloc, Teoc, benzyl, and *t*-butyl groups. In one embodiment, the protecting group P^1 is the Boc group.

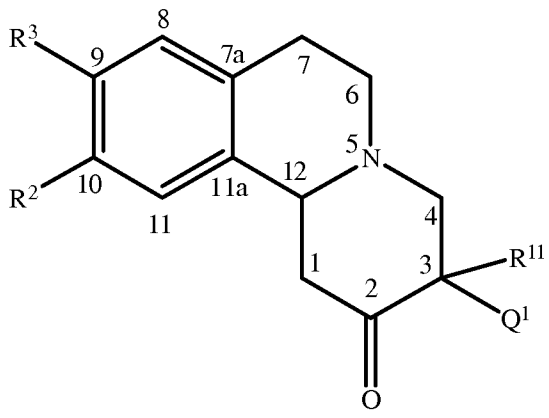
[0032] As noted, upon deprotection of first intermediate III, the deprotected first intermediate undergoes an amino cyclization reaction to provide a product TBZ compound having structure I. Depending on the structure of the first intermediate III, this amino cyclization reaction may take place at a rate at faster than the rate of deprotection (i.e. amino cyclization may take place at a rate which is faster than the rate of cleavage of the bond between the tetrahydroquinoline ring nitrogen and protecting group P^1). Under such conditions, the product of deprotection, in one embodiment structure III in which the protecting group P^1 has been replaced by hydrogen, is typically not isolable but is directly converted to TBZ compound I. In alternate embodiment, the amino cyclization reaction may take place at a rate which is slower than the rate of deprotection. Under such conditions, the product of deprotection, in one embodiment structure III in which the protecting group P^1 has been replaced by hydrogen, may be isolated, purified and subjected to the amino cyclization reaction in a separate step to afford the TBZ compound I.

[0033] As one of ordinary skill in the art will appreciate, the method of the present invention may be used to prepare compounds derived from TBZ compounds

encompassed by generic structure I. Thus, in one embodiment, the method of the present invention further comprises a step of transforming the TBZ compound I into a product which may or may not be encompassed by structure I. For example, epimerization (inversion of stereochemistry) at ring position-3 results in a further elaborated product encompassed by structure I. One of ordinary skill in the art will recognize that reactions which transform the carbonyl group of TBZ compound I will result in further elaborated products not encompassed by structure I. The method of the present invention thus contemplates additional process steps which transform the TBZ compound having structure I provided by the method of the present invention.

[0034] In one embodiment, the method of the present invention further comprises a step of transforming the carbonyl group of the product TBZ compound I. In one embodiment, the method of the present invention further comprises a step of reducing the carbonyl group of TBZ compound I to the corresponding dihydro-TBZ compound (DTBZ compound), i.e. a compound wherein the ketone moiety of the TBZ compound has been reduced to a secondary alcohol. In one embodiment, the method of the present invention provides a DTBZ compound which is a mixture of diastereomers. In another embodiment, the method of the present invention provides a DTBZ compound which is a single diastereomer.

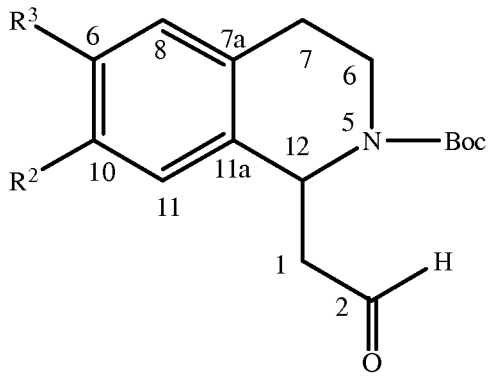
[0035] In another embodiment, the present invention provides a method of preparing a TBZ compound having structure V,



V

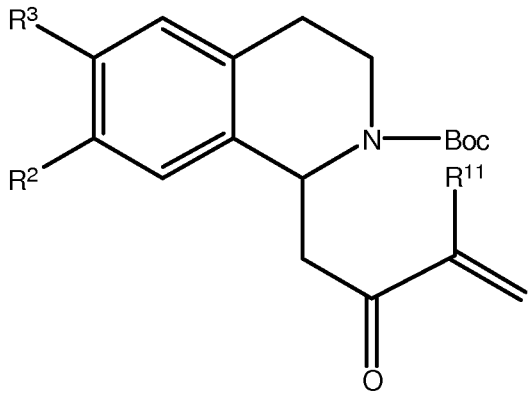
said method comprising:

(a) reacting a nucleophilic alkenyl species with aldehyde compound VI



VI

and oxidizing of the resultant allylic alcohol to provide a first intermediate having structure VII; and



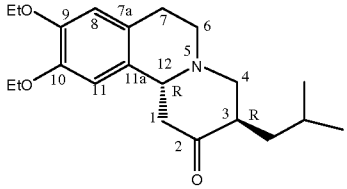
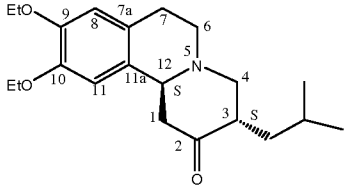
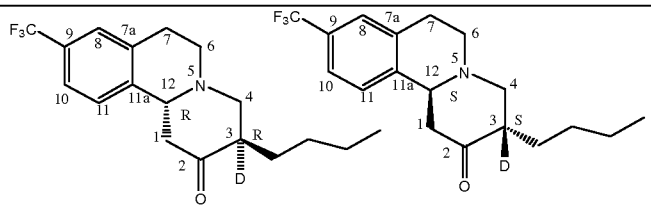
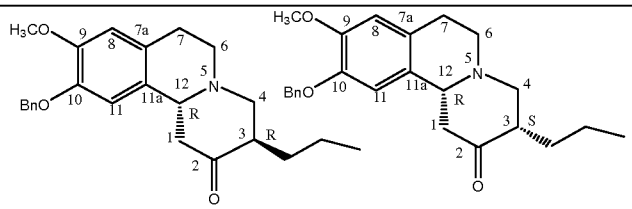
VII

(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure V,

wherein with respect to structures V, VI, and VII; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

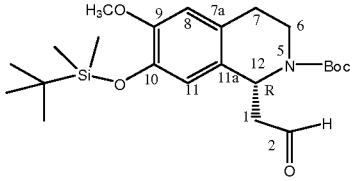
[0036] Representative TBZ compounds encompassed by generic formula V are illustrated in Table 5.

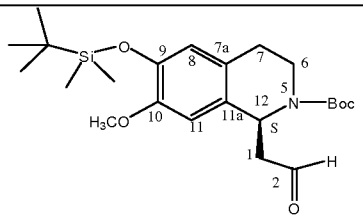
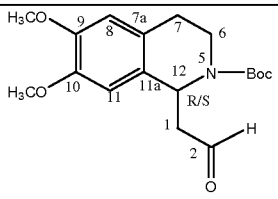
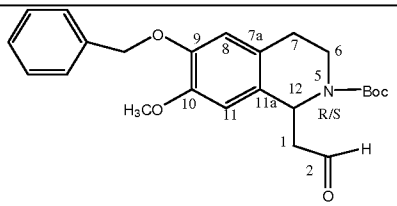
Table 5 Exemplary TBZ Compounds Encompassed By Generic Formula V

Entry	R^2	R^3	R^{11}	Q^1	Structure
5a	EtO	EtO	Iso-butyl	H	
5b	EtO	EtO	Iso-butyl	H	
5c	H	CF_3	n-butyl	D	
5d	O-benzyl	CH_3O	Propyl	H	

[0037] Representative aldehyde compounds encompassed by generic formula VI are illustrated in Table 6.

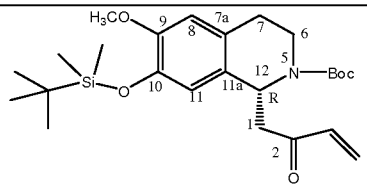
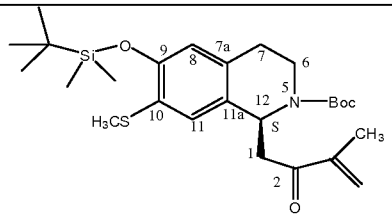
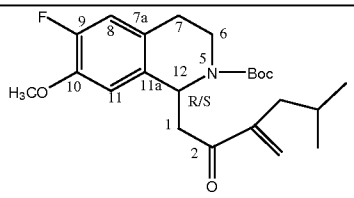
Table 6 Exemplary Aldehyde Compounds Encompassed by Generic Structure VI

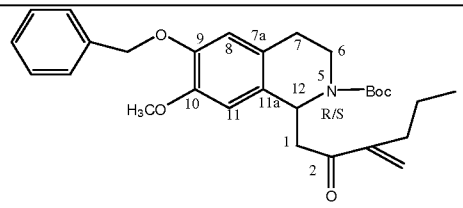
Entry	R^2	R^3	Structure
6a	t-Bu(Me)$_2$Si	CH_3O	

6b	CH_3O	t-Bu(Me)$_2$Si	
6c	CH_3O	CH_3O	
6d	CH_3O	O-benzyl	

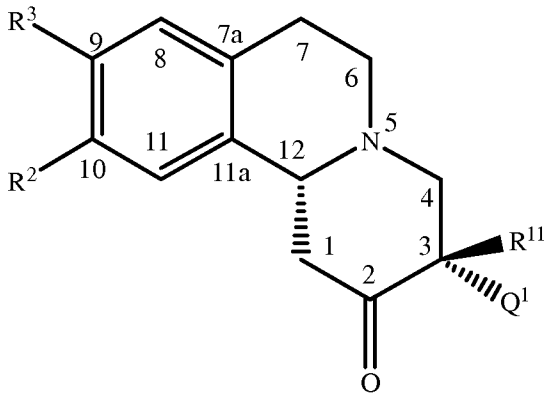
[0038] Representative first intermediate compounds encompassed by generic structure VII are illustrated in Table 7.

Table 7 Exemplary First Intermediate Compounds Encompassed by Generic Structure VII

Entry	R^2	R^3	R^{11}	Structure
7a	t-Bu(Me)$_2$Si	CH_3O	H	
7b	CH_3S	t-Bu(Me)$_2$Si	CH_3	
7c	CH_3O	F	isobutyl	

7d	CH_3O	O-benzyl	n-propyl	

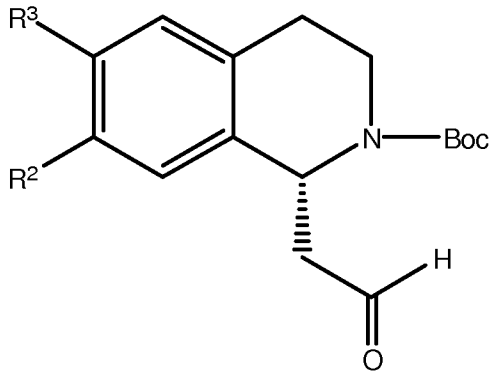
[0039] In another embodiment, the present invention provides a method of preparing an enantiomerically enriched TBZ compound comprising at least 95 mole percent enantiomer VIII,



VIII

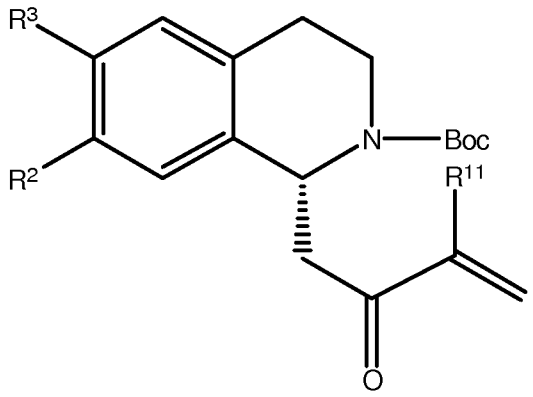
said method comprising:

(a) reacting a nucleophilic alkenyl species with an aldehyde compound comprising at least 95 mole percent enantiomer IX



IX

and oxidizing the resultant allylic alcohol to provide a first intermediate having structure X; and



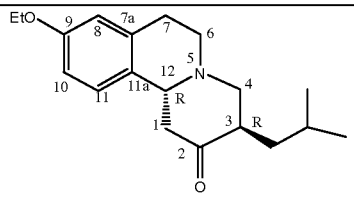
X

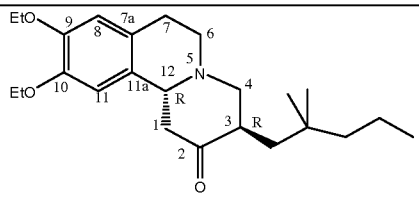
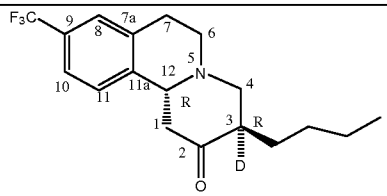
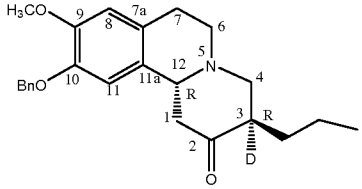
(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure VIII,

wherein with respect to structures VIII, IX, and X; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

[0040] Representative TBZ compounds encompassed by generic formula VIII are illustrated in Table 8.

