



(51) International Patent Classification:

C07D 471/08 (2006.01) *C07D 487/22* (2006.01)
C07D 401/06 (2006.01) *C07D 491/147* (2006.01)
C07D 209/04 (2006.01) *A61K 31/437* (2006.01)
C07D 487/14 (2006.01) *A61K 31/4439* (2006.01)

(21) International Application Number:

PCT/US2015/036045

(22) International Filing Date:

16 June 2015 (16.06.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/013,771 18 June 2014 (18.06.2014) US

(71) Applicant: **DEMEXX, INC.** [US/US]; 305 South Andrews Avenue, Suite 515, Fort Lauderdale, Florida 33301 (US).

(72) Inventors: **MORIARTY, Robert M.**; 305 South Andrews Avenue, Suite 515, c/o DemeRx, Inc., Fort Lauderdale, Florida 33301 (US). **KINCH, Mark**; 3579 Valley Centre Drive, Suite 300, c/o Foley & Lardner LLP, San Diego, California 92130 (US).

(74) Agents: **SWISS, Gerald F.** et al.; 3000 K Street N.W., Suite 600, Foley & Lardner LLP, Washington, District of Columbia 20007-5109 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: HALOGENATED INDOLE AND BENZOFURAN DERIVATIVES OF ISOQUINUCLIDENE AND PROCESSES FOR PREPARING THEM

(57) Abstract: Provided herein are halogenated indole and benzofuran derivatives of isoquinuclidene and intermediates thereto, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (-) and (+) noribogaine, in substantially enantiomerically pure forms.



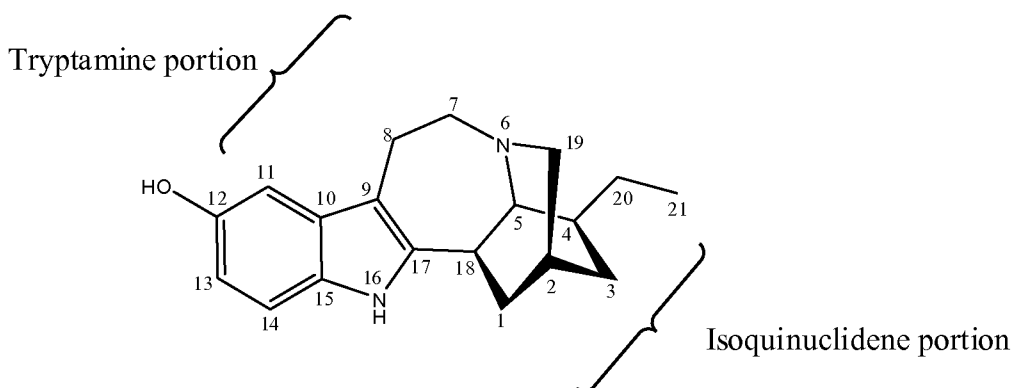
HALOGENATED INDOLE AND BENZOFURAN DERIVATIVES OF ISOQUINUCLIDENE AND PROCESSES FOR PREPARING THEM

FIELD OF THE INVENTION

[0001] Provided herein are halogenated indole and benzofuran derivatives of isoquinuclidene and intermediates thereto, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (-) and (+) noribogaine, in substantially enantiomerically pure forms.

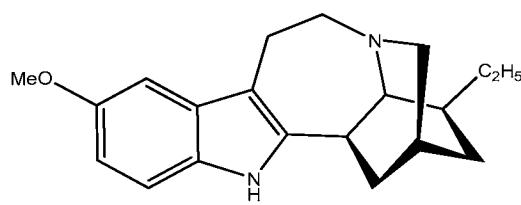
STATE OF THE ART

[0002] Noribogaine is a well-known compound whose structure combines the features, for example, of tyryptamine, and isoquinuclidene. The naturally occurring enantiomer of noribogaine can be depicted by the following formula:

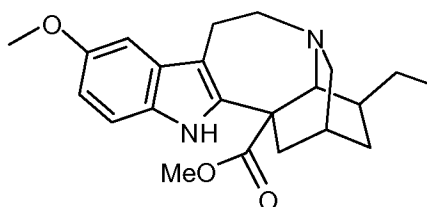


[0003] This enantiomer of noribogaine and its pharmaceutically acceptable salts have recently received significant attention as a non-addictive alkaloid useful in treating drug dependency (U.S. Patent No. 6,348,456) and as a potent analgesic (U.S. Patent No. 7,220,737). Both of these patents are incorporated herein by reference in their entirety.

[0004] Synthesizing compounds to include the isoquinuclidene moiety, especially in a substantially enantiomerically pure form is a challenging task. Heretofore, Iboga alkaloids, such as ibogaine:



were conventionally prepared from one of its naturally occurring precursors such as voacangine:



or isolated from plant sources. The naturally occurring enantiomer of noribogaine is prepared by O-demethylation of naturally occurring ibogaine or prepared by decarboxylation and O-demethylation of naturally occurring voacangine. Voacangine and Ibogaine are obtained from plants where both the supply is limited and the quality of the supply is unpredictable.

SUMMARY OF THE INVENTION

[0005] Provided herein are halogenated indole and benzofuran derivatives of isoquinuclidene and intermediates thereto, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (-) and (+) noribogaine, in substantially enantiomerically pure forms. Also provided herein are intermediates and processes for preparing noribogaine following the Nenitzescu indole synthesis.

DETAILED DESCRIPTION OF THE INVENTION

[0006] Before this invention is described in greater detail, the following terms will be defined.

Definitions

[0007] As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a salt” includes a plurality of such salts.

[0008] As used herein, “alkenyl” refers to hydrocarbyl groups having from 2 to 10 carbon atoms and at least one and up to 3 carbon carbon double bonds. Examples of alkenyl include vinyl, allyl, dimethyl allyl, and the like.

[0009] As used herein, “alkoxy” refers to –O-alkyl.

[0010] As used herein, “alkyl” refers to hydrocarbyl groups having from 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms, and still more preferably 1-4 carbon atoms. The alkyl group may contain linear or branched carbon chains. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, n-decyl and the like.

[0011] As used herein, “alkynyl” refers to hydrocarbyl groups having from 2 to 10 carbon atoms and at least one and up to 2 carbon carbon triple bonds. Examples of alkynyl include ethynyl, propargyl, dimethylpropargyl, and the like.

[0012] As used herein, “under amide formation conditions” refers to conditions, as is well known to the skilled artisan, under which a –CO₂H group or a –CO-L¹ group, wherein L¹ is a leaving group reacts with an amine to form an amide. A –COL¹ moiety can react with a suitable amine in the presence of a base, and optionally a nucleophilic catalyst such as N,N-dimethylamino pyridine or the likes, in an inert solvent such as dichloromethane, tetrahydrofuran, or the likes. Suitable bases include triethyl amine, pyridine, and well known modifications of each thereof. A CO₂H moiety reacts with a suitable amine in the presence of a reagent such as a carbodiimide or a variety of such reagents well known in chemistry and peptide chemistry.

[0013] As used herein, “amino” refers to –NR^xR^y wherein each R^x and R^y independently is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl, or R^x and R^y together with the nitrogen atom they are bonded to form a 5-10 membered heterocyclyl ring containing 1-2 nitrogen and/or oxygen atoms, which heterocyclyl ring is optionally substituted with 1-3, preferably, 1-2, or more preferably, a single, C₁-C₃ alkyl group.

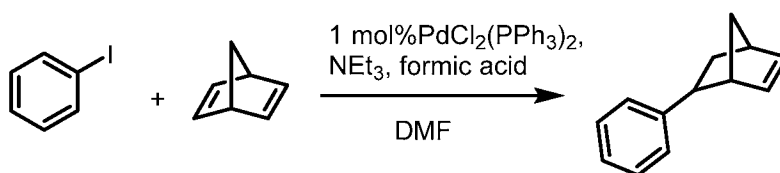
[0014] As used herein, “aryl” refers to an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-

benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom.

[0015] As used herein, “base” refers to a compound that can accept a proton or donate a lone electron pair. Examples of bases include, alkali (OH^-), carbonate, bicarbonate, alkoxides (alkyl- O^-), hydrides (alkali metal hydrides and CaH_2), amides (NH_2^- , R^bNH^- , or $(\text{R}^b)_2\text{N}^-$, wherein R^b is alkyl or 2 R^b s together with the nitrogen form a 5-6 membered ring), and neutral nitrogen containing bases such as $(\text{R}^b)_3\text{N}$, pyridine, 4-N,N-dialkylpyridine, and the like. As used herein nucleophilic bases refer to preferably neutral nitrogen containing bases that can catalyze the addition of an acyl halide or a sulfonyl halide (such as R^bCOX or $\text{R}^b\text{SO}_2\text{X}$) to an $-\text{OH}$, $-\text{NH}_2$, or an $-\text{NHR}^b$ group. Preferred examples include, 4-N,N-dialkylpyridines.

[0016] As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, but not excluding others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0017] As used herein, “a condition suitable for reductive Heck coupling” refers to a Heck coupling reaction condition where a β -hydride elimination is limited or is not possible. A Heck coupling, including obvious variants thereof, are well known to the skilled artisan. The reaction scheme below illustrates, without limitation, a reaction condition where a reductive Heck reaction takes place.



For example, a reaction may take place with a suitable hydride donor. In that case, a Heck reaction is carried out on a substrate which will not allow β -hydride elimination. The addition,

for example, of formic acid or ammonium formate leads to a σ -alkyl palladium intermediate and causes a "reductive Heck" reaction.

[0018] As used herein, "cycloalkyl" refers to cyclic hydrocarbyl groups of from 3 to 10 carbon atoms having single or multiple condensed rings, which condensed rings may be aromatic or contain a heteroatom, provided that the point of attachment is at a cycloalkyl carbon atom. Cycloalkyl includes, by way of example, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Cycloalkyl rings are preferably saturated, though, cycloalkyl rings including 1-2 carbon carbon double bonds are also contemplated provided that the ring is not aromatic.

[0019] As used herein, "C_x" refers to a group having x carbon atoms, wherein x is an integer, for example, C₄ alkyl refers to an alkyl group having 4 carbon atoms.