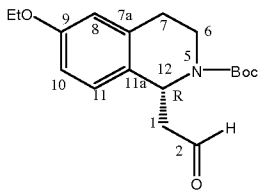
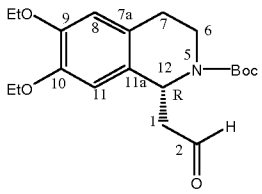
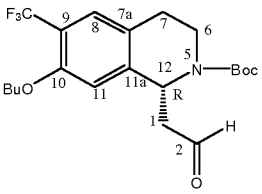
Table 8 Exemplary TBZ Compounds Encompassed By Generic Formula VIII

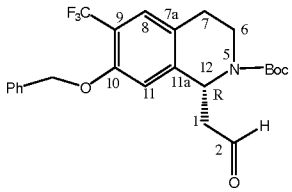
Entry	R^2	R^3	R^{11}	Q^1	Structure
8a	H	EtO	Iso-butyl	H	

8b	EtO	EtO	2,2-dimethyl pentyl	H	
8c	H	CF_3	n-butyl	D	
8d	O-benzyl	CH_3O	Propyl	D	

[0041] Representative aldehyde compounds encompassed by generic formula IX are illustrated in Table 9.

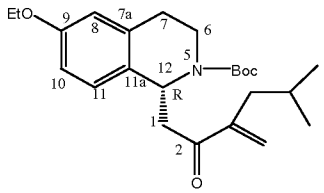
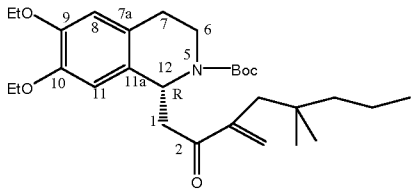
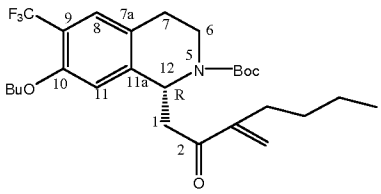
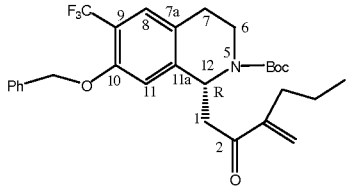
Table 9 Exemplary Aldehyde Compounds Encompassed By Generic Structure IX

Entry	R^2	R^3	Structure
9a	H	EtO	
9b	EtO	EtO	
9c	O-butyl	CF_3	

9d	O-benzyl	CH_3O	

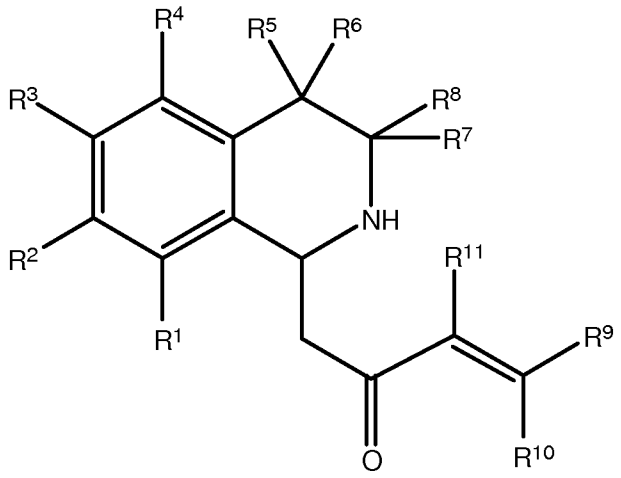
[0042] Representative first intermediate compounds encompassed by generic formula X are illustrated in Table 10.

Table 10 Exemplary First Intermediate Compounds Encompassed By Generic Structure X

Entry	R^2	R^3	R^{11}	Structure
10a	H	EtO	Iso-butyl	
10b	EtO	EtO	2,2-dimethyl-pentyl	
10c	O-butyl	CF_3	n-butyl	
10d	O-benzyl	CF3	Propyl	

[0043] As noted, conversion of first intermediate III to TBZ compound I is effected by removal of the protecting group P^1 and inducing an amino cyclization reaction. Techniques for the removal of protecting groups P^1 are well known to one

of ordinary skill in the art and include, for example, the acid catalyzed removal of a Boc protecting group P^1 as disclosed in the Examples section herein, photolysis of an o-nitrobenzyl protecting group P^1, and hydrogenolysis of a benzyl protecting group P^1. Removal of the protecting group P^1 from the first intermediate III results in the formation of a deprotected first intermediate having structure XI

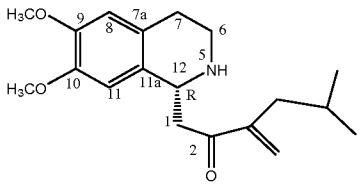


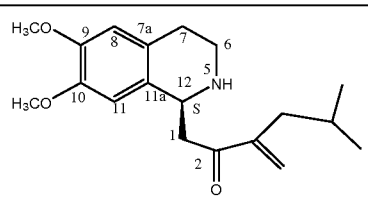
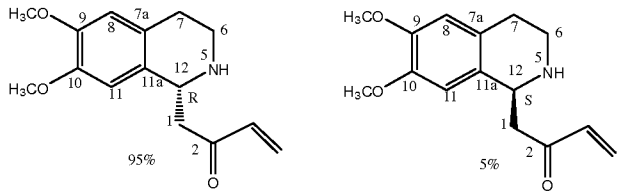
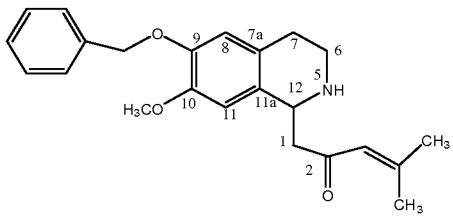
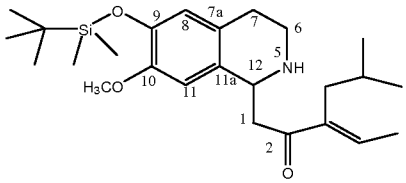
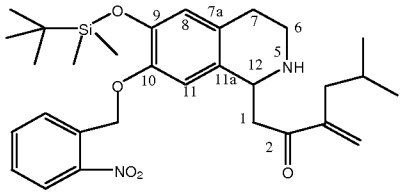
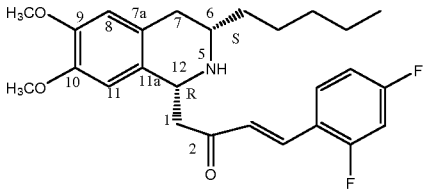
XI

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

[0044] Representative deprotected first intermediate compounds encompassed by generic formula XI are illustrated in Table 11.

Table 11 Exemplary Deprotected First Intermediate Compounds XI

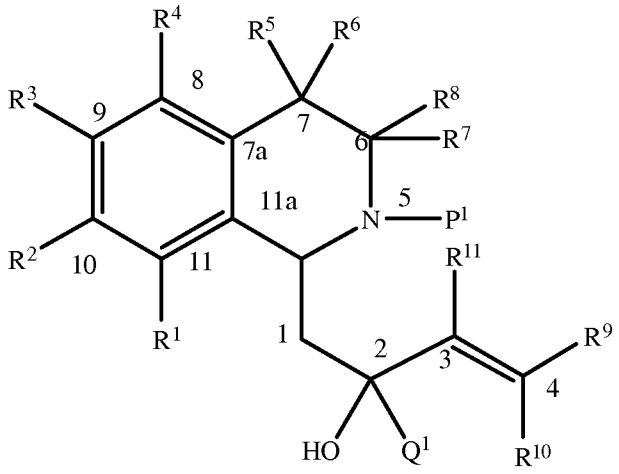
Entry	Compound Type	Ring Position* Stereo-chemistry	Structure
11a	Single "R" enantiomer	RP-12 "R"	

11b	Single "S" enantiomer	RP-12 "S"	
11c	Enantiomeric ally enriched mixture of "R" and "S" enantiomers	RP-12 "R/S"	 95% 5%
11d	Racemic mixture of "R" and "S" enantiomers	RP-12 "R/S"	
11e	Racemic mixture of "R" and "S" enantiomers	RP-12 "R/S"	
11f	Racemic mixture of "R" and "S" enantiomers	RP-12 "R/S"	
11g	Single "R,S" enantiomer	RP-12 "R", RP-6 "S"	

RP-12 = Ring position-12, RP-6 = Ring position-6

[0045] As discussed herein, the method of the present invention comprises a step in which an nucleophilic alkenyl species is reacted with aldehyde compound II which results in the formation of an allylic alcohol which is oxidized to a first intermediate having structure III. The allylic alcohol is itself a valuable intermediate

and is, in certain embodiments, isolable. In general, the allylic alcohol precursor to first intermediate III has structure XII

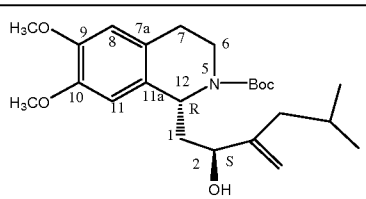


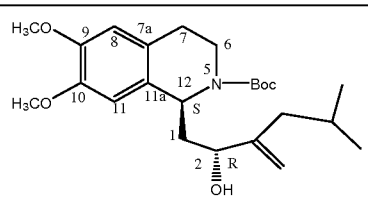
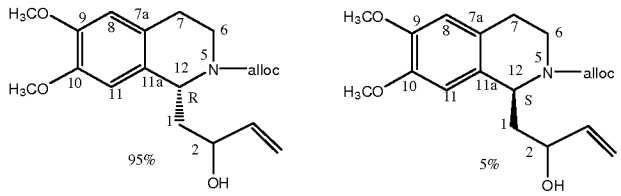
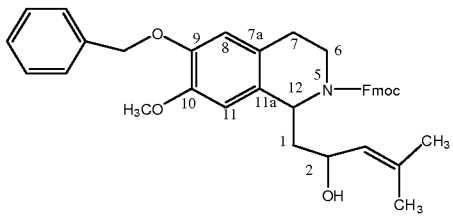
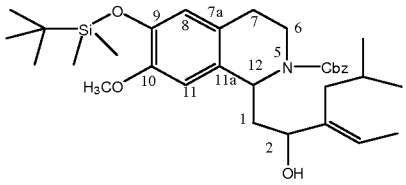
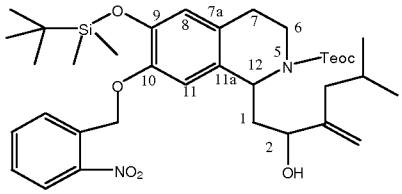
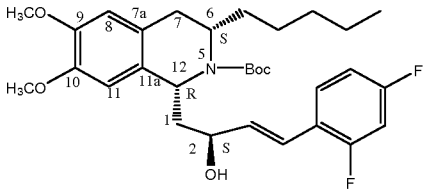
XII

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; P^1 is a protecting group, and Q^1 is hydrogen or an isotope thereof.

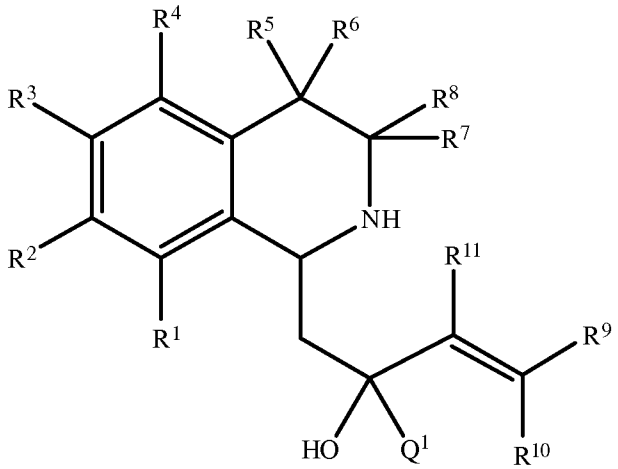
[0046] Representative allylic alcohol compounds encompassed by generic formula XII are illustrated in Table 12.