[0020] As used herein, "ee" refers to enantiomeric excess and is expressed as (e¹-e²)% where e¹ and e² are the two enantiomers. For example, if the % of e¹ is 95 and the % of e² is 5, then the e¹ enantiomer is present in an ee of 90%. The ee of an enantiomer in a mixture of enantiomers is determined following various methods well known to the skilled artisan, such as using chiral lanthanide based nuclear magnetic resonance shift reagents, forming derivatives with chiral compounds such as chiral hydroxyacids, amino acids, and the like. Various physical measurements such as circular dichroism, optical rotation, etc. are also useful in determining the ee of a mixture of enantiomers.

[0021] As used herein, -CO₂H "ester" refers to -CO₂R^E wherein R^E is selected from the group consisting of C₆-C₁₀ aryl and C₁-C₆ alkyl optionally substituted with 1-3 C₆-C₁₀ aryl groups.

[0022] As used herein, "halo" refers to F, Cl, Br, or I.

[0023] As used herein, "halogenating agent" refers to a compound that can convert an indole, to a 2- halo indole. Non-limiting examples of such reagents include N-halosuccinimides such as N-iodosuccinimide. Conditions suitable for halogenation include contacting the reactants in an inert solvent.

[0024] As used herein, "heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur within the ring, wherein the nitrogen and/or sulfur atom(s) of the heteroaryl are optionally oxidized

(e.g., N-oxide, -S(O)- or -S(O)₂-), provided that the ring has at least 5 ring atoms and up to 14, or preferably from 5-10, ring atoms. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. Examples of heteroaryls include pyridyl, pyrrolyl, indolyl, thiophenyl, furyl, and the like.

[0025] As used herein, “heterocyclyl” or heterocycle refers to a cycloalkyl group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur within the ring, wherein the nitrogen and/or sulfur atom(s) of the heteroaryl are optionally oxidized (e.g., N-oxide, -S(O)- or -S(O)₂-), provided that the ring has at least 3 and up to 14, or preferably from 5-10 ring atoms. Such heterocyclyl groups can have a single ring or multiple condensed rings wherein the condensed rings may not contain a heteroatom and/or may contain an aryl or a heteroaryl moiety, provided that the point of attachment is through an atom of the non-aromatic heterocyclyl group. Examples of heterocyclyl include pyrrolidinyl, piperadinyl, piperazinyl, and the like. Heterocyclyl rings are preferably saturated, though, heterocyclyl rings including 1-2 carbon carbon double bonds are also contemplated provided that the ring is not aromatic.

[0026] As used herein, “hydrogenation conditions” refer to conditions including hydrogen gas at atmospheric or higher pressure and catalysts that catalyze the reaction of the hydrogen with a hydrogen reactive group, such as a benzyl group or a carbon carbon double/triple bond. Catalysts useful for hydrogenation include palladium, platinum, and rhodium metals and their oxides or hydroxides, preferably supported on a material such as carbon or alumina.

[0027] As used herein, “leaving group” refers to a group or an atom that can be displaced by a nucleophile such as an amine. Non-limiting examples of leaving groups include halo, preferably, chloro, bromo, or iodo, and -OSO₂R⁶⁰ wherein R⁶⁰ is C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or is C₃-C₈ heterocyclyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl, is optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, or C₁-C₆ alkoxy.

[0028] As used herein, “nucleophilic substitution conditions” refer to those suitable for a nucleophilic substitution at an aliphatic saturated carbon atom, with a nucleophile such as an amine. The reaction are carried out preferably in an aprotic solvent. A non-nucleophilic base, e.g., a base that does not compete with the reacting amine as a nucleophile, such as K₂CO₃ may be employed to neutralize any acid generated in the process.

[0029] As used herein, “protecting group” or “Pg” refers to well known functional groups which, when bound to a functional group, render the resulting protected functional group inert to the reaction to be conducted on other portions of the compound and the corresponding reaction condition, and which can be reacted to regenerate the original functionality under deprotection conditions. The protecting group is selected to be compatible with the remainder of the molecule. In one embodiment, the protecting group is an “amine protecting group” which protects an –NH– or an –NH₂– moiety, for example during the syntheses described here. Examples of amine protecting groups include, for instance, benzyl, acetyl, oxyacetyl, carbonyloxybenzyl (Cbz), Fmoc, and the like. In another embodiment, the protecting group is a “hydroxy protecting group” which protects a hydroxyl functionality during the synthesis described here. Examples of hydroxyl protecting groups include, for instance, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, dialkylsilyl ethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, and benzyl. As the skilled artisan would appreciate, one or more of these protecting groups are also useful as amine protecting groups. Additional examples of amine, hydroxy, and keto protecting groups are found in standard reference works such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 2d Ed., 1991, John Wiley & Sons, and McOmie *Protective Groups in Organic Chemistry*, 1975, Plenum Press. Methods for

protecting and deprotecting hydroxyl, -NH-, -NH₂-, and keto groups disclosed herein can be found in the art, and specifically in Greene and Wuts, *supra*, and the references cited therein.

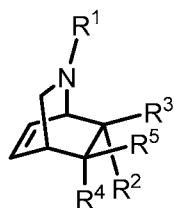
[0030] As used herein, “reducing agent” refers to a compounds that can donate electrons or a hydride in a reaction. Preferred examples include aluminum hydrides, such as LiAlH₄, borohydrides such as NaBH₄/CeCl₃, and alanes such as diisobutyl aluminum hydride. A reducing agent reduces under reduction conditions. Typically the reducing agent and the compound to be reduced, such as a keto-containing compound is reacted in an inert solvent such as ether, tetrahydrofuran, or dioxane. The reaction mixture can be refluxed.

[0031] As used herein, a salt refers to preferably a salt of a mineral acid, or an organic acid such as a carboxylic acid or a sulfonic acid, and/or to alkali, alkaline earth, and various ammonium (including tetraalkyl ammonium, pyridinium, imidazolium and the like) salts. Non limiting examples of acid salts include salts of hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methane sulfonic acid, phosphorous acid, nitric acid, perchloric acid, acetic acid, tartaric acid, lactic acid, succinic acid, and citric acid.

[0032] As used herein, “substantially enantiomerically enriched,” “substantially enantiomerically pure” or “substantial enantiomeric excess” or grammatical equivalents thereof refers to an enantiomer in an enantiomeric mixture with at least 95% ee, preferably 98% ee, or more preferably 99% ee.

Compounds

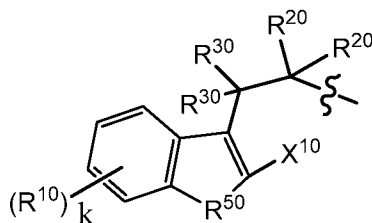
[0033] In one aspect, provided herein is a compound of Formula (I) :



(I)

or a tautomer thereof or a salt of each thereof wherein

R^1 is selected from the group consisting of hydrogen, $-\text{CO}_2R^{11}$, $-\text{COR}^{12}$, $-\text{C}(R^{13})_3$, an amine protecting group, and



R^{11} is selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 substituents selected from $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ heterocyclyl, halo, amino, $-\text{N}_3$, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ cycloalkyl, and $\text{C}_3\text{-C}_8$ heterocyclyl,

R^{12} and R^{13} independently are selected from the group consisting of hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 substituents selected from $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ heterocyclyl, halo, amino, $-\text{N}_3$, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ cycloalkyl, and $\text{C}_3\text{-C}_8$ heterocyclyl;

k is 0, 1, 2, or 3;

each R^{10} is independently a substituent (i.e., when k is 0, the indole moiety includes 4 hydrogens in the phenyl portion) selected from the group consisting of halo, amino, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, cyano, nitro, $-\text{N}_3$, and $-\text{CO}_2\text{H}$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-\text{N}_3$, phenyl optionally substituted with 1-3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ alkoxy, and $-\text{CO}_2\text{H}$ or an ester thereof;

R^{20} is hydrogen or $\text{C}(R^{20})_2$ is a keto group;

R^{30} is selected from the group consisting of hydrogen, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3

substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, -N₃, and -CO₂H or an ester thereof;

R⁵⁰ is selected from the group consisting of -O- and N-R⁵¹; and

R⁵¹ is selected from the group consisting of hydrogen and C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, -N₃, and -CO₂H or an ester thereof;

X¹⁰ is a leaving group, preferably, halo or -OSO₂R⁷¹, more preferably bromo or iodo, or is -OH or hydrogen;

R⁴ and R⁵ independently are selected from the group consisting of hydrogen, halo, C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, vinyl, ethynyl, and CO₂H or an ester thereof;

R² and R³ are independently selected from hydrogen, -CHO, R⁶-C(=O)-, R⁶-CH(OR⁷)-, provided that at least one of R² and R³ is hydrogen; or R² and R³ together with the carbon atom they are bonded to, form a =CHR⁶ moiety;

R⁶ is C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl;

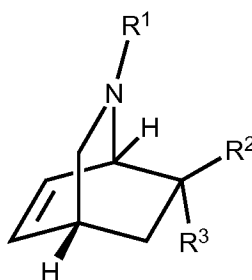
R⁷ is hydrogen or SO₂R⁷¹;

R⁷¹ is C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or is C₃-C₈ heterocyclyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl;

wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl, is optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, and CO₂H or an ester thereof.

[0034] A keto substituent, as used herein, substitutes a $-\text{CH}_2-$ group to a $-\text{C}(=\text{O})$ -group. In one embodiment, X^{10} is a leaving group, preferably, halo or $-\text{OSO}_2\text{R}^{71}$, more preferably bromo or iodo, or is $-\text{OH}$. . In one embodiment, X^{10} is more preferably, halo

[0035] In one embodiment, the compound is of Formula (II):

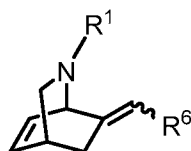


(II)


wherein R^1 , R^2 , and R^3 are defined as above.

[0036] In another embodiment, R^1 is hydrogen or CO_2R^{11} and R^{11} is C_1 - C_6 alkyl.

[0037] In another embodiment, provided herein is a compound of Formula (III):

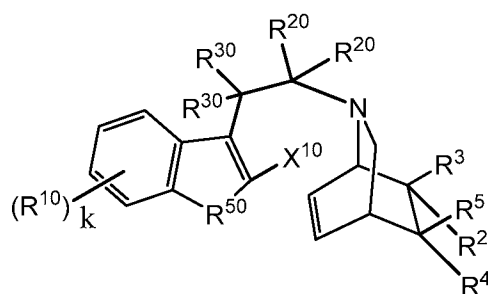


(III)

wherein  refers to a cis or a trans stereochemistry and R^1 is defined as in any aspect or embodiment herein.

[0038] In another embodiment, one of R^2 and R^3 is hydrogen, and the other is $-\text{CHO}$, COCH_3 , CHOHCH_3 , $-\text{CHOSO}_2\text{R}^{71}$ wherein R^{71} is defined as herein.

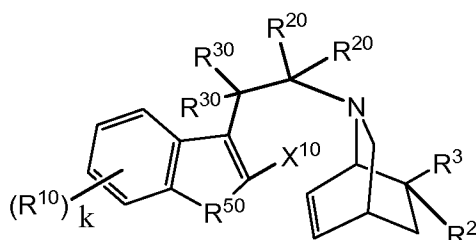
[0039] In another embodiment, provide herein is a compound of Formula (IV):



(IV)

wherein the variables are defined as in any aspect or embodiment herein.

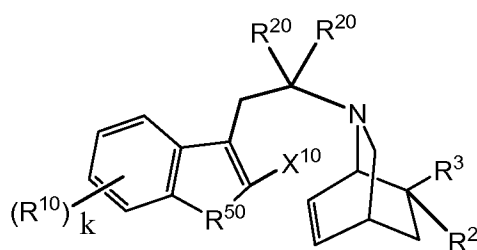
[0040] In another embodiment, provided herein is a compound of Formula (IVA):



(IVA)

wherein the variables are defined as in any aspect and embodiment above.

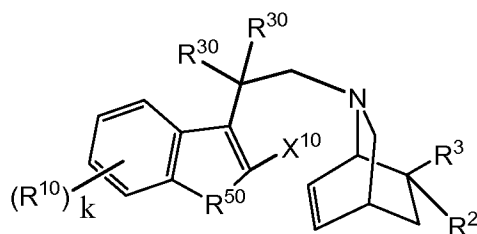
[0041] In another embodiment, provided herein is a compound of Formula (IVB):



(IVB)

wherein the variables are defined as in any aspect or embodiment above.

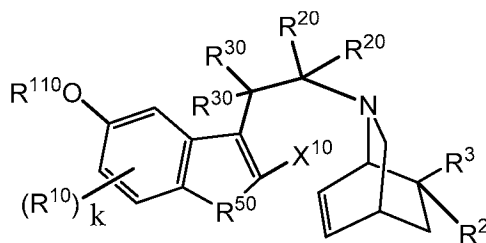
[0042] In another embodiment, provided herein is a compound of Formula (IVC):



(IVC)

wherein the variables are defined as in any aspect or embodiment above.

[0043] In another embodiment, provided herein is a compound of Formula (VA):



(VA)

wherein R^{110} is selected from the group consisting of

hydrogen;

C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-N_3$, $-CO_2H$ or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

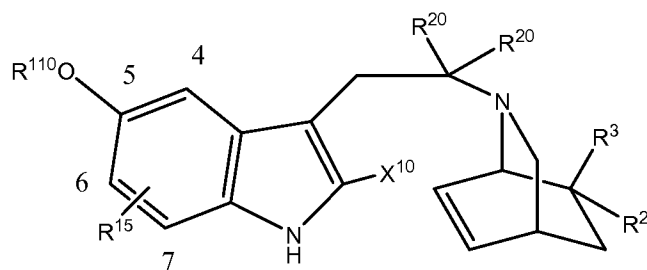
$-COR^{11}$; and

$-CO_2R^{11}$;

k is 0, 1 or 2;

and the remaining variables are defined as in any aspect and embodiment herein.

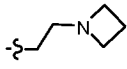
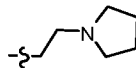
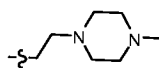
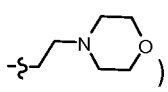
[0044] In another embodiment, provided herein is a compound of Formula (VB) :

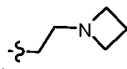
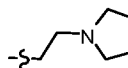
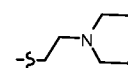
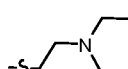


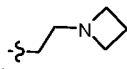


(VB)

wherein the variables are as tabulated below:

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	C=O	CR^2R^3 is C=CR ⁴⁸ H, R ⁴⁸ is Me, Et, Pr, Bu	--	--
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH ₂	CR^2R^3 is C=CR ⁴⁸ H, R ⁴⁸ is Me, Et, Pr, Bu	--	--

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	C=O	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g., , , , or )</p>

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g.,</p> <p>$CO_2(CH_2)_2NMe_2$, , , , or )</p>

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	C=O	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g.,</p> <p>$CO_2(CH_2)_2NMe_2$, , , , or</p>

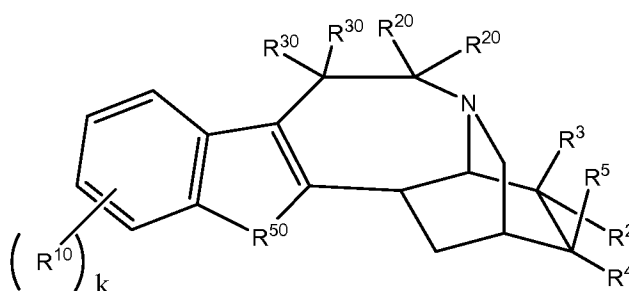
[0048] In another embodiment, CR^2R^3 is $=CHMe$.

[0049] In another embodiment, k is 0. In another embodiment, k is 0 and preferably, the phenyl ring is substituted with the $-OR^{110}$ group. In another embodiment, R^{110} is C_1-C_6 alkyl optionally substituted with 1-3 substituents selected from phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1-C_6 alkyl and C_1-C_6 alkoxy.

Preparation

Cyclization e.g., by Reductive Heck Coupling

[0050] In another aspect, provided herein is a process of preparing a compound of Formula (VI):



(VI)

or a tautomer thereof or a salt of each thereof wherein

k is 0, 1, 2, or 3;

each R^{10} is independently a substituent selected from the group consisting of halo, amino, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1-C_6 alkyl and C_1-C_6 alkoxy, and $-CO_2H$ or an ester thereof;

R^{20} is hydrogen or $C(R^{20})_2$ is a keto group;

R^{30} is selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

R^{50} is selected from the group consisting of $-O-$ and $N-R^{51}$; and

R^{51} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

R^4 and R^5 independently are selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, vinyl, ethynyl, and CO_2H or an ester thereof;

R^2 and R^3 are independently selected from hydrogen, $-CHO$, $R^6-C(=O)-$, $R^6-CH(OR^7)-$, provided that at least one of R^2 and R^3 is hydrogen; or R^2 and R^3 together with the carbon atom they are bonded to, form a $=CHR^6$ moiety;

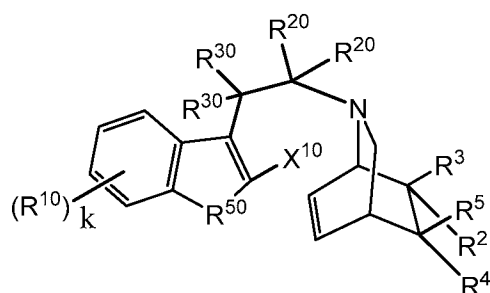
R^6 is C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or C_3 - C_8 heterocyclyl;

R^7 is hydrogen or SO_2R^{71} ;

R^{71} is C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or is C_3 - C_8 heterocyclyl, C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or C_3 - C_8 heterocyclyl;

wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl, is optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_6 - C_{10} aryl, cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof;

the process comprising subjecting a compound of Formula(IV):



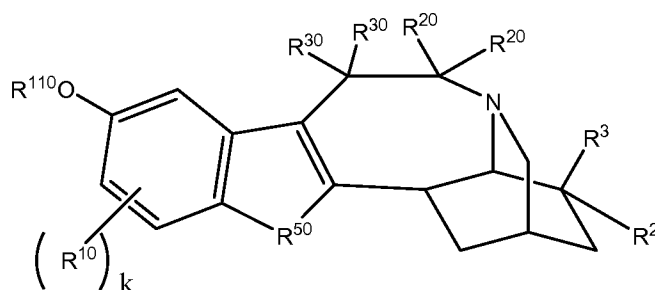
(IV)

wherein X^{10} is a leaving group, preferably, halo or $-\text{OSO}_2\text{R}^{71}$, more preferably bromo or iodo and

the remaining variables are defined as above, e.g., for Formula (VI);

to a condition suitable for reductive Heck coupling to provide the compound of Formula (VI).

[0051] In one embodiment, the compound prepared is of Formula (VIA):



(VIA)

wherein R^{110} is selected from the group consisting of

hydrogen;

$\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-\text{N}_3$, $-\text{CO}_2\text{H}$ or an ester thereof, and

phenyl optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl and C₁-C₆ alkoxy;

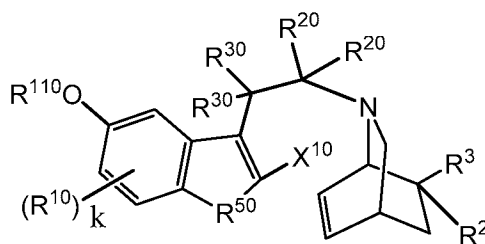
-COR¹¹; and

-CO₂R¹¹;

k is 0, 1 or 2;

and the remaining variables are defined as in any aspect and embodiment above,

wherein the compound of Formula (VIA) is prepared comprising subjecting a compound of Formula (VA):

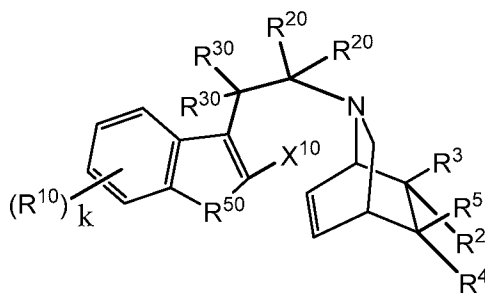


(VA)

wherein X¹⁰ is halo, preferably, bromo or iodo, more preferably, iodo, to a condition suitable for reductive Heck coupling to provide the compound of Formula (VIA).