Table 12 Exemplary Allylic Alcohol Compounds XII

Entry	Compound Type	Ring Position* Stereo-chemistry	Structure
12a	Single "R,S" enantiomer	RP-12 "R", RP-2 "S"	

12b	Single "S,R" enantiomer	RP-12 "S", RP-2 "R"	
12c	Enantiomerically enriched mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
12d	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
12e	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
12f	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
12g	Single "R,S, S" enantiomer	RP-12 "R", RP-6 "S", RP-2 "S"	

[0047] In one embodiment, the present invention provides a deprotected allylic alcohol compound having structure XIII



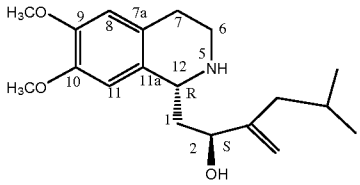
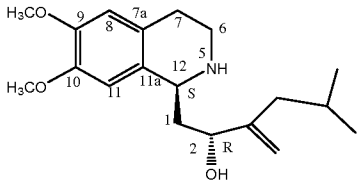
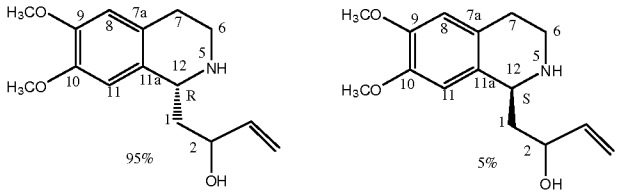
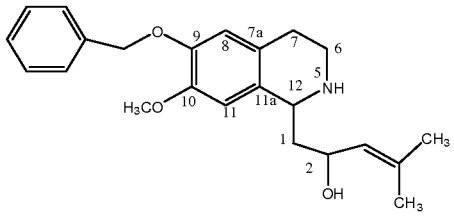
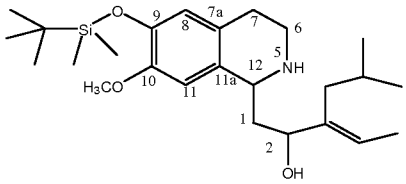
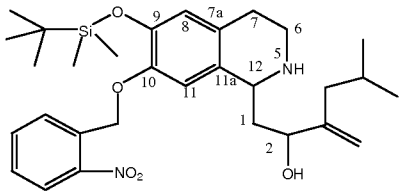
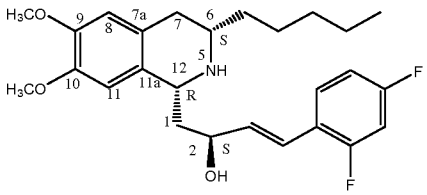
XIII

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

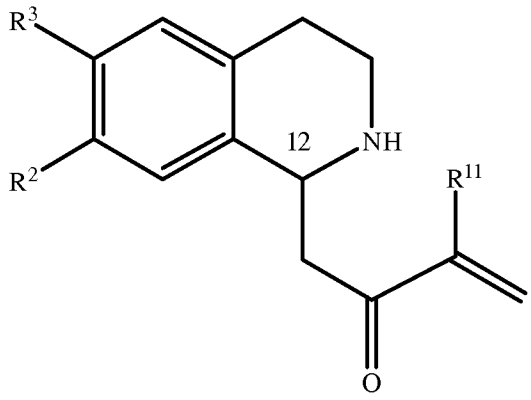
[0048] Deprotected allylic alcohol compound XIII is typically derived from allylic alcohol compound XII. One of ordinary skill in the art will recognize that compound XIII is identical to compound XII except that the protecting group P^1 of compound XII has been removed and is replaced by a hydrogen atom in compound XIII. Allylic alcohol compound XIII is thus referred to as a "deprotected allylic alcohol". Deprotection of allylic alcohol XII may be effected by a variety of methods known to those skilled in the art, including those methods used to effect deprotection of first intermediate III, as disclosed herein. In one aspect, the deprotected allylic alcohol compounds XIII provided by the present invention are useful in the preparation of TBZ compounds. Thus, oxidation of deprotected allylic alcohol XIII with the Dess-Martin reagent may provide the TBZ compound I in a process believed to involve formation of a deprotected first intermediate having structure XI followed by an amino cyclization reaction to afford TBZ compound I.

[0049] Representative deprotected allylic alcohol compounds encompassed by generic formula XIII are illustrated in Table 13.

Table 13 Exemplary Deprotected Allylic Alcohol Compounds XIII

Entry	Compound Type	Ring Position* Stereo-chemistry	Structure
13a	Single "R,S" enantiomer	RP-12 "R", RP-2 "S"	
13b	Single "S,R" enantiomer	RP-12 "S", RP-2 "R"	
13c	Enantiomerically enriched mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
13d	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
13e	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
13f	Racemic mixture of "R" and "S" enantiomers, epimeric at RP-2	RP-12 "R/S", RP-2 "R/S"	
13g	Single "R,S, S" enantiomer	RP-12 "R", RP-6 "S", RP-2 "S"	

[0050] In one embodiment, the present invention provides a deprotected first intermediate having structure XIV



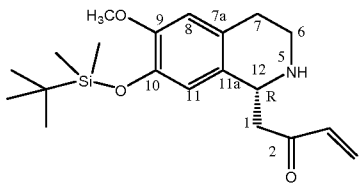
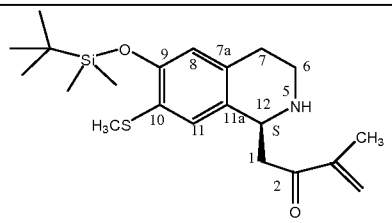
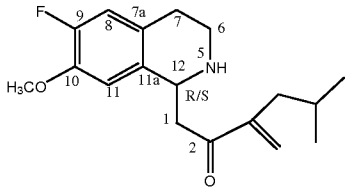
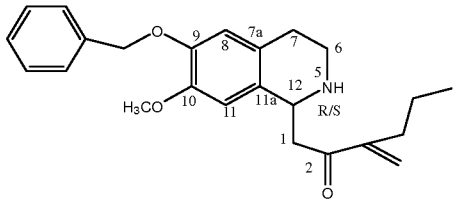
XIV

wherein R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

[0051] Deprotected first intermediate XIV may be prepared by removing the protecting group P^1 in first intermediate VII. Removal of the protecting group P^1 in first intermediate VII can be effected by methods known to one of ordinary skill in the art. In addition, the present disclosure provides detailed guidance on the removal of protecting groups. Representative deprotected first intermediate compounds encompassed by generic formula XIV are given in Table 14.

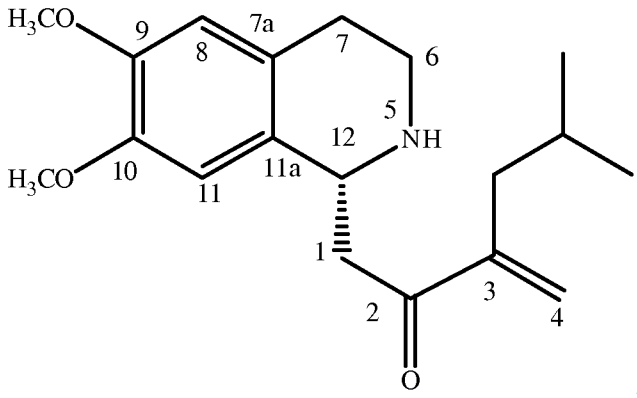
Table 14 Exemplary Deprotected First Intermediate Compounds XIV

Entry	R^2	R^3	R^{11}	Structure

14a	t-Bu(Me)$_2$Si	CH_3O	H	
14b	CH_3S	t-Bu(Me)$_2$Si	CH_3	
14c	CH_3O	F	isobutyl	
14d	CH_3O	O-benzyl	n-propyl	

[0052] In one embodiment, the present invention provides a deprotected first intermediate having structure XV. One of ordinary skill in the art will appreciate that deprotected first intermediate having structure XV may be obtained from first intermediate X wherein each of R^2 and R^3 is the C_1 aliphatic radical, methoxy, and R^{11} is the C_4 aliphatic radical, isobutyl, by removal of protecting group P^1. Removal of the protecting group P^1 in first intermediate X can be effected by methods known to one of ordinary skill in the art. In addition, the present disclosure provides detailed guidance on the removal of protecting groups. One of ordinary skill in the art will recognize that the deprotected first intermediate having structure XV represents a single enantiomer having the "R" configuration at ring position-12. In one embodiment, deprotected first intermediate XV is obtained essentially as a single enantiomer, for example a composition containing essentially a single component, that component being a single enantiomer. In another embodiment, deprotected first intermediate XV is obtained as a component of a highly enantiomerically enriched

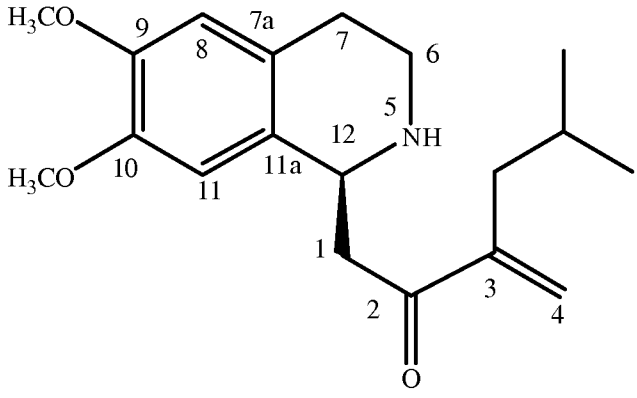
composition comprising about 95 mole percent deprotected first intermediate XV together with about 5 mole percent of its optical antipode, deprotected first intermediate XVI. In another embodiment deprotected first intermediate XV is a component of a diastereomeric mixture. Although under a wide variety of conditions, deprotected first intermediate XV is rapidly converted via amino cyclization to (+)-tetrabenazine XVII, it nonetheless represents a highly valuable and useful composition of matter.



XV

[0053] In alternate embodiment, the present invention provides a deprotected first intermediate having structure XVI. One of ordinary skill in the art will appreciate that deprotected first intermediate having structure XVI may be obtained from first intermediate VII wherein the absolute stereochemistry at ring position-12 is "S", each of R^2 and R^3 is the C_1 aliphatic radical, methoxy, and R^{11} is the C_4 aliphatic radical, isobutyl, by removal of protecting group P^1. Removal of the protecting group P^1 in first intermediate VII can be effected by methods known to one of ordinary skill in the art. In addition, the present disclosure provides detailed guidance on the removal of protecting groups. One of ordinary skill in the art will recognize that the deprotected first intermediate having structure XVI represents a single enantiomer having the "S" configuration at ring position-12. In one embodiment, deprotected first intermediate XVI is obtained essentially as a single enantiomer, e.g. a composition containing no component which is the mirror image of compound XVI. In another embodiment, deprotected first intermediate XVI is obtained as a component of a highly enantiomerically enriched composition comprising about 95 mole percent deprotected first intermediate XVI together with about 5 mole percent of its optical antipode, deprotected first intermediate XV. In another embodiment,

deprotected first intermediate XVI is a component of a diastereomeric mixture. Although under a wide variety of conditions, deprotected first intermediate XVI is rapidly converted via amino cyclization to (-)-tetrabenazine XVIII, it nonetheless represents a highly valuable and useful composition of matter.

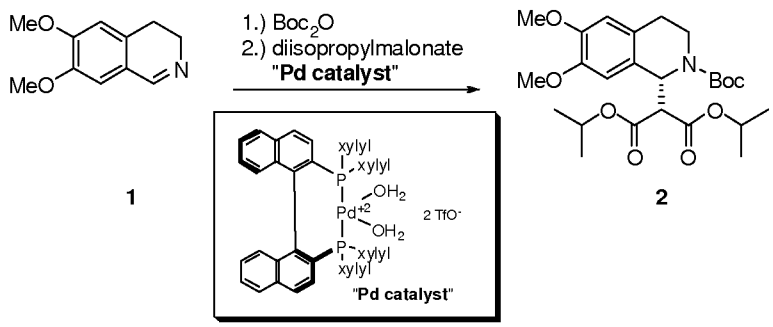


XVI

EXAMPLES

[0054] The following examples are intended only to illustrate methods and embodiments in accordance with the invention, and as such should not be construed as imposing limitations upon the claims.

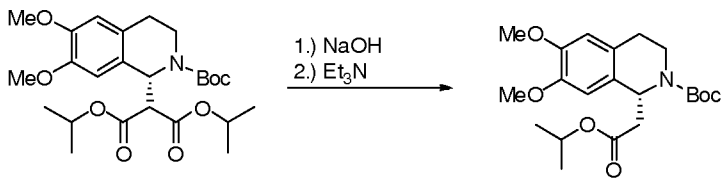
Example 1 Preparation of Protected Diester **2**



The dihydroisoquinoline **1** (1.0 eq.) and Boc anhydride (1.5 eq.) were dissolved in CH_2Cl_2 at room temperature to provide a 1.5 M solution with respect to the dihydroisoquinoline. The mixture was allowed to stir for 30 min. Following the allotted time, the reaction mixture was cooled to 0 °C and then diisopropylmalonate (1.5 eq.) followed by a pre-chilled solution of the Pd catalyst (0.008 eq.) in

dichloromethane were added successively to the reaction mixture to provide a final reaction concentration of 0.84 M with respect to the starting dihydroisoquinoline. The reaction mixture was allowed to continue stirring at ~2.5 °C for 15 h. Following this time EtOAc and brine were added to the reaction mixture. The aqueous layer was extracted with three portions of EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the crude product. The crude material was dissolved in a minimal amount of dichloromethane and purified by flash chromatography on SiO_2 (15-30% EtOAc-hexanes, elution was observed at 285 nm and 228 nm). The product **2** was a colorless solid that existed as a mixture of rotamers in solution at room temperature 94%: $[\alpha]^{26}_D$ –69.0 (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.81–1.02 (m, 6H), 1.06–1.17 (m, 6H), 1.23–1.38 (m, 9H), 2.51–2.63 (m, 1H), 2.64–2.77 (m, 1H), 3.20–3.29 (m, 0.6H), 3.32–3.41 (m, 0.4H), 3.51–3.58 (m, 1H), 3.62–3.70 (m, 6H), 3.70–3.76 (m, 0.4H), 3.91–4.01 (m, 0.6H), 4.65–4.82 (m, 1H), 4.83–4.98 (m, 1H), 5.71 (apparent d, J = 5.7 Hz, 0.6H), 5.78 (apparent d, J = 7.9 Hz, 0.4H), 6.42–6.49 (m, 1H), 6.77 (s, 0.6H), 6.81 (s, 0.4H); ^{13}C NMR ($CDCl_3$) δ 21.02, 21.09, 21.18, 21.32, 27.24, 27.95, 28.02, 37.60, 39.34, 52.11, 52.83, 55.48, 55.52, 59.28, 60.08, 68.58, 68.76, 68.82, 79.46, 80.03, 110.09, 110.73, 111.13, 126.11, 126.18, 126.37, 127.07, 146.81, 146.87, 147.93, 153.86, 154.30, 166.29, 166.78, 166.94, 167.06.

Example 2 Selective Hydrolysis and Decarboxylation of Protected Ester **3**

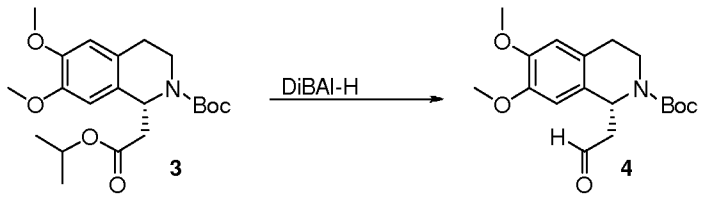


2 **3**

[0055] The starting material **2** was taken up in isopropanol to provide a 0.2 M solution of **2**. To this solution was added 1M aqueous NaOH solution bringing the final concentration of the reaction mixture to 0.1M with respect to the malonate **2**. The reaction mixture was heated to and maintained 70 °C for 22 min. (timing was started when the temperature of the reaction mixture temp exceeded 65 °C). Following the allotted time the reaction mixture was quickly cooled to 0 °C. The reaction mixture carefully acidified with 2M aqueous HCl and extracted with three

portions of dichloromethane. The combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The isolated material was taken up in THF to provide a 0.1 M solution (based on the original quantity of **2** used in the reaction mixture) and triethylamine (1.0 eq) was added to the reaction mixture at room temperature. The reaction mixture was heated to its reflux temperature and maintained at this temperature for 90 min. The reaction mixture was concentrated under reduced pressure, dissolved in a minimal quantity of CH_2Cl_2 and was immediately purified by column chromatography on SiO_2 (15-40% EtOAc–hexanes; 40%, the eluant was monitored at 284 nm). The product **3** existed as a mixture of rotamers at room temperature and was a colorless foam 79%: $[\alpha]^{26}_D$ –82 (*c* 0.24, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.19–1.25 (m, 6H), 1.43–1.49 (m, 9H), 2.58–2.69 (m, 2H), 2.70–2.77 (m, 1H), 2.78–2.92 (m, 1H), 3.13–3.43 (m, 1H), 3.81–3.85 (m, 6H), 3.86–4.01 (m, 1H), 4.91–5.05 (m, 1H), 5.38–5.61 (m, 1H), 6.56–6.61 (m, 1H), 6.64–6.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.75, 21.90, 27.93, 28.08, 28.44, 37.53, 38.75, 42.22, 42.81, 51.11, 51.87, 55.92, 56.02, 68.08, 79.74, 80.21, 109.60, 109.99, 111.44, 111.54, 126.28, 126.48, 128.54, 128.76, 147.51, 147.97, 154.39, 154.51, 170.36, 170.59; LRMS-(ESI+) calcd for ($C_{21}H_{31}NO_6$ + H) ($[M+H]^+$ 394.22, found 394.16.

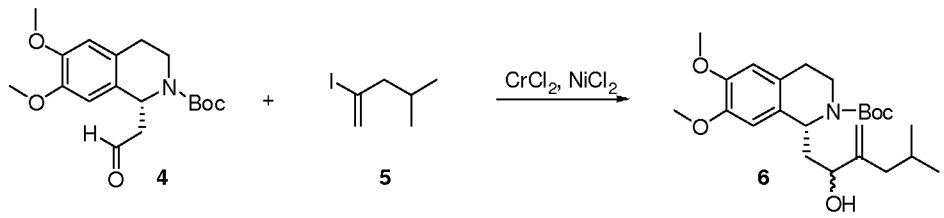
Example 3 Preparation of Aldehyde Compound **4**



[0056] To a 0.12 M solution of the starting monoester (**3**, 1.0 eq.) in toluene at -78 °C was added a 1.5 M solution of DiBAl-H in hexanes (1.5 eq.) dropwise via a syringe pump. Following the addition the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched by the addition of EtOAc and was then acidified with saturated aqueous citric acid solution. The reaction mixture was allowed to warm to room temperature and continue stirring for 30 min. The phases were separated, and the aqueous layer extracted with three portions of EtOAc. The combined organic extracts were washed with two portions of 2 M aqueous HCl

solution, brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was subjected purification on SiO_2 (15-35% EtOAc-hexanes; Elution was observed at 285 nm and 228 nm). The isolated product aldehyde compound 4 was a colorless foam. The product existed as a 1:1 mixture of rotamers at room temperature 76%: $[\alpha]^{26}_D$ –116 (*c* 0.26,CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.58 (apparent t, *J* = 3.8 Hz, 0.5H), 2.61 (apparent t, *J* = 3.5 Hz, 0.5H), 2.68–2.88 (m, 3H), 3.02–3.27 (m, 1H), 3.78 (apparent s, 6H), 3.87–3.99 (m, 0.5H), 4.08–4.23 (m, 0.5H), 5.37–5.68 (m, 1H), 6.55 (s, 1H), 6.58 (s, 1H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.90, 28.02, 28.27, 37.23, 38.65, 49.29, 49.93, 51.12, 55.83, 55.96, 80.13, 80.64, 109.42, 109.52, 111.52, 126.34, 126.51, 127.78, 127.82, 147.72, 147.97, 153.85, 154.62, 200.08, 200.33.

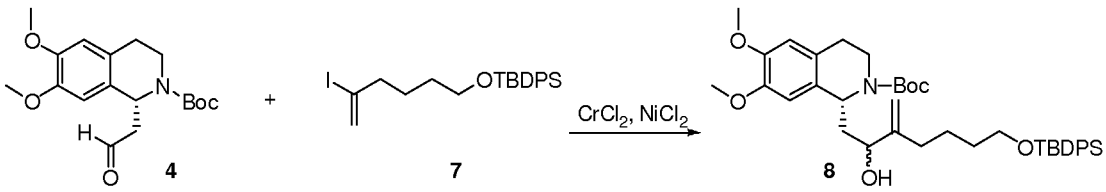
Example 4 Reaction Of Aldehyde Compound **4** With Nucleophilic Alkenyl Species Derived From Alkenyl Iodide **5** With To Provide Allylic Alcohol **6**



[0057] To a neat mixture of the alkenyl iodide **5** (1.0 eq) and the aldehyde compound **4** (1.0 eq.) at room temperature was added 2.65 eq. of chromium chloride doped with 0.5% $NiCl_2$ (w/w). The mixture was vortexed for about 2 min. to provide a homogeneous, green/grey paste and then stirred under nitrogen for an additional 10 min. after which time anhydrous DMF was added to bring the final reaction concentration to 0.36 M. The reaction mixture was deep green in color and was permitted to continue stirring at room temperature for 14h. Following the allotted time, the reaction mixture was diluted with 1:1 EtOAc-hexanes and an aqueous 0.5 M EDTA solution (pH 9) was added and the entire mixture was allowed to stir for 1.5 h. The aqueous layer was extracted with three portions of EtOAc, dried ($MgSO_4$), filtered, and the filtrate was concentrated under reduced pressure to provide a green oil. The crude material was subjected to column chromatography on SiO_2 (35%

EtOAc-hexanes; elution was observed at 285 nm and 228 nm). The product allylic alcohol **6** was a pale yellow oil isolated in 53% yield as a mixture of diastereomers which was taken on to the next step without additional characterization or analysis.

Example 5 Reaction Of Aldehyde Compound **4** With Nucleophilic Alkenyl Species Derived From Alkenyl Iodide 7 With To Provide Allylic Alcohol **8**

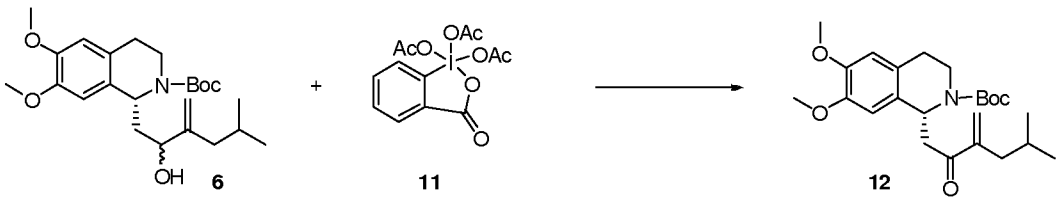


[0058] To a neat mixture of the alkenyl iodide **7** (1.0 eq) and the aldehyde compound **4** (1.25 eq.) at room temperature was added 2.5 eq. of chromium chloride doped with 0.5% $NiCl_2$ (w/w). The mixture was vortexed for about 2 min. to provide a homogeneous, green/grey paste and then stirred under nitrogen for an additional 10 min. after which time anhydrous DMF was added to bring the final reaction concentration to 0.32 M. The reaction mixture was deep green in color and was permitted to continue stirring at room temperature for 14 h. Following the allotted time, the reaction mixture was diluted with 1:1 EtOAc-hexanes and an aqueous 0.5 M EDTA solution (pH 9) was added and the entire mixture was allowed to stir for 1.5 h. The aqueous layer was extracted with three portions of EtOAc, dried ($MgSO_4$), filtered, and the filtrate was concentrated under reduced pressure to provide a green oil. The crude material was subjected to column chromatography on SiO_2 (20% EtOAc-hexanes to 35% EtOAc-hexanes; elution was observed at 285 nm and 228 nm). The product allylic alcohol **8** was a pale yellow oil isolated in 54% yield as a mixture of diastereomers which was taken on to the next step without additional characterization or analysis.