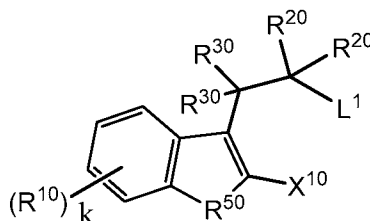
Amide and amine formation

[0052] In one aspect, provided herein is a process of preparing a compound of formula (IV):



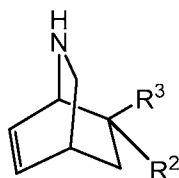
(IV)

wherein X^{10} is a leaving group, $C(R^{20})_2$ is $C=O$, and the remaining variables are as defined herein, such as above, is prepared comprising contacting a compound of Formula (VIIC) :



(VIIC)

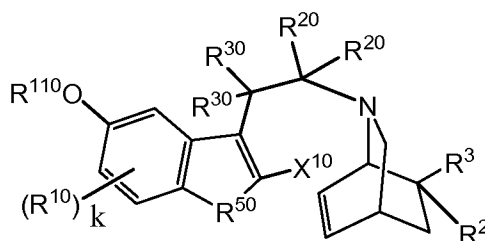
wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

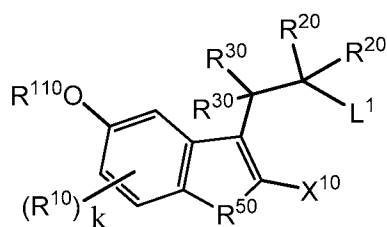
under amide formation conditions to prepare the compound of Formula (IV); or

wherein the compound of Formula (VIIC):



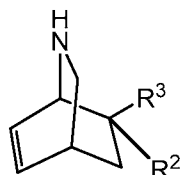
(VIIC)

wherein $C(R^{20})_2$ is $C=O$ and the remaining variables are as defined herein, such as above, is prepared comprising contacting a compound of Formula (VIID)



(VIID)

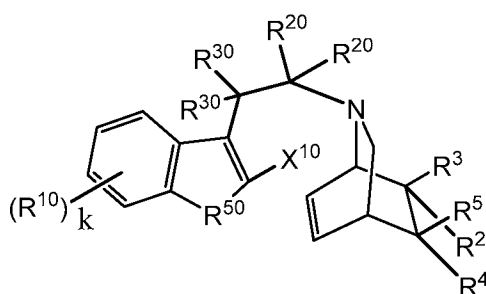
wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

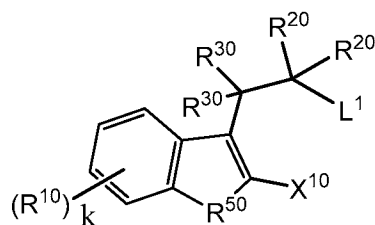
under amide formation conditions to prepare the compound of Formula (VIIC).

[0053] In one aspect, provided herein is a process of preparing a compound of formula (IV):



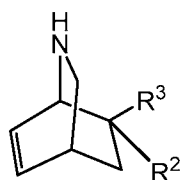
(IV)

wherein X^{10} is a leaving group and $C(R^{20})_2$ is CH_2 is prepared comprising contacting a compound of Formula (VIIC) :



(VIIC)

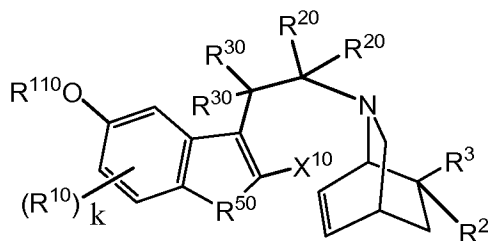
wherein L^1 is a leaving group with a compound of Formula (IX):



(IX)

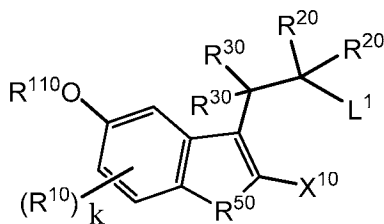
under nucleophilic substitution conditions to prepare the compound of Formula (IV); or

wherein the compound of Formula (VIIC):



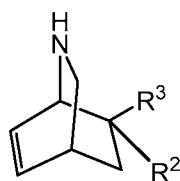
(VIIC)

wherein $C(R^{20})_2$ is CH_2 is prepared comprising contacting a compound of Formula (VIID)



(VIID)

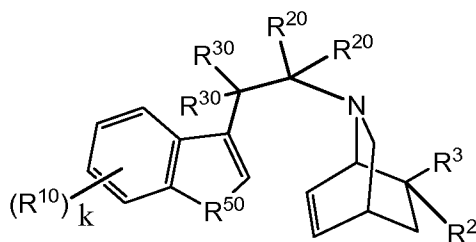
wherein L^1 is a leaving group with a compound of Formula (IX):



(IX)

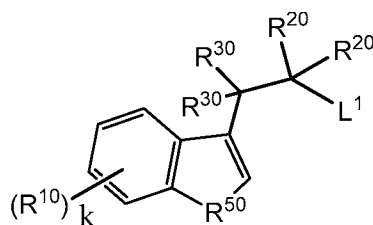
under nucleophilic substitution conditions to prepare the compound of Formula (VIIC).

[0054] In another embodiment, provided herein a process for preparing a compound of Formula (VIIA):



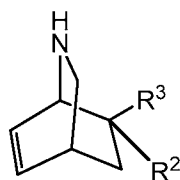
(VIIA)

wherein $C(R^{20})_2$ is $C=O$ is prepared comprising contacting a compound of Formula (VIII A)



(VIII A)

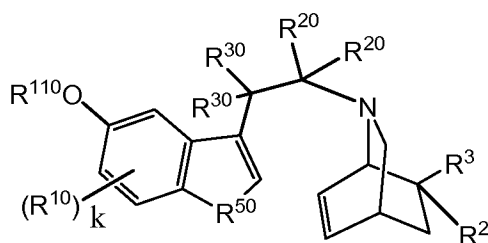
wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

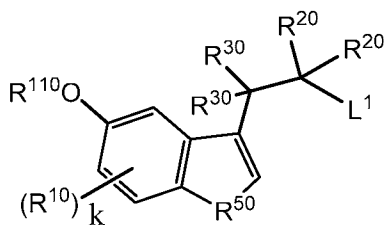
under amide formation conditions to prepare the compound of Formula (VIII A); or

wherein the compound of Formula (VII B):



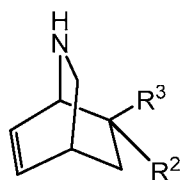
(VII B)

wherein $C(R^{20})_2$ is $C=O$ is prepared comprising contacting a compound of Formula (VII B)



(VIII B)

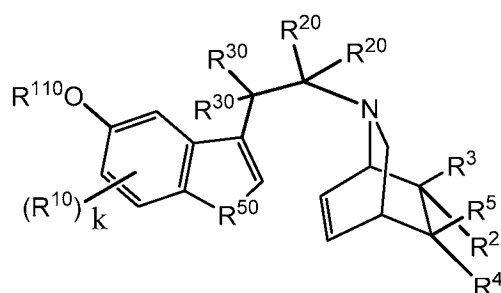
wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

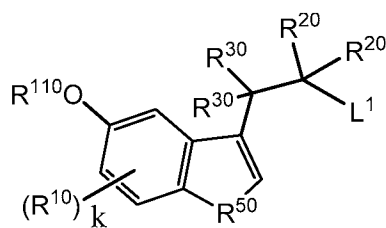
under amide formation conditions to prepare the compound of Formula (VIIB).

[0055] In one aspect, provided herein is a process of preparing a compound of formula (IV):



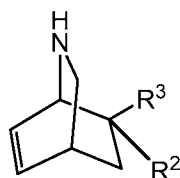
(IV)

wherein $C(R^{20})_2$ is CH_2 is prepared comprising contacting a compound of Formula (VIII C) :



(VIII C)

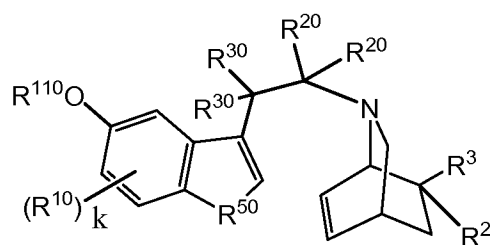
wherein L^1 is a leaving group with a compound of Formula (IX):



(IX)

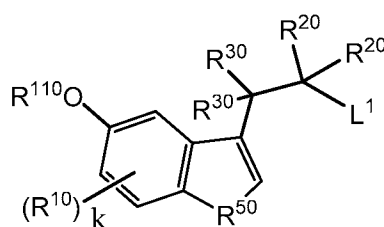
under nucleophilic substitution conditions to prepare the compound of Formula (IV); or

wherein the compound of Formula (VIIC):



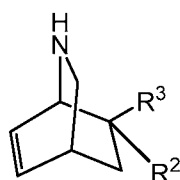
(VIIC)

wherein $C(R^{20})_2$ is CH_2 is prepared comprising contacting a compound of Formula (VIID)



(VIID)

wherein L^1 is a leaving group with a compound of Formula (IX):

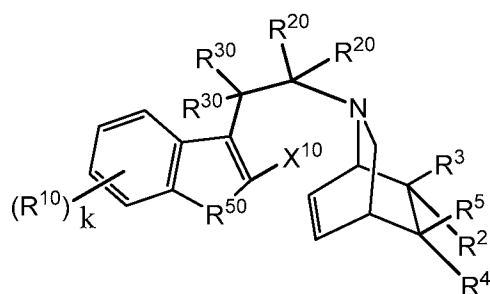


(IX)

under nucleophilic substitution conditions to prepare the compound of Formula (VIIC).