Example 6 Reaction Of Aldehyde Compound **4** With Nucleophilic Alkenyl Species Derived From Alkenyl Iodide **9** With To Provide Allylic Alcohol **10**

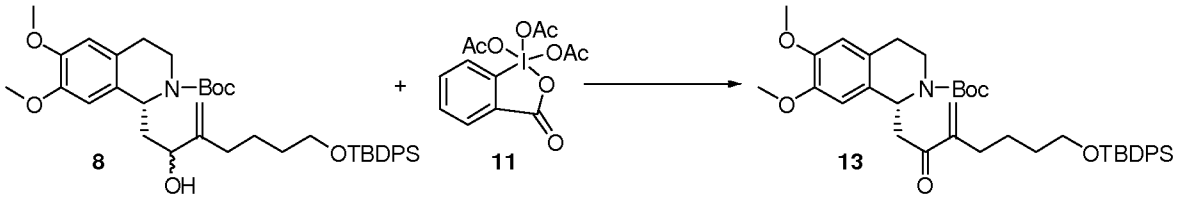
[0059] To a neat mixture of the alkenyl iodide **9** (1.5 eq) and the aldehyde **4** (1.0 eq.) at room temperature was added 2.5 eq. of chromium chloride doped with 0.5% $NiCl_2$ (w/w). The mixture was vortexed for about 2 min. to provide a homogeneous, green/grey paste and then stirred under nitrogen for an additional 10 min. after which time anhydrous DMF was added to bring the final reaction concentration to 0.36 M. The reaction mixture was deep green in color and was permitted to continue stirring at room temperature for 14h. Following the allotted time, the reaction mixture was diluted with 1:1 EtOAc-hexanes and an aqueous 0.5 M EDTA solution (pH 9) was added and the entire mixture was allowed to stir for 1.5 h. The aqueous layer was extracted with three portions of EtOAc, dried ($MgSO_4$), filtered, and the filtrate was concentrated under reduced pressure to provide a green oil. The crude material was subjected to column chromatography on SiO_2 (40% EtOAc-hexanes; elution was observed at 285 nm and 228 nm) to afford the product allylic alcohol **10** as a pale yellow oil that existed as a 1:1 mixture of diastereomers (47%): ^1H NMR (CD_2Cl_2) δ 0.94–1.00 (m, 6H), 1.13–1.16 (m, 9H), 1.54–1.57 (m, 9H), 1.67–1.74 (m, 2H), 1.79–1.86 (m, 0.5H), 1.87–1.94 (m, 1H), 1.96–2.05 (m, 0.5H), 2.09–2.24 (m, 2H), 2.66–2.77 (m, 1H), 2.85–2.99 (m, 1H), 3.16–3.22 (m, 0.5H), 3.36–3.44 (m, 0.5H), 3.80–3.92 (m, 8H), 4.01–4.08 (m, 0.5H), 4.12–4.17 (m, 0.5H), 4.30–4.38 (m, 0.5H), 4.66–4.77 (m, 0.5H), 4.86–4.96 (m, 1H), 5.23–5.30 (m, 0.5H), 5.34–5.39 (m, 1H), 5.39–5.43 (m, 0.5H), 6.68–6.72 (m, 1H), 6.73–6.77 (m, 0.5H), 6.77–6.81 (m, 0.5H), 7.43–7.52 (m, 6H), 7.75–7.82 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.12, 26.83, 27.33, 27.45, 27.54, 27.59, 28.29, 28.41, 33.46, 33.48, 38.30, 39.45, 43.64, 43.82, 44.93, 45.05, 45.48, 45.95, 50.95, 52.25, 55.89, 55.99, 56.01, 61.14, 69.99, 73.06, 80.03, 80.49, 110.21, 110.56, 111.87, 112.00, 112.02, 112.39, 125.92, 126.32, 126.35, 127.77, 129.57, 129.69, 130.17, 134.15, 135.68, 147.85, 147.88, 147.99, 148.11, 148.71, 149.59, 149.61, 155.79, 156.39.

Example 7 Oxidation Of Allylic Alcohol **6** To Provide First Intermediate **12**



[0060] To a 0.1 M solution of allylic alcohol **6** (1.0 eq) in dichloromethane at 0 °C was added 1.1 eq. of the Dess-Martin reagent **11**. The reaction mixture was allowed to stir, slowly warming to room temperature over 2.5 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and diluted with ethyl acetate. The organic and aqueous layers were partitioned and separated and the aqueous layer extracted with three additional portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (10-30% EtOAc-hexanes, elution was observed at 285 nm and 228 nm). The product first intermediate **12** was a colorless, foul-smelling oil that existed at 26 °C as a 60:40 mixture of rotamers in solution (66%): ^{1}H NMR ($CDCl_3$) δ 0.82 (apparent t, J = 7.6 Hz, 6H), 1.42 (s, 9H), 1.70 (apparent sept, J = 6.62 Hz, 1H), 2.08–2.15 (m, 1H), 2.15–2.24 (m, 1H), 2.62–2.70 (m, 1H), 2.75–2.91 (m, 1H), 2.93–3.07 (m, 1H), 3.07–3.29 (m, 1.6H), 3.30–3.43 (m, 0.4H), 3.79 (s, 3H), 3.81 (s, 3.4H), 4.04–4.16 (m, 0.6H), 5.52–5.62 (m, 1H), 5.69 (s, 1H), 5.90 (s, 0.6H), 6.04 (s, 0.4H), 6.57 (s, 1H), 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.45, 27.04, 27.25, 28.11, 28.41, 38.01, 39.33, 40.39, 45.20, 45.90, 51.62, 55.92, 55.98, 79.75, 80.23, 109.85, 110.25, 110.28, 111.41, 125.65, 125.72, 126.26, 129.25, 147.57, 147.87, 148.16, 148.29, 148.35, 154.40, 154.51, 199.53; HRMS-(ESI+) calcd for ($C_{24}H_{35}NO_5$) + H) ($[M+H]^+$ 418.2594, found 418.2590.

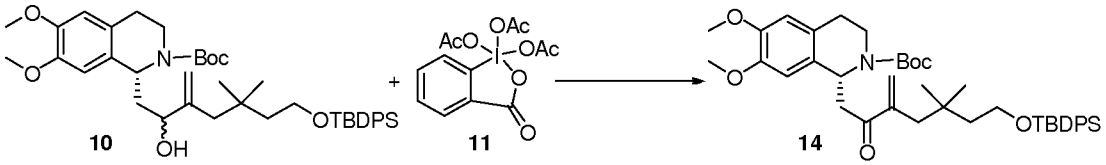
Example 8 Oxidation Of Allylic Alcohol **8** To Provide First Intermediate **13**



[0061] To a 0.1 M solution of **8** (1.0 eq) in dichloromethane at 0 °C was added 1.1 eq. of the Dess-Martin reagent **11**. The reaction mixture was allowed to stir,

slowly warming to room temperature over 2.5 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and diluted with dichloromethane. The organic and aqueous layers were partitioned and separated and the aqueous layer extracted with three additional portions of dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (10-50% EtOAc-hexanes, elution was observed at 285 nm and 228 nm). The product first intermediate **13** was a colorless, oil that existed at 26 °C as a 50:50 mixture of rotamers in solution (82%): ^{1}H NMR (CD_2Cl_2) δ 1.19 (s, 9H), 1.55 (s, 9H), 1.63–1.83 (m, 5H), 2.34–2.57 (m, 2H), 2.70–2.85 (m, 1H), 2.85–3.05 (m, 1H), 3.05–3.41 (m, 2.5H), 3.41–3.56 (m, 0.5H), 3.81–3.83 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.97–4.08 (m, 0.5H), 4.20–4.35 (m, 0.5H), 5.68 (apparent t, J = 6.6Hz, 1H), 5.87 (s, 1H), 6.09 (s, 0.5H), 6.19 (s, 0.5H), 6.71 (s, 1H), 6.76 (s, 1H), 7.45–7.60 (m, 6H), 7.77–7.95 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.19, 24.66, 24.75, 26.83, 28.06, 28.28, 30.57, 32.43, 37.75, 39.20, 45.16, 45.66, 63.84, 79.46, 79.77, 110.21, 110.49, 111.81, 124.37, 124.67, 126.45, 127.76, 129.19, 129.68, 134.13, 135.61, 147.79, 148.19, 149.20, 154.09, 154.41, 199.15, 199.27; HRMS-(ESI+) calcd for ($C_{40}H_{53}NO_6Si$ + H) ($[M+H]^+$ 672.3720, found 672.3715.

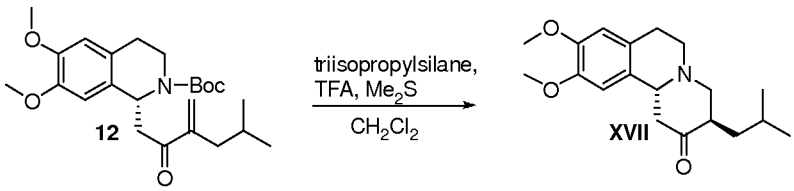
Example 9 Oxidation Of Allylic Alcohol **10** To Provide First Intermediate **14**



[0062] To a 0.1 M solution of allylic alcohol **10** (1.0 eq) in dichloromethane at 0 °C was added 1.1 eq. of the Dess-Martin reagent **11**. The reaction mixture was allowed to stir, slowly warming to room temperature over 5 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and diluted with dichloromethane. The organic and aqueous layers were partitioned and separated and the aqueous layer extracted with three additional portions of dichloromethane. The combined organic extracts were washed with brine, dried

($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (10-50% EtOAc-hexanes, elution was observed at 285 nm and 228 nm). The product first intermediate **14** was a yellow foam that existed at 26 °C as a 50:50 mixture of rotamers in solution (93%): ^{1}H NMR (CD_2Cl_2) δ 0.85 (s, 6H), 1.14 (s, 9H), 1.48–1.57 (m, 9H), 1.65 (t, J = 7.3Hz, 2H), 2.30–2.50 (m, 2H), 2.70–2.80 (m, 1H), 2.85–2.98 (m, 1H), 3.07–3.17 (m, 1H), 3.22–3.37 (m, 1.5H), 3.38–3.50 (m, 0.5H), 3.81 (s, 3H), 3.85 (s, 3H), 3.85–3.92 (m, 2H), 3.94–4.02 (m, 0.5H), 4.18–4.25 (m, 0.5H), 5.65–5.72 (m, 1H), 5.74 (s, 1H), 6.07 (s, 0.5H), 6.14 (s, 0.5H), 6.69 (s, 1H), 6.76 (s, 1H), 7.45–7.54 (m, 6H), 7.77–7.82 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.09, 26.80, 26.92, 26.97, 28.13, 28.22, 28.28, 33.22, 37.94, 39.39, 41.79, 41.87, 44.49, 45.33, 46.02, 51.16, 51.44, 55.79, 55.83, 61.05, 79.47, 79.76, 110.18, 110.51, 111.74, 126.40, 127.26, 127.36, 127.76, 129.48, 129.69, 134.09, 135.66, 146.93, 147.06, 147.78, 148.10, 154.16, 154.47, 199.36; HRMS-(ESI+) calcd for ($C_{42}H_{57}NO_6Si$ – $C_5H_9O_2$(Boc) + H) ([M–Boc+H]$^+$ 600.3509, found 600.3496.

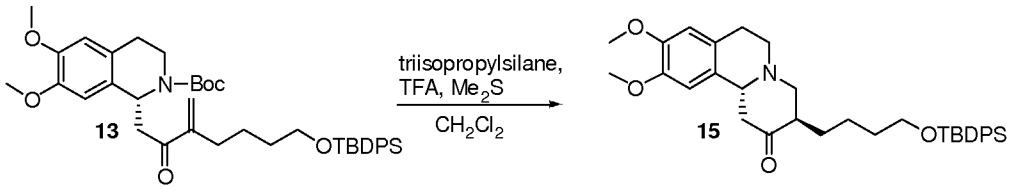
Example 10 Removal The Boc Protecting Group From First Intermediate **12** And Amino Cyclization Provide (+)-Tetrabenazine **XVII**



[0063] First intermediate **12** (1.0 eq) was dissolved in 10% Me_2S-dichloromethane to provide an 82 mM solution. The solution was cooled to 0 °C and triisopropylsilane (1.1 eq.) followed by TFA (precooled to 0 °C) was added to the reaction mixture to provide a final concentration of 41 mM. The reaction mixture was permitted to stir at 0 °C for 1 h. Following the allotted time the reaction mixture was quenched at 0 °C by the addition of saturated aqueous potassium carbonate solution and concentrated under reduced pressure to remove the majority of the dimethylsulfide. The mixture was extracted with five portions of dichloromethane,

and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide the crude product as a yellow solid. The crude product was recrystallized from 3.5% dimethoxyethane in hexanes. The resulting colorless crystals were washed with hexanes to provide pure (+)-tetrabenazine (**XVII**) 46%: mp 126.0 °C (3.5% DME-hexanes) (a crystal polymorph was observed at 116 °C); $[\alpha]^{26}_{D}$ +37.2 (*c* 0.41, CH_2Cl_2); ^1H NMR (CD_2Cl_2) δ 0.89 (apparent t, *J* = 7.2 Hz, 6H), 0.98 (ddd, *J* = 12, 6.0, 4.0 Hz, 1H), 1.59–1.68 (m, 1H), 1.74 (ddd, *J* = 12, 5.9, 5.7 Hz, 1H), 2.32 (apparent t, *J* = 11.7 Hz, 1H), 2.46 (apparent t, *J* = 12.3 Hz, 1H), 2.55 (ddd, *J* = 12, 10.0, 3.8 Hz, 1H), 2.65–2.73 (m, 2H), 2.83 (dd, *J* = 5.5, 2.8Hz, 1H), 2.97–3.07 (m, 1H), 3.07–3.14 (m, 1H), 3.25 (dd, *J* =9.7, 6.3 Hz, 1H), 3.47 (apparent d, *J* = 12Hz, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 6.55 (s, 1H), 6.60 (s, 1H) ^{13}C NMR (CD_2Cl_2) δ 21.98, 23.02, 25.51, 29.46, 35.16, 47.47, 47.63, 50.47, 55.87, 56.01, 61.47, 62.46, 108.46, 111.72, 126.37, 128.96, 147.65, 147.98, 209.72; HRMS-(ESI+) calcd for ($C_{19}H_{27}NO_3$ + H) ($[M+H]^+$ 318.2069, found 318.2082.

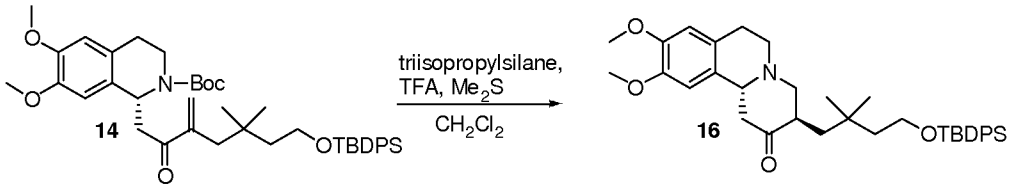
Example 11 Removal The Boc Protecting Group From First Intermediate **13** And Amino Cyclization Provide (+)-TBZ Compound **15**



[0064] The first intermediate starting material **13** (1.0 eq) was dissolved in 10% Me_2S-dichloromethane to provide an 26 mM solution. The solution was cooled to 0 °C and triisopropylsilane (1.1 eq.) followed by TFA (precooled to 0 °C) was added to the reaction mixture to provide a final concentration of 13 mM. The reaction mixture was permitted to stir at 0 °C for 1 h. Following the allotted time the reaction mixture was quenched at 0 °C by the addition of saturated aqueous potassium carbonate solution and concentrated under reduced pressure to remove the majority of the dimethylsulfide. The mixture was extracted with five portions of dichloromethane, and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide an orange oil.

The isolated material was immediately subjected to purification by flash chromatography on SiO_2 (20-30% EtOAc-hexanes, elution was observed at 285 nm and 228 nm). The semipure product (existed as a mixture of diasteremers heavily favoring the desired product) was subjected to crystallization from 3.5% dimethoxyethane in hexanes over several days. The resulting colorless crystals were washed with hexanes to provide (+)-TBZ compound **15** as a single diastereomer 42%: $[\alpha]^{26}_D$ +40.1 (*c* 0.63, CH_2Cl_2); ^1H NMR (CD_2Cl_2) δ 1.14 (s, 9H), 1.18–1.30 (m, 1H), 1.45–1.56 (m, 2H), 1.60–1.75 (m, 2H), 1.86–1.98 (m, 1H), 2.41 (apparent t, *J* = 11.4 Hz, 1H), 2.47 (apparent t, *J* = 12.6 Hz, 1H), 2.59–2.82 (m, 3H), 2.93 (dd, *J* = 13.1, 2.8Hz, 1H), 3.06–3.20 (m, 2H), 3.34 (dd, *J* = 9.6, 6.1 Hz, 1H), 3.55 (apparent d, *J* = 11.6 Hz, 1H), 3.78 (apparent t, *J* = 6.3 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.64 (s, 1H), 6.69 (s, 1H), 7.40–7.53 (m, 6H), 7.70–7.81 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.14, 23.43, 25.98, 26.74, 29.47, 32.77, 47.55, 49.42, 50.44, 55.74, 55.86, 61.06, 62.36, 63.81, 108.31, 111.68, 126.31, 127.68, 128.91, 129.60, 134.15, 135.59, 147.59, 147.90, 209.36; HRMS-(ESI+) calcd for ($C_{35}H_{45}NO_4Si$ + H) ($[M+H]^+$ 572.3196, found 572.3187.

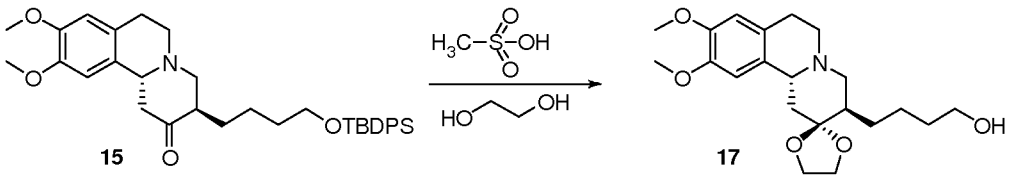
Example 12 Removal The Boc Protecting Group From First Intermediate **14** And Amino Cyclization Provide (+)-TBZ Compound **16**



[0065] The starting material **14** (1.0 eq) was dissolved in 10% Me_2S-dichloromethane to provide a 176 mM solution of the starting material. The solution was cooled to 0 °C and triisopropylsilane (1.1 eq.) followed by TFA (precooled to 0 °C) was added to the reaction mixture to provide a final concentration of 88 mM. The reaction mixture was permitted to stir at 0 °C for 1 h. Following the allotted time the reaction mixture was quenched at 0 °C by the addition of saturated aqueous potassium carbonate solution and concentrated under reduced pressure to remove the majority of the dimethylsulfide. The mixture was extracted with five portions of dichloromethane, and the combined organic extracts were washed with brine, dried

($MgSO_4$), filtered and concentrated under reduced pressure to provide a yellow foam. The crude product was purified by flash chromatography on SiO_2 (0.2% triethylamine-10% EtOAc-89.8% hexanes to 0.2% triethylamine-50% EtOAc-49.8% hexanes, elution was observed at 285 nm and 228 nm). The product (+)-TBZ compound **16** was a colorless foam consisting of only the desired diastereomer 73%: ^{1}H NMR (CD_2Cl_2) δ 0.79 (dd, *J* = 13.8, 3.8 Hz, 1H), 0.92 (s, 6H), 1.14 (s, 9H), 1.59–1.72 (m, 2H), 2.27 (dd, *J* = 13.2, 5.1 Hz, 1H), 2.52–2.65 (m, 2H), 2.68–2.82 (m, 2H), 2.94 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.06–3.18 (m, 2H), 3.25 (dd, *J* = 9.8, 6.3 Hz), 3.55 (dd, *J* = 11.6, 1.8 Hz, 1H), 3.83–3.88 (m, 8H), 6.65 (s, 1H), 6.69 (s, 1H), 7.44–7.53 (m, 6H), 7.74–7.82 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.09, 26.79, 27.10, 29.48, 32.31, 36.90, 44.38, 46.02, 47.45, 50.15, 55.77, 55.91, 61.09, 62.53, 63.50, 108.38, 111.75, 126.30, 127.74, 128.93, 129.67, 134.13, 135.65, 147.66, 147.98, 208.73; HRMS-(ESI+) calcd for ($C_{37}H_{49}NO_4Si$ + H) ([M+H]$^+$ 600.3509, found 600.3499.

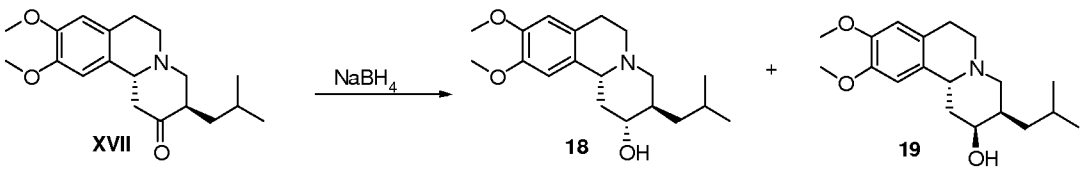
Example 13 Ketalization Of TBZ Compound **15** To Provide Ketal **17**



[0066] To an 87 mM solution of the TBZ compound **15** (1.0 eq) in ethylene glycol was added methane sulfonic acid (1.76 eq). The reaction mixture was heated to and maintained at 85 °C for 20 h in a sealed vessel. Following the allotted time, the reaction mixture was quenched be the addition of 1 mL of saturated aqueous potassium carbonate solution and EtOAc was added. The reaction mixture was stirred for an additional hour at room temperature after which time the aqueous and organic layers were partitioned and separated. The aqueous layer was extracted with three portions of CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Purification of the crude material was undertaken by flash chromatography on SiO_2 (1% triethylamine-DCM to 1% triethyamine-9% methanol-90% DCM; elution was observed at 284nm and 240 nm). Pools believed to contain the desired product were collected to provide ketal **17** as a colorless oil 73%: ^{1}H NMR (CD_2Cl_2) δ 1.03–1.15 (m, 1H), 1.20–1.35

(m, 2H), 1.37–1.61 (m, 4H), 1.87–1.99 (m, 1H), 2.08–2.17 (br s, 1H), 2.20–2.29 (m, 2H), 2.42–2.51 (m, 1H), 2.55–2.64 (m, 1H), 2.92–3.03 (m, 3H), 3.27 (apparent d, J = 11 Hz, 1H), 3.57 (apparent t, J = 6.3 Hz, 2H), 3.758 (s, 3H), 3.764 (s, 3H), 3.92–4.00 (m, 2H), 4.00–4.09 (m, 2H), 6.56 (s, 1H), 6.57 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.74, 25.30, 29.31, 33.25, 41.00, 43.90, 55.74, 56.07, 58.68, 59.82, 62.64, 63.68, 65.17, 63.35, 108.50, 109.65, 111.78, 126.82, 129.81, 147.31, 147.67; LRMS-(ESI+) calcd for ($C_{21}H_{31}NO_5$ + H) ([M+H]$^+$ 378.23, found 378.25.

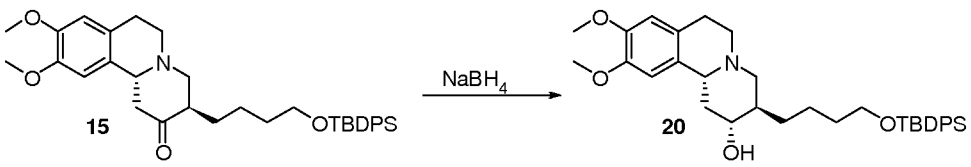
Example 14 Reduction of (+)-tetrabenazine **XVII** To a Diasteromeric Mixture of Dihydrotetrabenazine Compounds **18** and **19**



[0067] To a 0.11 M solution of (+)-TBZ (**XVII**) in ethanol at 0 °C was added $NaBH_4$ (2.85 eq). The reaction mixture was allowed to stir for 60 min. at room temperature. The solvent was carefully removed under reduced pressure, and the residue was taken up in dichloromethane and washed with three portions of saturated aqueous K_2CO_3. The aqueous washings were back extracted with two portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a colorless oil that crystallized on standing under high vacuum. Purification of the crude product was achieved by chromatography on SiO_2 (2.5-5% MeOH-CH_2Cl_2, elution was observed at 285 nm) UV active fractions were reanalyzed by TLC. Two products, **18** and **19**, were isolated from this procedure. The major product **18** was a colorless solid 74%: $[\alpha]^{26}_D$ +48 (*c* 0.30, CH_2Cl_2) ^{1}H NMR (CD_2Cl_2) δ 0.93 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.04 (ddd, J = 14.6, 8.7, 4.3 Hz, 1H), 1.42 (dd, J = 20.2, 11.4 Hz, 1H), 1.59 (ddd, J = 13.7, 9.6, 3.3 Hz, 1H), 1.64–1.78 (m, 2H), 1.96 (apparent t, J = 11.4 Hz, 1H), 2.27 (br s, 1H), 2.40–2.48 (m, 1H), 2.54 (ddd, J = 12.3, 3.7, 2.3 Hz, 1H), 2.60–2.67 (m, 1H), 2.95–3.09 (m, 3H), 3.11 (apparent d, J = 11.1 Hz, 1H), 3.35 (ddd, J = 10.4, 10.4, 4.5

Hz, 1H), 3.80–3.81 (m, 6H), 6.60 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 21.61, 24.02, 25.33, 29.30, 39.68, 40.81, 41.58, 51.83, 55.74, 55.91, 60.02, 60.92, 74.32, 108.42, 111.73, 126.68, 129.76, 147.35, 147.61; HRMS-(ESI+) calcd for ($C_{19}H_{29}NO_3$ + H) ([M+H]$^+$ 320.2226, found 320.2242. The minor product **19** was a yellow oil 4%: ^{1}H NMR (CD_2Cl_2) δ 0.94 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.13–1.20 (m, 1H), 1.24–1.34 (m, 2H), 1.60–1.77 (m, 2H), 1.89–2.00 (m, 1H) 2.36–2.44 (m, 2H), 2.53 (ddd, *J* = 10.5, 10.5, 3.8 Hz, 1H), 2.58–2.70 (m, 2H), 2.91–2.98 (m, 1H), 2.98–3.09 (m, 1H), 3.48 (apparent d, *J* = 11.6 Hz, 1H), 3.80–3.82 (apparent s, 6H), 4.07 (apparent d, *J* = 3.1Hz, 1H), 6.60 (s, 1H), 6.68 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 22.74, 22.81, 24.87, 29.30, 37.83, 38.87, 39.42, 52.44, 55.76, 55.96, 56.32, 56.43, 67.88, 108.45, 111.78, 127.18, 130.38, 147.30, 147.54.