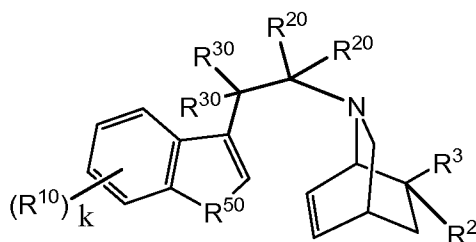
Halogenation

[0056] In one aspect, provided herein is a process of preparing a compound of formula (IV):



(IV)

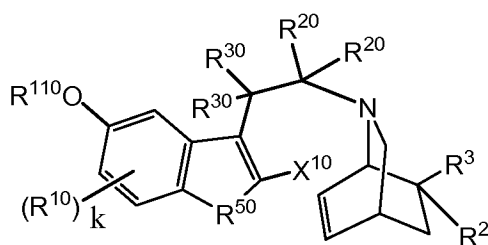
wherein X^{10} is halo is prepared comprising contacting a compound of Formula (VIIA) :



(VIIA)

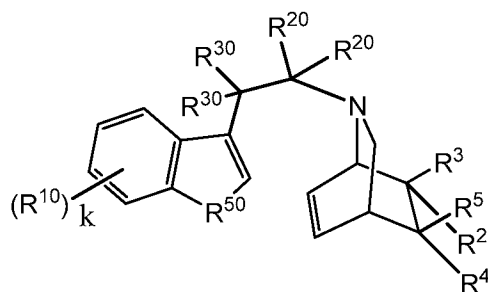
with a halogenating agent under conditions suitable for halogenation to provide the compound of Formula (IVA), or

wherein the compound of Formula (VA)



(VA)

wherein X^{10} is halo is prepared comprising contacting a compound of Formula (VIIB):



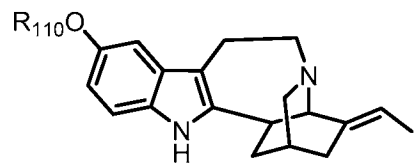
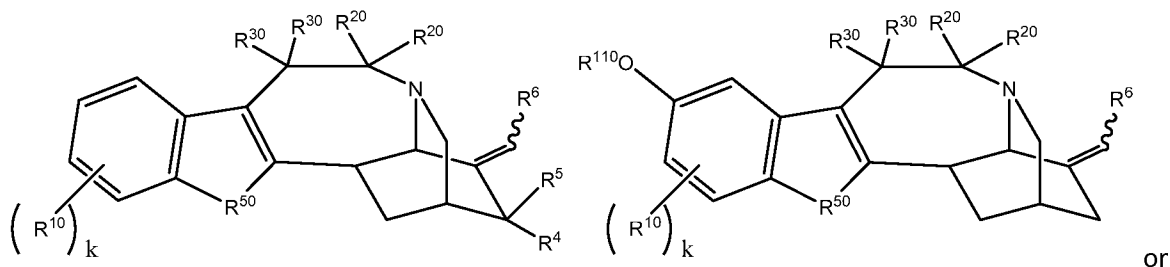
(VIIB)

with a halogenating agent under conditions suitable for halogenation to provide the compound of formula (VA).

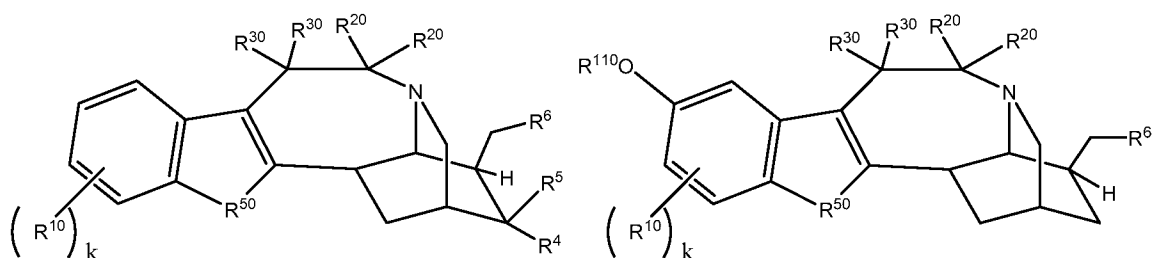
[0057] As will be apparent to the skilled artisan, amides prepared as above can be reduced to the corresponding-CH₂-N< compounds by reacting with borohydrides or aluminum hydrides under reducing conditions.

Hydrogenation

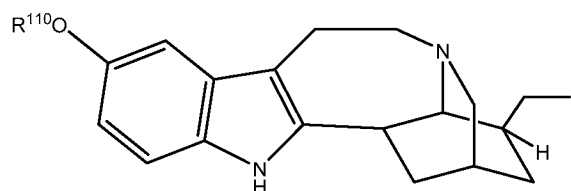
[0058] In one aspect, provided herein is a method of subjecting a compound of formula:



under hydrogenation condition to provide a compound of formula:



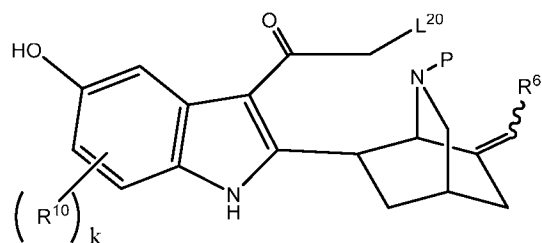
or



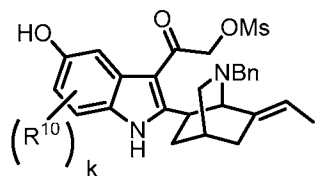
respectively.

Nenitzescu reaction

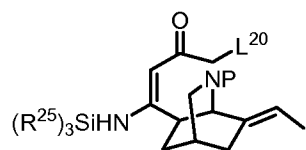
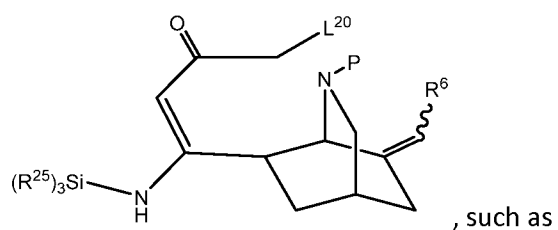
[0059] In another aspect, provided here is a method of making a compound of formula:



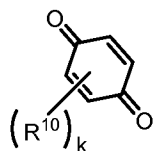
such as:



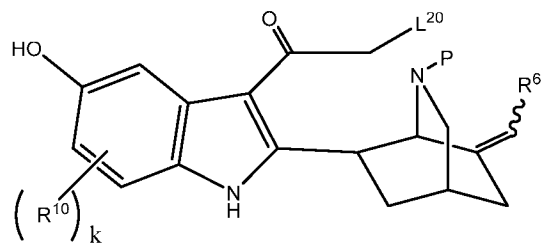
wherein R^{10} is defined as in any embodiment herein, k is 0, 1, or 2, L^{20} is a leaving group, preferably tosyl, mesyl, or another sulfonate, and P is a nitrogen protecting group, preferably, benzyl, comprising contacting a compound of formula:



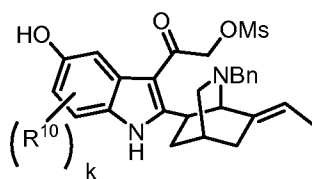
where each R²⁵ independently is C₁-C₆ alkyl or C₆-C₁₀ aryl, preferably phenyl, with a compound of formula:



under Nenitzescu indole formation condition to provide a compound of formula:



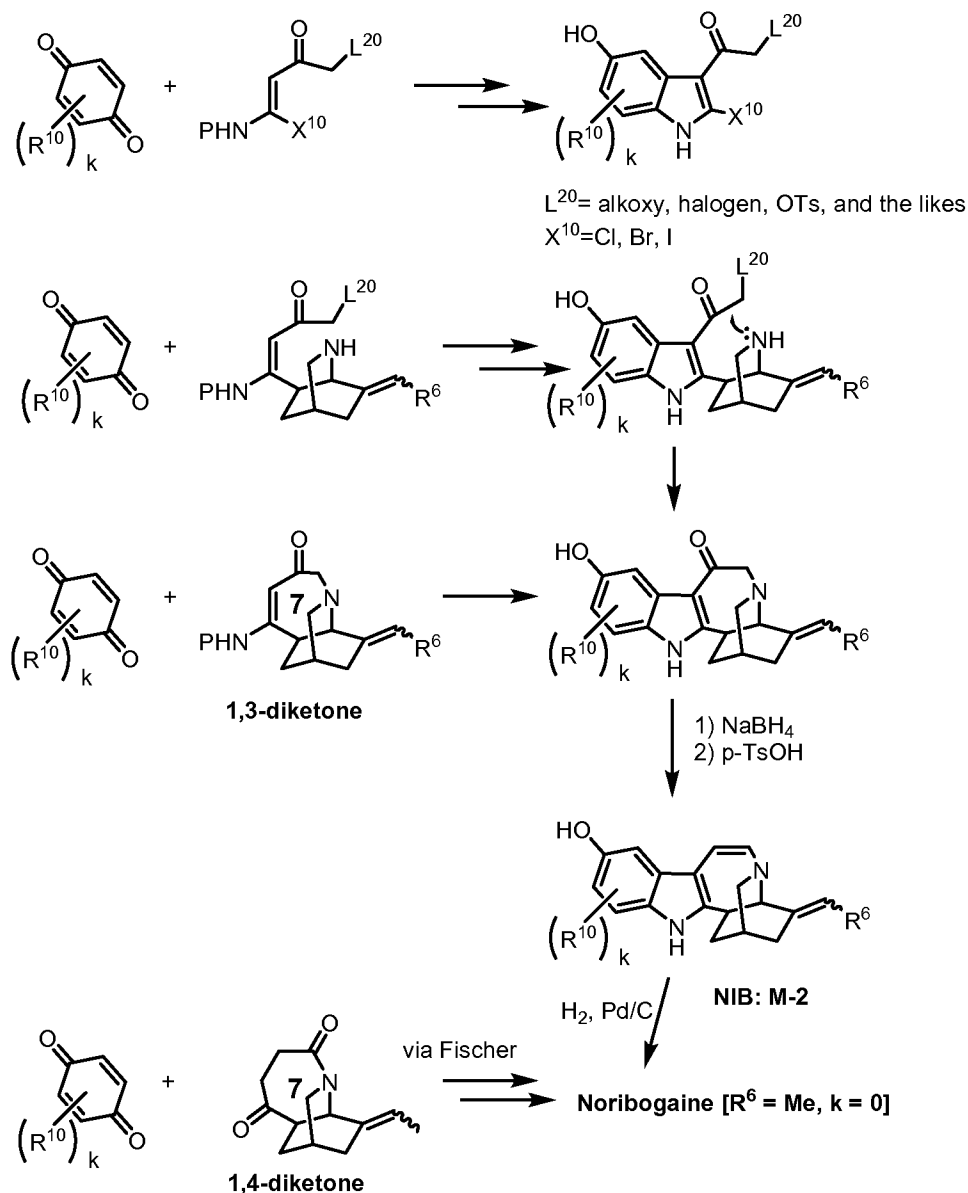
In one embodiment, the compound provided is of formula:



The protected alpha, beta unsaturated keto amine is reacted at a slight to about 2 fold molar excess of the quinone. Lewis acid catalysts may be employed optionally.

Other non limiting methods and intermediates are shown below:

Illustrative Nenitzescu and Fischer Indole Syntheses



[0060] In one embodiment, $C(R^{20})_2$ is CH_2 . In another embodiment, $C(R^{20})_2$ is $C=O$. A compound hereinabove, wherein $C(R^{20})_2$ is $C=O$ can be converted to one wherein $C(R^{20})_2$ is CH_2 upon contacting with a reducing agent under reduction conditions.

[0061] In one embodiment, R^{110} is benzyl or a substituted benzyl group that is deprotected to provide a compound with R^{110} being hydrogen upon hydrogenation.

[0062] In one embodiment, X^{10} is halo.

[0063] In one embodiment, R^4 , R^5 , R^{20} , and R^{30} are hydrogen.

[0064] In another embodiment, R^{50} is NR^{51} . In one embodiment, R^{50} is NH. In another embodiment, R^{50} is O.

[0065] In another embodiment, CR^2R^3 is =CHMe.

[0066] In another embodiment, k is 0. In another embodiment, k is 0 and preferably, the phenyl ring is substituted with the $-OR^{110}$ group. In another embodiment, R^{110} is C_1-C_6 alkyl optionally substituted with 1-3 substituents selected from phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1-C_6 alkyl and C_1-C_6 alkoxy.

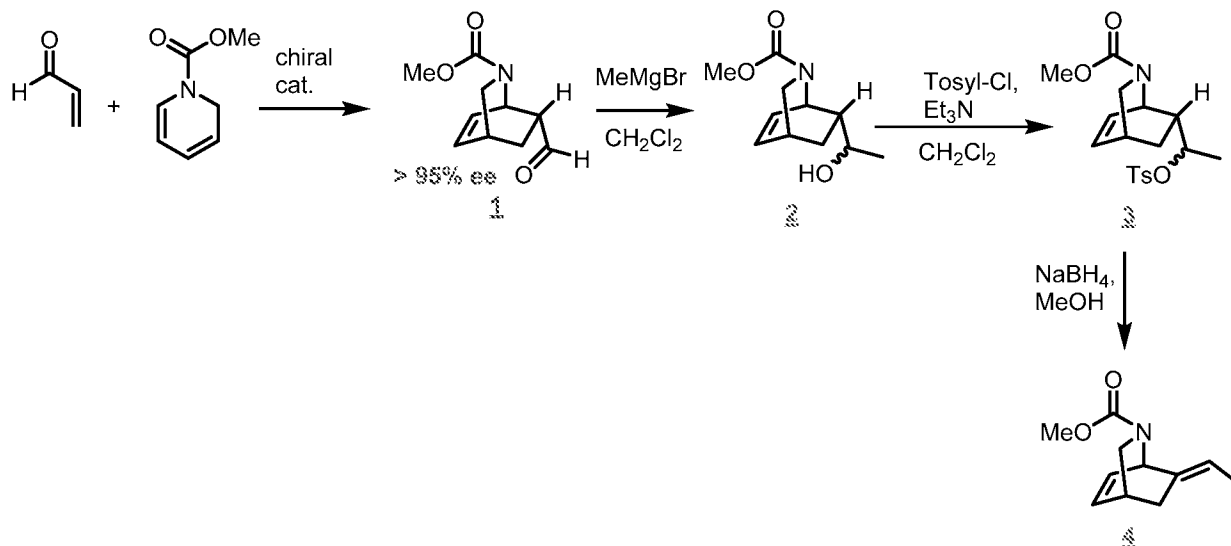
[0067] Starting materials useful for preparing the compounds and in the processes provided herein are well known in the art and available commercially, for example, from Sigma-Aldrich Co. The reactions are carried out under suitable conditions to effect reaction completion. Typically, the reaction is carried out in an inert solvent for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, 1H -nuclear magnetic resonance (NMR) spectroscopy, and the likes. As the skilled artisan will know or can ascertain based on this disclosure, certain reactions can be heated. As the skilled artisan will also understand, certain functionalities may have to be protected with protecting groups during one or more preparative steps and eventually deprotected. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification. Procedures useful in this invention is disclosed in PCT patent application publication nos. WO 2013/112757 and WO 2013/112622, which can be adapted in view of this disclosure to prepare compounds and in methods provided herein.

EXAMPLES

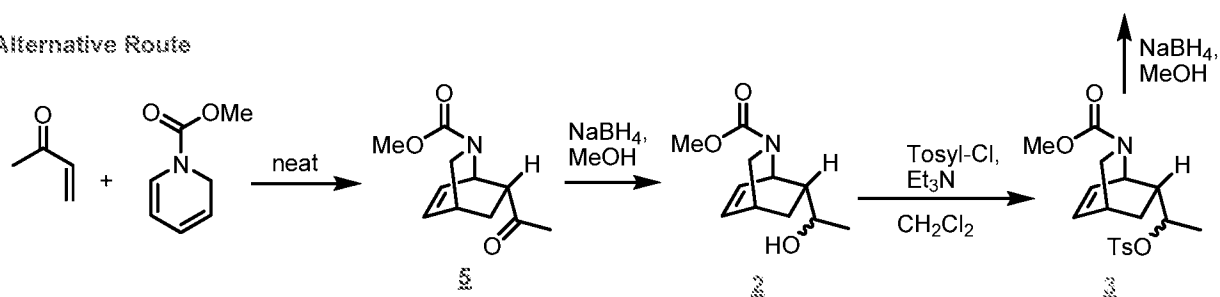
[0068] Certain illustrative and non-limiting processes of synthesizing certain compounds provided herein are schematically disclosed below.

Example 1

Stereoselective Route

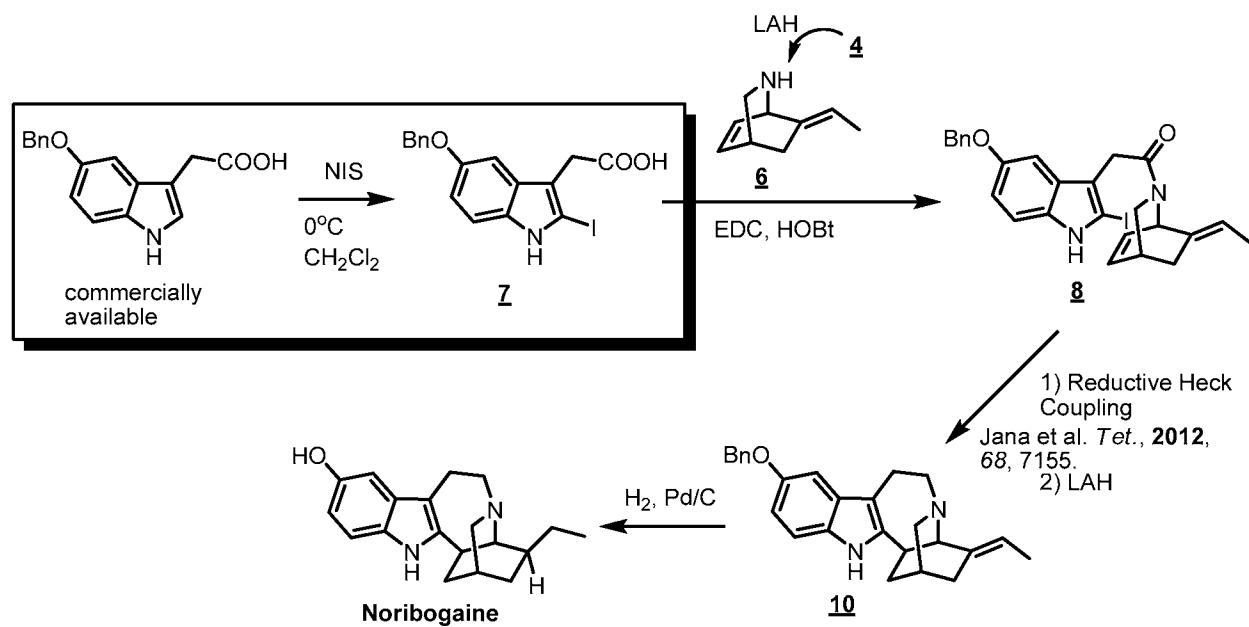


Alternative Route

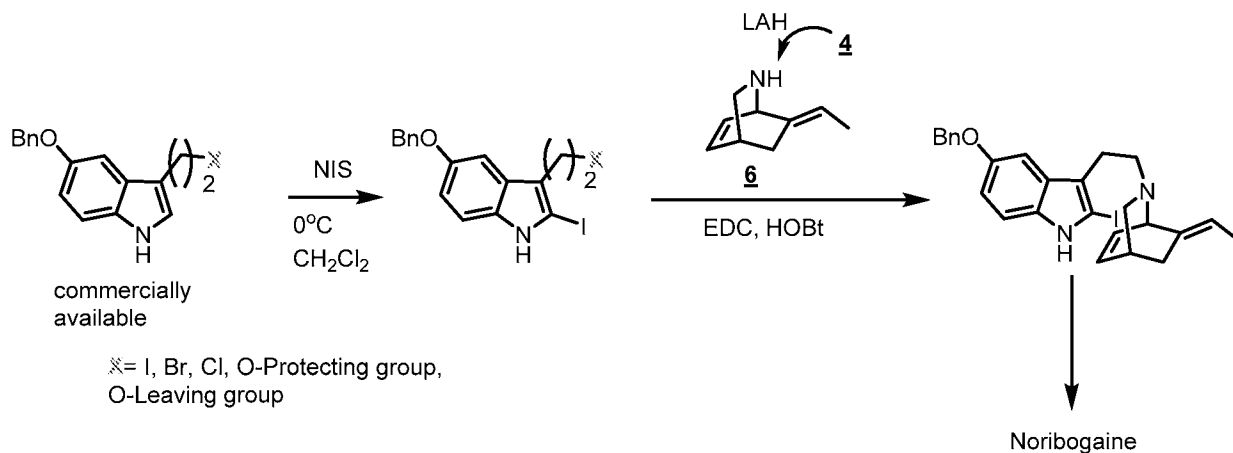


In addition to the selective approach, compound **4** can be made as a racemic mixture (by the alternative route). It is contemplated that the enantiomers of compound **4** can be separated via diastereomeric salt formation through the nitrogen atom or chiral high-performance column chromatography (HPLC), as would be well known to the skilled artisan.