Example 15 Reduction of TBZ compound **15** DTBZ Compound **20**



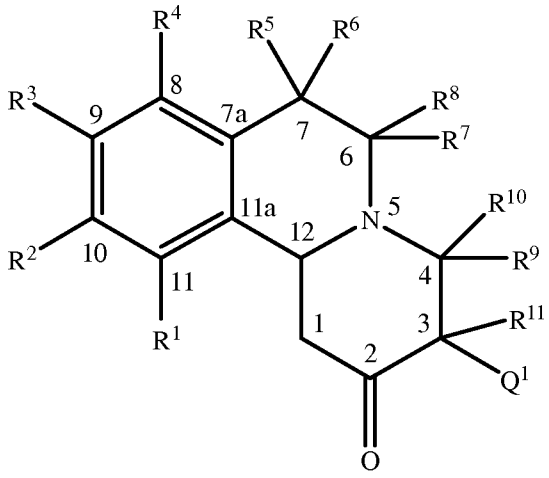
[0068] To a 0.1 M solution of TBZ compound **15** in ethanol at 0 °C was added $NaBH_4$ (2.85 eq). The reaction mixture was allowed to stir for 60 min. at room temperature. The excess solvent was carefully removed under reduced pressure, and the residue was taken up in dichloromethane and washed with three portions of saturated aqueous K_2CO_3. The aqueous washings were back extracted with two portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow foam. Purification of the crude product was achieved by chromatography on SiO_2 (2.5-5% MeOH-CH_2Cl_2 , elution was observed at 285 nm). The product DTBZ compound **20** was a colorless foam 78%: ^{1}H NMR (CD_2Cl_2) δ 1.09–1.22 (m, 11H), 1.44 (dd, *J* = 20.1, 11.6 Hz, 2H), 1.55–1.72 (m, 4H), 1.78–1.88 (m, 1H), 2.02 (apparent t, *J* = 11.4 Hz, 1H), 2.46 (ddd, *J* = 4.6, 11.3, 10.3 Hz, 1H), 2.57 (ddd, *J* = 13.1, 3.8, 2.5 Hz, 1H), 2.65 (dd, J = 14.3, 4.0 Hz, 1H), 2.94–3.10 (m, 3H), 3.14 (apparent d, *J* = 11.1 Hz, 1H), 3.40 (ddd, *J* = 9.5, 9.5, 4.6 Hz, 1H), 3.76 (apparent t, *J* = 6.3 Hz, 2H), 3.83 (apparent s, 6H), 6.63 (s, 1H), 6.73 (s, 1H), 7.42–7.49 (m, 6H), 7.71–7.76 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.17, 23.21, 26.75, 29.38, 29.79, 33.03, 40.89, 43.88, 51.86,

55.76, 55.94, 59.78, 60.95, 63.93, 73.92, 108.48, 111.76, 126.75, 127.69, 129.61, 129.81, 134.23, 135.62, 147.38, 147.63; HRMS-(ESI+) calcd for ($C_{35}H_{47}NO_4Si$ + H) ($[M+H]^+$ 574.3353, found 574.3333.

[0069] The foregoing examples are merely illustrative, serving to illustrate only some of the features of the invention. The appended claims are intended to claim the invention as broadly as it has been conceived and the examples herein presented are illustrative of selected embodiments from a manifold of all possible embodiments. Accordingly, it is the Applicants' intention that the appended claims are not to be limited by the choice of examples utilized to illustrate features of the present invention. As used in the claims, the word "comprises" and its grammatical variants logically also subtend and include phrases of varying and differing extent such as for example, but not limited thereto, "consisting essentially of" and "consisting of." Where necessary, ranges have been supplied, those ranges are inclusive of all sub-ranges there between. It is to be expected that variations in these ranges will suggest themselves to a practitioner having ordinary skill in the art and where not already dedicated to the public, those variations should where possible be construed to be covered by the appended claims. It is also anticipated that advances in science and technology will make equivalents and substitutions possible that are not now contemplated by reason of the imprecision of language and these variations should also be construed where possible to be covered by the appended claims.

CLAIMS:

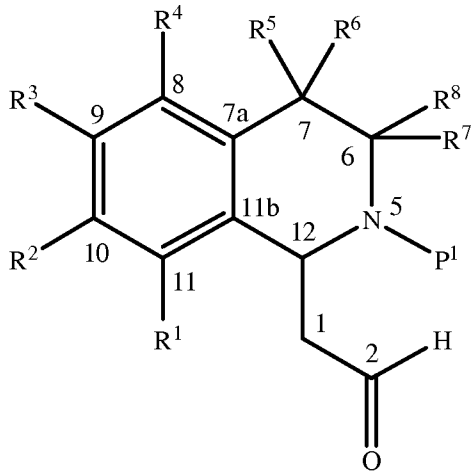
1. A method of preparing a TBZ compound having structure I,



I

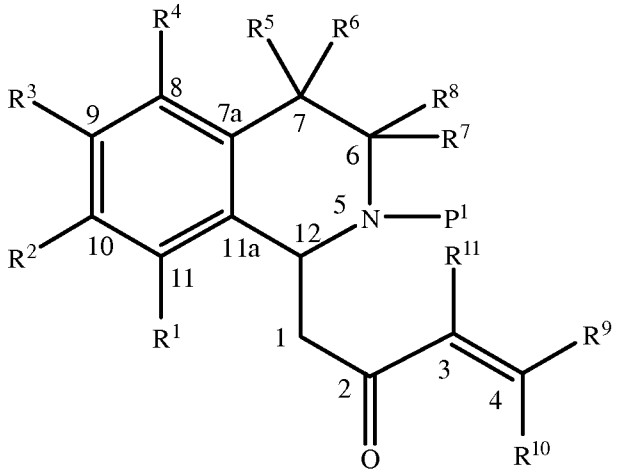
said method comprising:

(a) reacting a nucleophilic alkenyl species with aldehyde compound II



II

and oxidizing the resultant allylic alcohol to provide a first intermediate having structure III; and



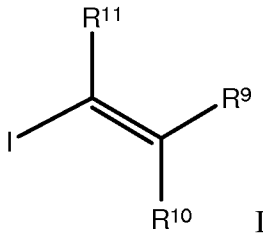
III

(b) removing protecting group P^1 and inducing an amino cyclization reaction to provide a product TBZ compound having structure I,

wherein with respect to structures I, II, and III; R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; P^1 is a protecting group, and Q^1 is hydrogen or an isotope thereof.

2. The method according to claim 1, wherein nucleophilic alkenyl species is an alkenyl anion.

3. The method according to claim 1, wherein said nucleophilic alkenyl species is derived from alkenyl iodide IV



IV

wherein R^9-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

4. The method according to claim 1, wherein said nucleophilic alkenyl species is prepared by a metal halogen exchange reaction.

5. The method according to claim 1, wherein said nucleophilic alkenyl species is prepared in the course of an "NHK" coupling reaction.

6. The method according to claim 1, wherein said oxidation is effected with an oxidant selected from the group consisting of manganese oxide, Dess-Martin Reagent, pyridinium chlorochromate, Cornforth Reagent, chlorosulfonium choride, and Jones Reagent, Swern Oxidation reagent, Moffatt Oxidation reagent, von Doering Oxidation reagent, Corey-Kim Oxidation reagent, Oppenhauer Oxidation reagent, tetrapropylammonium peruthinate, and the catalytic TEMPO oxidation in the presence of sodium hypochlorite solution.

7. The method according to claim 1, wherein said protecting group P^1 comprises a carbonyl group.

8. The method according to claim 1, wherein the protecting group P^1 is selected from the group consisting of Boc, Fmoc, Cbz, Alloc, Teoc, benzyl, and *t*-butyl.

9. The method according to claim 1, wherein the protecting group P^1 is a Boc group.

10. The method according to claim 1, wherein the amino cyclization reaction occurs at a rate faster than the rate of deprotection.

11. The method according to claim 1, wherein the amino cyclization reaction occurs at a rate slower than the rate of deprotection.

12. The method according to claim 1, wherein the product TBZ compound having structure I is enantiomerically enriched.

13. The method according to claim 12, wherein the product TBZ compound having structure I is comprised of at least 95 mole % of an enantiomer having the R configuration at ring position-12.

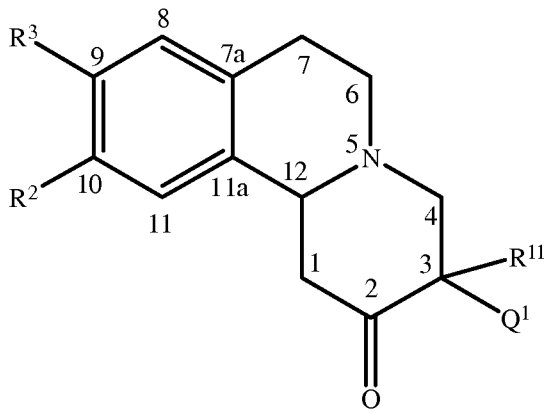
14. The method according to claim 12, wherein the product TBZ compound having structure I is comprised of at least 95 mole % of an enantiomer having the R configuration at ring position-3.

15. The method according to claim 1, wherein the aldehyde compound II is comprised of at least 95 mole % of an enantiomer having the R configuration at ring position-12.

16. The method according to claim 1, wherein the product TBZ compound having structure I is a mixture of diastereomers.

17. The method according to claim 1, further comprising the step of reducing the product TBZ compound having structure I to a corresponding DTBZ compound.

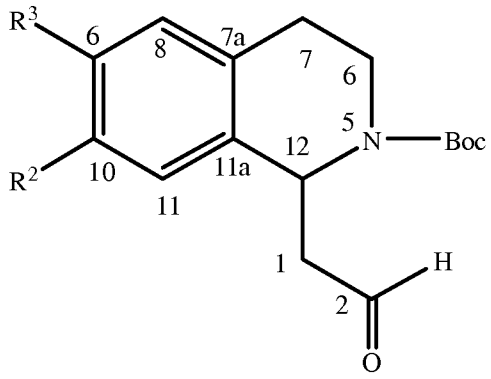
18. A method of preparing a TBZ compound having structure V,



V

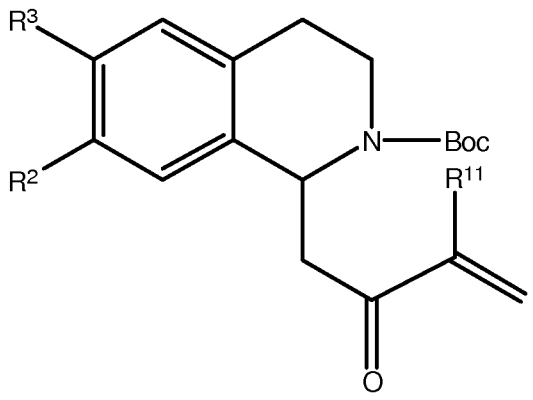
said method comprising:

(a) reacting a nucleophilic alkenyl species with aldehyde compound VI



VI

and oxidizing of the resultant allylic alcohol to provide a first intermediate having structure VII; and



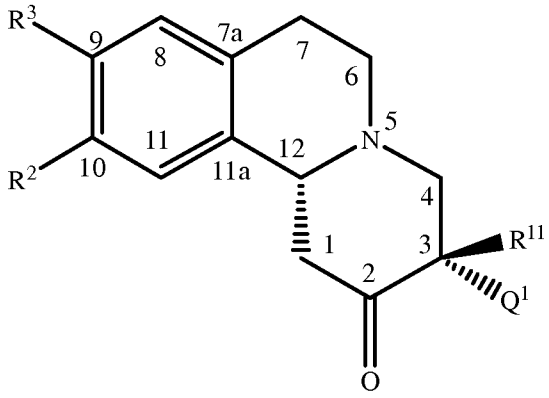
VII

(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure V,

wherein with respect to structures V, VI, and VII; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

19. The method according to claim 18, further comprising the step of reducing the product TBZ compound having structure V to a corresponding DTBZ compound.

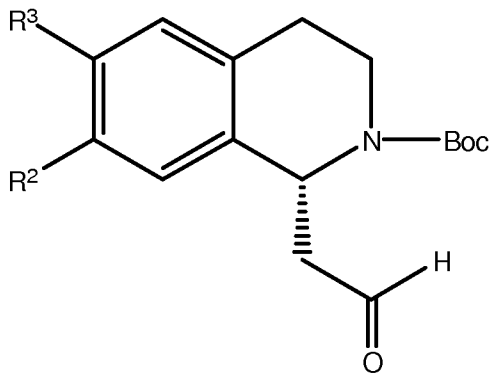
20. A method of preparing an enantiomerically enriched TBZ compound comprising at least 95 mole percent enantiomer VIII,



VIII

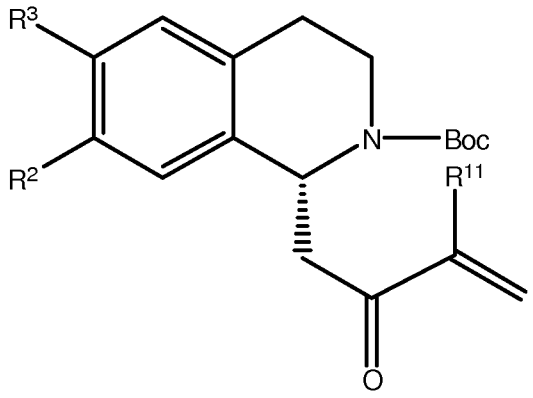
said method comprising:

(a) reacting a nucleophilic alkenyl species with an aldehyde compound comprising at least 95 mole percent enantiomer IX



IX

and oxidizing the resultant allylic alcohol to provide a first intermediate having structure X; and



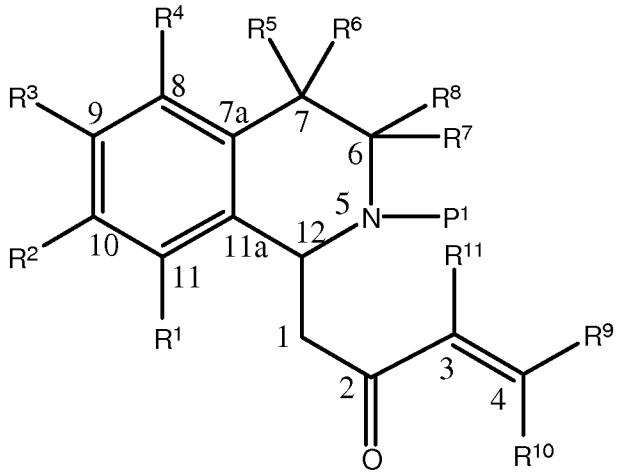
X

(b) removing the Boc protecting group and inducing an amino cyclization reaction to provide a product TBZ compound having structure VIII,

wherein with respect to structures VIII, IX, and X; R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

21. The method according to claim 20, wherein R^2 and R^3 are methoxy groups, R^{11} is an isobutyl group, and Q^1 is hydrogen.

22. A tetrahydroisoquinoline compound having structure III



III

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^1-R^4 is not hydrogen; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and P^1 is a protecting group.

23. The tetrahydroisoquinoline compound according to claim 22, wherein said protecting group P^1 comprises a carbonyl group.

24. The tetrahydroisoquinoline compound according to claim 22, wherein the protecting group P^1 is selected from the group consisting of Boc, Fmoc, Cbz, Alloc, benzyl, and *t*-butyl.

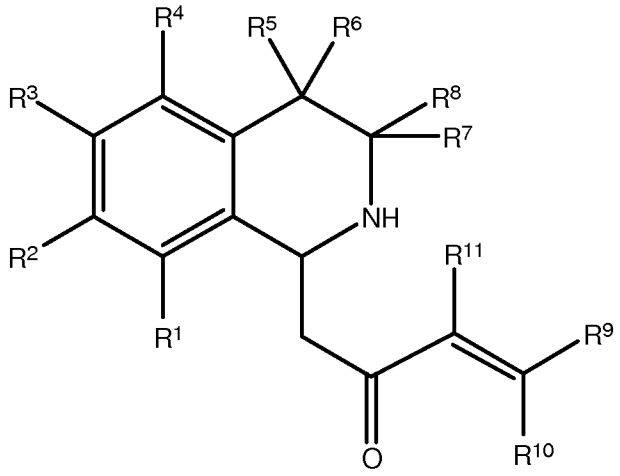
25. The tetrahydroisoquinoline compound according to claim 22, wherein the protecting group P^1 is a Boc group.

26. The tetrahydroisoquinoline compound according to claim 22, which is enantiomerically enriched.

27. The tetrahydroisoquinoline compound according to claim 26, at least 95 mole % of which is comprsied of an enantiomer having the R configuration at ring position-12.

28. The tetrahydroisoquinoline compound according to claim 26, at least 95 mole % of which is comprsied of an enantiomer having the S configuration at ring position-12.

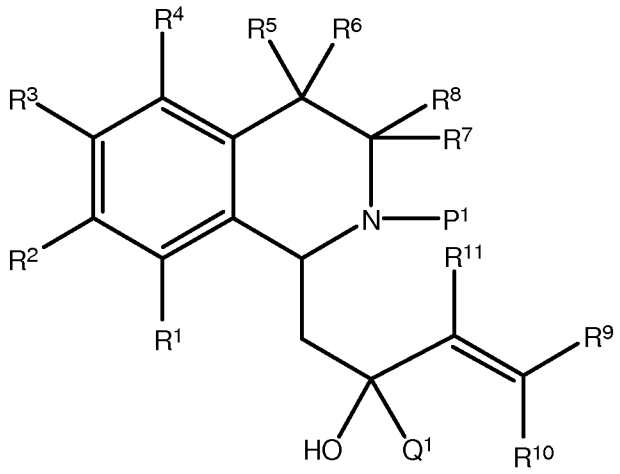
29. A tetrahydroisoquinoline compound having structure XI



XI

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^1-R^4 is not hydrogen; and R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

30. A tetrahydroisoquinoline compound having structure XII



XII

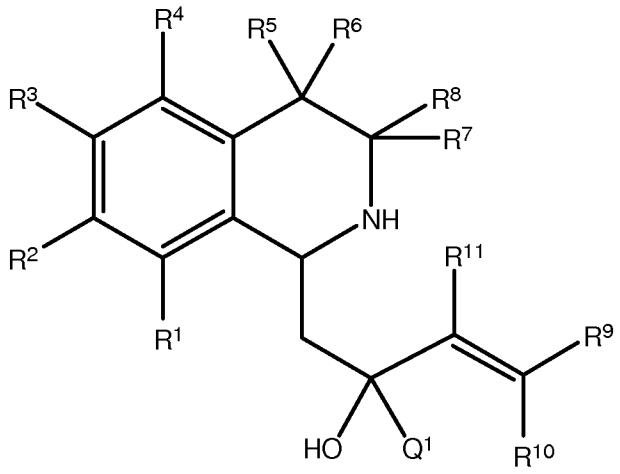
wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^1-R^4 is not hydrogen; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; P^1 is a protecting group; and Q^1 is hydrogen or an isotope thereof.

31. The tetrahydroisoquinoline compound according to claim 30, which is enantiomerically enriched.

32. The tetrahydroisoquinoline compound according to claim 31, at least 95 mole % of which is comprised of an enantiomer having the R configuration at ring position-12.

33. The tetrahydroisoquinoline compound according to claim 31, at least 95 mole % of which is comprised of an enantiomer having the S configuration at ring position-12.

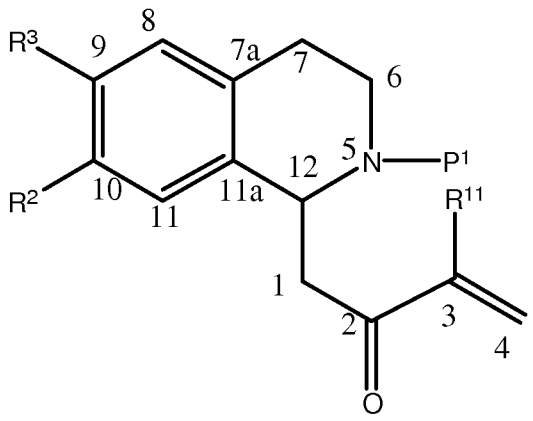
34. A tetrahydroisoquinoline compound having structure XIII



XIII

wherein R^1-R^4 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^1-R^4 is not hydrogen; R^5-R^{11} are independently hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and Q^1 is hydrogen or an isotope thereof.

35. A tetrahydroisoquinoline compound having structure VII



VII

wherein R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^2-R^3 is not hydrogen; R^{11} is hydrogen or an isotope thereof, a

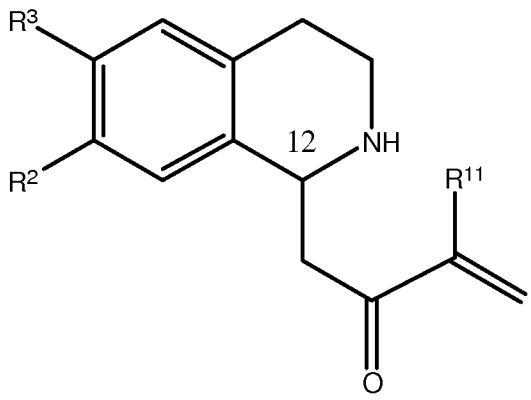
C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical; and P^1 is a protecting group.

36. The tetrahydroisoquinoline compound according to claim 35, which is enantiomerically enriched.

37. The composition according to claim 36, at least 95 mole % of which is comprised of an enantiomer having the R configuration at ring position-12.

38. The composition according to claim 36, at least 95 mole % of which is comprised of an enantiomer having the S configuration at ring position-12.

39. A tetrahydroisoquinoline compound having structure XIV



XIV

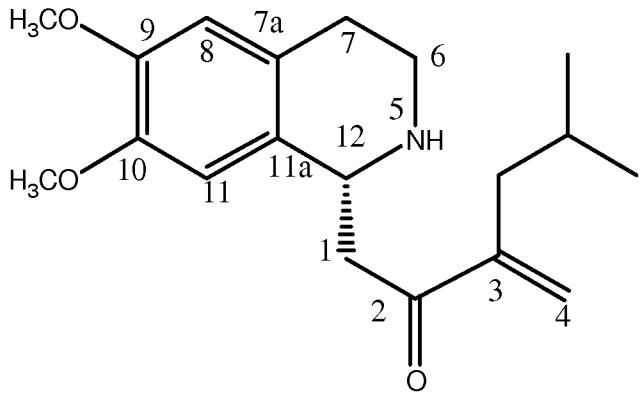
wherein R^2-R^3 are independently hydrogen or an isotope thereof, a halogen atom, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical, wherein at least one of R^2-R^3 is not hydrogen; and R^{11} is hydrogen or an isotope thereof, a C_1-C_{20} aliphatic radical, a C_2-C_{20} cycloaliphatic radical, or a C_2-C_{20} aromatic radical.

40. The tetrahydroisoquinoline compound according to claim 39, which is enantiomerically enriched.

41. The tetrahydroisoquinoline compound according to claim 40, at least 95 mole % of which is comprised of an enantiomer having the R configuration at ring position-12.

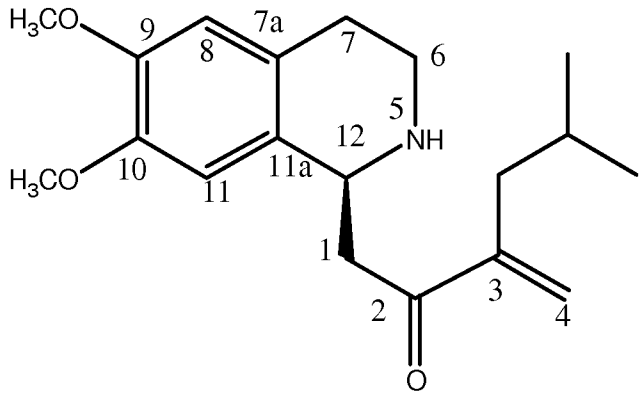
42. The tetrahydroisoquinoline compound according to claim 40, at least 95 mole % of which is comprised of an enantiomer having the S configuration at ring position-12.

43. A tetrahydroisoquinoline compound having structure XV



XV.

44. A tetrahydroisoquinoline compound having structure XVI



XVI.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/65738

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 217/00, C07D 217/24, C07D 455/00 (2008.04)
USPC - 514/309, 546/141, 546/95
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)
USPC - 514/309, 546/141, 546/95
IPC(8) - C07D 217/00, C07D 217/24, C07D 455/00 (2008.04)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/309, 546/141, 546/95
IPC(8) - C07D 217/00, C07D 217/24, C07D 455/00 (2008.04) (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT,PGPB,EPAB,JPAB); Google, Google Scholar, ChemSpider (structure and name search)
Search terms used: tetrabenazine tetrahydroisoquinoline alkenyl intermediate allylic alcohol aldehyde nucleophilic reaction quinolizine benzo amino cyclization TBZ NHK halogen exchange precursor oxidation protecting group nitrogen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,193,998 A (Szantay et al.) 18 March 1980 (18.03.1980), entire document; abstract	1-44
A	US 2002/0055637 A1 (Liu et al.) 09 May 2002 (09.05.2002), entire document; para [0029], [0047]-[0049]	1-44
A	US 3,132,147 A (Schopf et al.) 05 May 1964 (05.05.1964), entire document, col 1-2; col 7; col 2, ln 57-col 3, ln 8; col 7, ln 60-67	1-44
A	US 5,278,308 A (Kung) 11 January 1994 (11.01.1994), entire document	1-44
A	US 5,272,270 A (Hirsenkorn et al.) 21 December 1993 (21.12.1993), entire document, col 5, ln 60-63	1-44
A	US 5,118,690 A (Minchin et al.) 11 May 1993 (11.05.1993), entire document; abstract; claim 1	1-44
A	US 4,686,226 A (Huff et al.) 11 August 1987 (11.08.1987), entire document	1-44
A	US 2004/0082647 A1 (Babiak et al.) 20 April 2004 (29.03.2004), entire document	1-44

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 2008 (03.09.2008)	09 SEP 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)