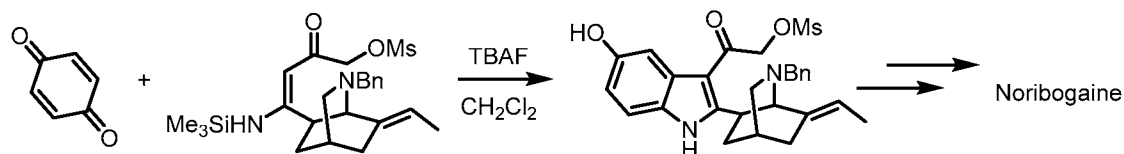
Example 2



Example 3. Nucleophilic Substitution

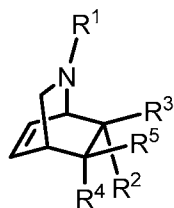


Example 4-Nenitzescu Variation



CLAIMS

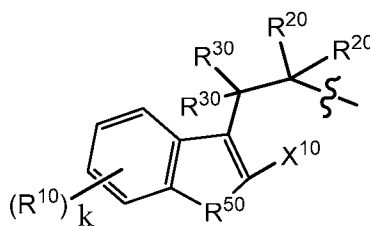
1. A compound of Formula (I) :



(I)

or a tautomer thereof or a salt of each thereof wherein

R¹ is selected from the group consisting of hydrogen, -CO₂R¹¹, -COR¹², -C(R¹³)₃, an amine protecting group, and



R¹¹ is selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, and CO₂H or an ester thereof, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, C₂-C₁₀ heteroaryl, C₃-C₈ cycloalkyl, and C₃-C₈ heterocyclyl,

R¹² and R¹³ independently are selected from the group consisting of hydrogen, C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, and CO₂H or an ester thereof, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, C₂-C₁₀ heteroaryl, C₃-C₈ cycloalkyl, and C₃-C₈ heterocyclyl;

k is 0, 1, 2, or 3;

each R^{10} is independently a substituent selected from the group consisting of halo, amino, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy, and $-CO_2H$ or an ester thereof;

R^{20} is hydrogen or $C(R^{20})_2$ is a keto group;

R^{30} is selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

R^{50} is selected from the group consisting of $-O-$ and $N-R^{51}$; and

R^{51} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

X^{10} is a leaving group, preferably, halo or $-OSO_2R^{71}$, more preferably bromo or iodo, or is $-OH$ or hydrogen;

R^4 and R^5 independently are selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, vinyl, ethynyl, and CO_2H or an ester thereof;

R^2 and R^3 are independently selected from hydrogen, $-CHO$, $R^6-C(=O)-$, $R^6-CH(OR^7)-$, provided that at least one of R^2 and R^3 is hydrogen; or R^2 and R^3 together with the carbon atom they are bonded to, form a $=CHR^6$ moiety;

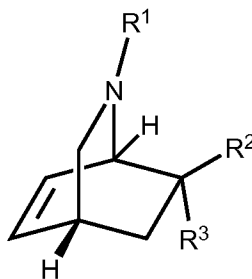
R^6 is C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or C_3 - C_8 heterocyclyl;

R^7 is hydrogen or SO_2R^{71} ;

R^{71} is C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or is C_3 - C_8 heterocyclyl, C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, or C_3 - C_8 heterocyclyl;

wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl, is optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_6 - C_{10} aryl, cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof.

2. The compound of claim 1, of Formula (II):

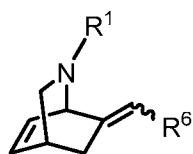


(II)

wherein R^1 , R^2 , and R^3 are defined as in claim 1.

3. The compound of claim 2, wherein R^1 is hydrogen or CO_2R^{11} and R^{11} is C_1 - C_6 alkyl.

4. The compound of claim 1, of Formula (III):

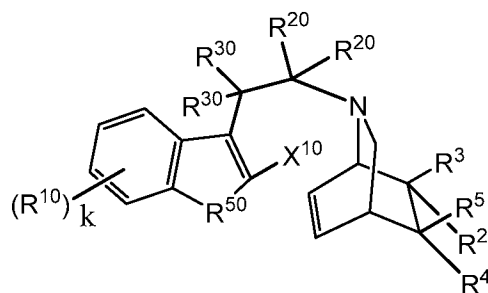


(III)

wherein  refers to a cis or a trans stereochemistry and R^1 is defined as in claim 1.

5. The compound of claim 2, wherein one of R^2 and R^3 is hydrogen, and the other is $-CHO$, $COCH_3$, $CHOHCH_3$, $-CHOSO_2R^{71}$ wherein R^{71} is defined as in claim 1.

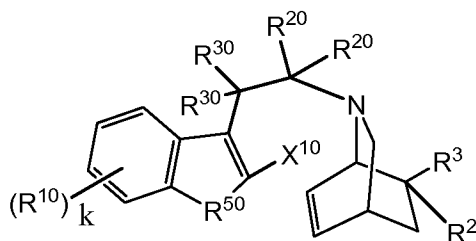
6. The compound of claim 1 of Formula (IV):



(IV)

wherein the variables are defined as in claim 1.

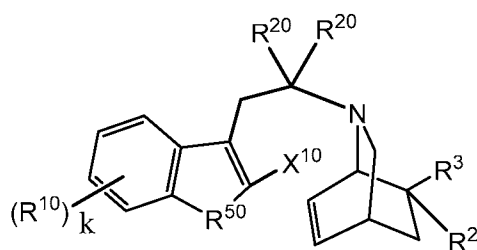
7. The compound of claim 1 of Formula (IVA):



(IVA)

wherein the variables are defined as in claim 1 above.

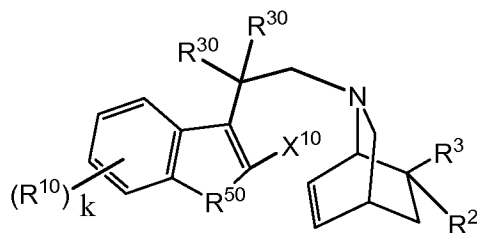
8. The compound of claim 1 of Formula (IVB):



(IVB)

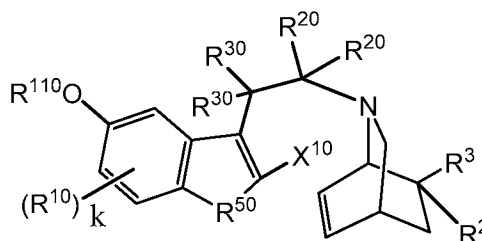
wherein the variables are defined as in claim 1 above.

9. The compound of claim 1 of Formula (IVC):



(IVC).

10. The compound of claim 1 of Formula (VA):



(VA)

wherein R^{110} is selected from the group consisting of

hydrogen;

C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-N_3$, $-CO_2H$ or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

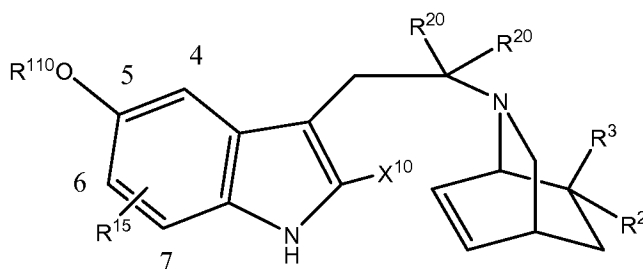
$-COR^{11}$; and

$-CO_2R^{11}$;

k is 0, 1 or 2;

and the remaining variables are defined as in claim 1 above.

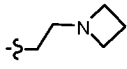
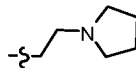
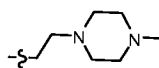
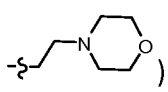
11. The compound of claim 1 of Formula (VB) :

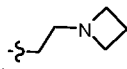
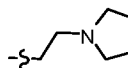
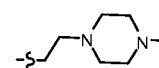
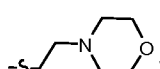


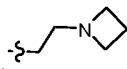



(VB)

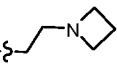
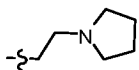
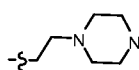
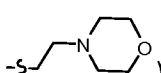
wherein the variables are as tabulated below:

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6- OH, 7-OH, 4- OMe, 6-OMe, or 7-OMe	Bn	C=O	CR^2R^3 is $C=CR^{48}H$, R^{48} is Me, Et, Pr, Bu	--	--
H, 4-Me, 6-Me, 7-Me, 4-OH, 6- OH, 7-OH, 4- OMe, 6-OMe, or 7-OMe	Bn	CH_2	CR^2R^3 is $C=CR^{48}H$, R^{48} is Me, Et, Pr, Bu	--	--

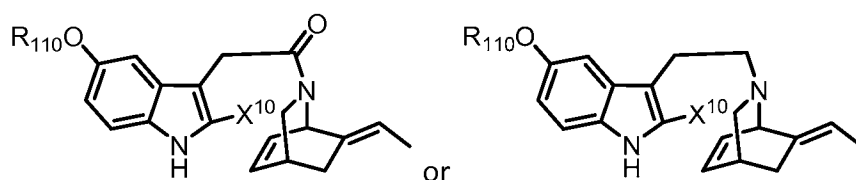
R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	C=O	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g., , , , or )</p>

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g.,</p> <p>$CO_2(CH_2)_2NMe_2$, , , , or )</p>

R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	C=O	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g.,</p> <p>$CO_2(CH_2)_2NMe_2$, ,</p> <p>,</p> <p>,</p> <p>or</p> <p>)</p>

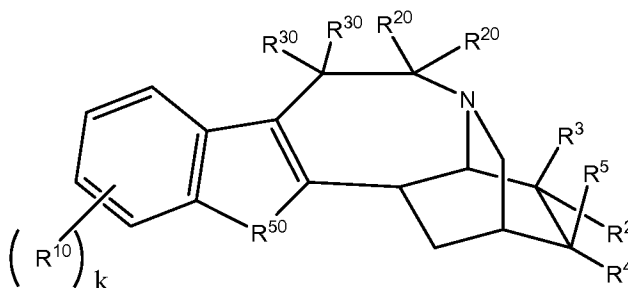
R^{15}	R^{110}	$C(R^{20})_2$	R^2	R^3	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	CH_2	$CH_2CH_2R^{47}$	H	C_1 - C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe , $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH , $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g., $CO_2(CH_2)_2NMe_2$,  ,  ,  , or )

12. The compound of claim 1 of formula;



wherein X^{10} is hydrogen, chloro, bromo, or iodo.

13. A process of preparing a compound of Formula (VI):



or a tautomer thereof or a salt of each thereof wherein

k is 0, 1, 2, or 3;

each R^{10} is independently a substituent selected from the group consisting of halo, amino, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy, and $-CO_2H$ or an ester thereof;

R^{20} is hydrogen or $C(R^{20})_2$ is a keto group;

R^{30} is selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

R^{50} is selected from the group consisting of $-O-$ and $N-R^{51}$; and

R^{51} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

R^4 and R^5 independently are selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10}

aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, vinyl, ethynyl, and CO₂H or an ester thereof;

R² and R³ are independently selected from hydrogen, -CHO, R⁶-C(=O)-, R⁶-CH(OR⁷)-, provided that at least one of R² and R³ is hydrogen; or R² and R³ together with the carbon atom they are bonded to, form a =CHR⁶ moiety;

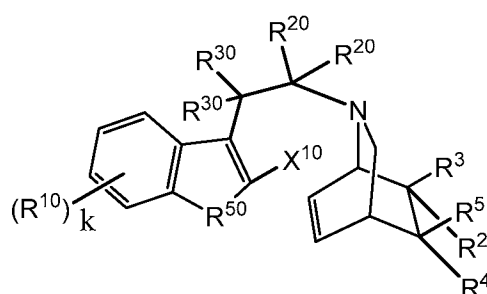
R⁶ is C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl;

R⁷ is hydrogen or SO₂R⁷¹;

R⁷¹ is C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or is C₃-C₈ heterocyclyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl;

wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl, is optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, cycloalkyl, C₂-C₁₀ heteroaryl, C₃-C₈ heterocyclyl, halo, amino, -N₃, hydroxy, C₁-C₆ alkoxy, silyl, nitro, cyano, and CO₂H or an ester thereof;

the process comprising subjecting a compound of Formula(IV):



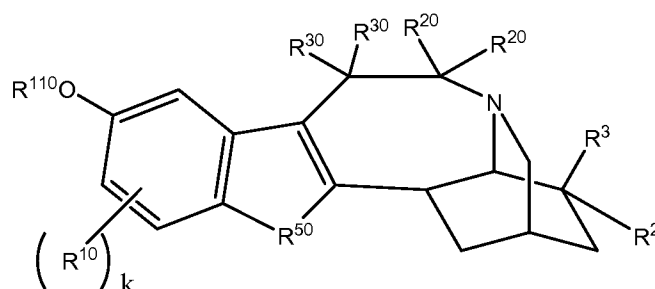
(IV)

wherein X¹⁰ is a leaving group, preferably, halo or -OSO₂R⁷¹, more preferably bromo or iodo and

the remaining variables are defined as above;

to a condition suitable for reductive Heck coupling to provide the compound of Formula (V).

14. The process of claim 13, wherein the compound prepared is of Formula (VIA):



(VIA)

wherein R^{110} is selected from the group consisting of

hydrogen;

C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-N_3$, $-CO_2H$ or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

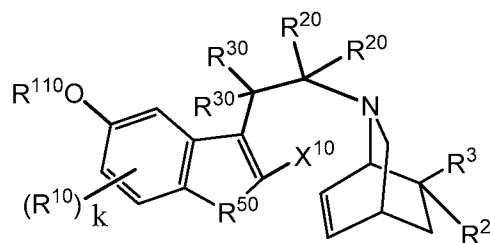
$-COR^{11}$; and

$-CO_2R^{11}$;

k is 0, 1 or 2;

and the remaining variables are defined as in claim 1 above,

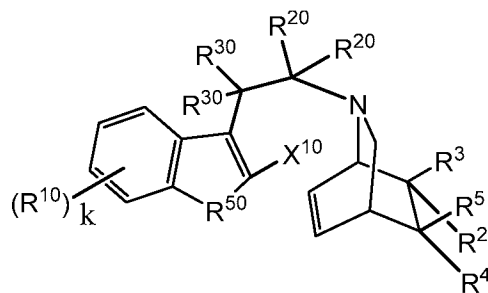
wherein the compound of Formula (VA) is prepared comprising subjecting a compound of Formula (VA):



(VA)

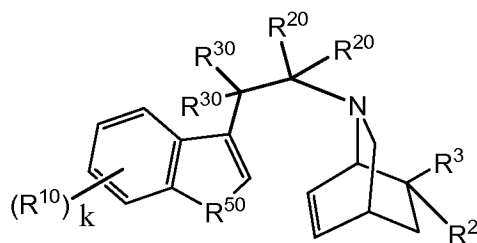
wherein X^{10} is halo, preferably, bromo or iodo, to a condition suitable for reductive Heck coupling to provide the compound of Formula (VIA).

15. The process of claim 13 or 14, wherein the compound of formula (IV):



(IV)

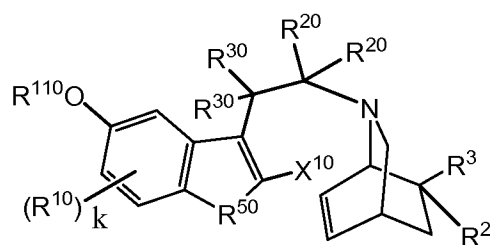
wherein X^{10} is halo is prepared comprising contacting a compound of Formula (VIIA) :



(VIIA)

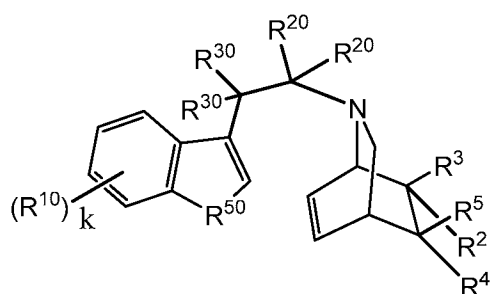
with a halogenating agent under conditions suitable for halogenation to provide the compound of formula (IVA), or

wherein the compound of Formula (VA):



(VA)

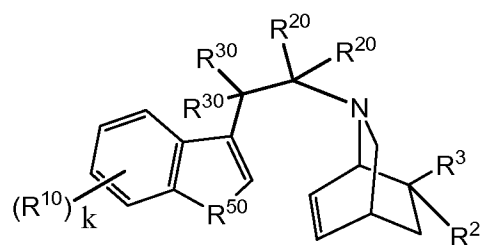
wherein X^{10} is halo is prepared comprising contacting a compound of Formula (VIIB):



(VIIB)

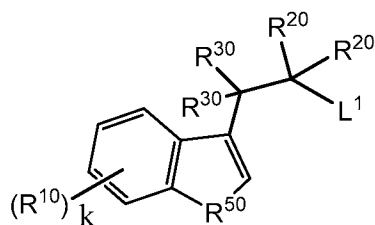
with a halogenating agent under conditions suitable for halogenation to provide the compound of Formula (VA).

16. The process of claim 21, wherein the compound of Formula (VIIA):



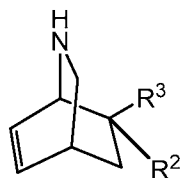
(VIIA)

wherein $C(R^{20})_2$ is $C=O$ is prepared comprising contacting a compound of Formula (VIIIA)



(VIII A)

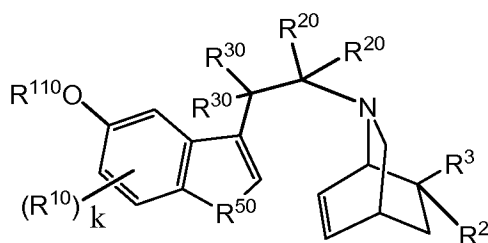
wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

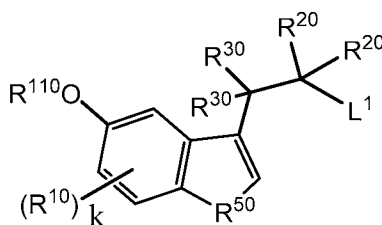
under amide formation conditions to prepare the compound of Formula (VIII A); or

wherein the compound of Formula (VII B):



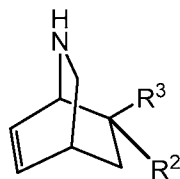
(VII B)

wherein $C(R^{20})_2$ is $C=O$ is prepared comprising contacting a compound of Formula (VIII B)



(VIIB)

wherein L^1 is OH or another leaving group selected from halo, preferably chloro or bromo with a compound of Formula (IX):



(IX)

under amide formation conditions to prepare the compound of Formula (VIIB).

17. The process of any one of claims 13-16, wherein R^4 , R^5 , R^{20} , and R^{30} are hydrogen.
18. The process of any one of claims 13-17, wherein R^{50} is NR^{51} .
19. The process of any one of claims 13-18, wherein R^{50} is NH.
20. The process of any one of claims 13-19, wherein CR^2R^3 is =CHMe.
21. The process of any one of claims 14-20, wherein k is 0 and the indole or the bezofuran phenyl ring is substituted with $-OR^{110}$.
22. The process of any one of claims 14-21, wherein R^{110} is C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy.