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(54) Benævnelse: **FREMGANGSMÅDER TIL FREMSTILLING AF CYTOTOKSISKE BENZODIAZEPINDERIVATER**

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# DESCRIPTION

## FIELD OF THE INVENTION

**[0001]** The present invention relates to novel methods for preparing cytotoxic indolinobenzodiazepine derivatives.

## BACKGROUND OF THE INVENTION

**[0002]** It has been shown that cell-binding agent conjugates of indolinobenzodiazepine dimers that have one imine functionality and one amine functionality display a much higher therapeutic index (ratio of maximum tolerated dose to minimum effective dose) *in vivo* compared to previously disclosed benzodiazepine derivatives having two imine functionalities. See, for example, WO 2012/128868. The previously disclosed method for making the indolinobenzodiazepine dimers with one imine functionality and one amine functionality involves partial reduction of indolinobenzodiazepine dimers having two imine functionalities. The partial reduction step generally leads to the formation of fully reduced by-product and unreacted starting material, which requires cumbersome purification step and results in low yield.

**[0003]** WO 2016/036794 A1 (ImmunoGen, Inc.) describes conjugates comprising cell-binding agents and cytotoxic agents, wherein the cell-binding agent is covalently linked to the cytotoxic agent through an aldehyde group obtained from oxidation of a 2-hydroxy ethylamine moiety on the cell-binding agent; methods of preparing and compositions comprising such conjugates; and methods for inhibiting abnormal cell growth or treating a proliferative disorder in a mammal using such conjugates.

**[0004]** WO 2016/036801 A1 (ImmunoGen, Inc.) describes benzodiazepine derivatives having antiproliferative activity, conjugates of the benzodiazepine compounds linked to a cell-binding agent and compositions and methods useful for inhibiting abnormal growth or treating a proliferative disorder in a mammal using these compounds or conjugates.

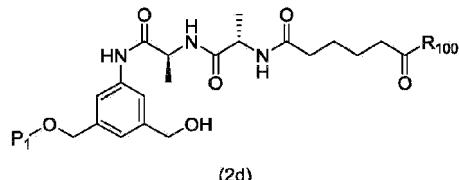
**[0005]** Thus, there exists a need for improved methods for preparing the indolinobenzodiazepine dimers that are more efficient and suitable for large scale manufacturing process.

## SUMMARY OF THE INVENTION

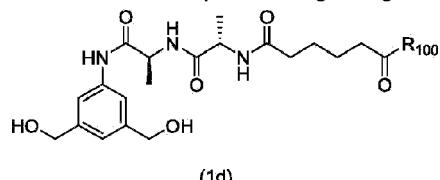
**[0006]** The present invention provides various methods for preparing indolinobenzodiazepine dimer compounds and their synthetic precursors. Compared to the previously disclosed

method, the methods of the present invention can produce the desired dimer compounds with higher yield without the need of cumbersome purification steps. These methods are more suitable for large scale manufacturing process.

**[0007]** In a first disclosure, there is provided a method of preparing a compound of formula (2d),

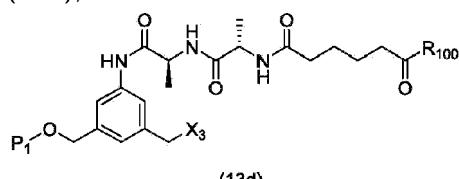


or a salt thereof, said method comprising introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1d) by reacting the compound of formula (1d) with an alcohol protecting reagent,

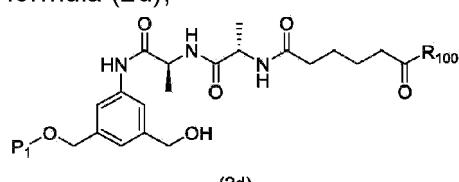


wherein  $P_1$  is the alcohol protecting group; and  $R_{100}$  is  $(C_1-C_3)$ alkoxy.

**[0008]** In a second disclosure, there is provided a method of preparing a compound of formula (13d),

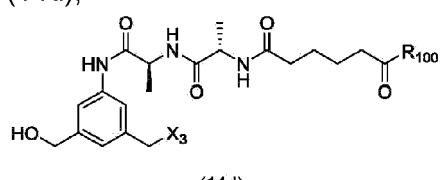


or a salt thereof, said method comprising reacting a chlorinating reagent with a compound of formula (2d),

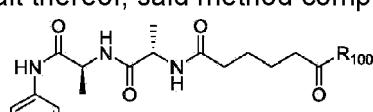


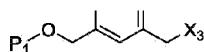
wherein  $P_1$  is an alcohol protecting group;  $X_3$  is  $-Cl$ ; and  $R_{100}$  is  $(C_1-C_3)$ alkoxy.

**[0009]** In a third disclosure, there is provided a method of preparing a compound of formula (14d),



or a salt thereof, said method comprising reacting a compound of formula (13d)

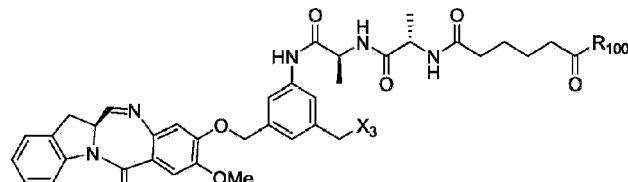




(13d)

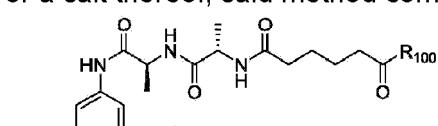
with an alcohol deprotecting reagent, wherein  $P_1$  is an alcohol protecting group;  $X_3$  is -Cl; and  $R_{100}$  is ( $C_1$ - $C_3$ )alkoxy.

**[0010]** In a fourth disclosure, there is provided a method of preparing a compound of formula (16d),



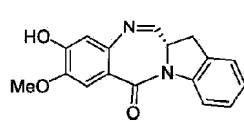
(16d)

or a salt thereof, said method comprising reacting a compound of formula (14d)



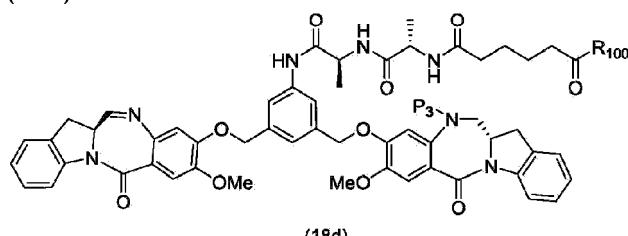
(14d)

with a monomer compound of formula (a<sub>1</sub>),

(a<sub>1</sub>)

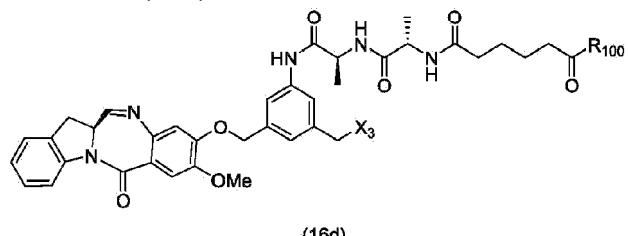
wherein  $X_3$  is -Cl; and  $R_{100}$  is ( $C_1$ - $C_3$ )alkoxy.

**[0011]** In a fifth disclosure, there is provided a method of preparing a compound of formula (18d):



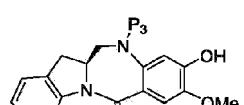
(18d)

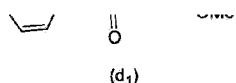
a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula (16d):



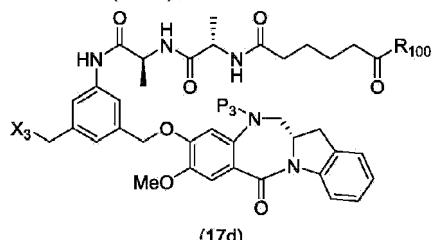
(16d)

with a reduced monomer of formula (d<sub>1</sub>):

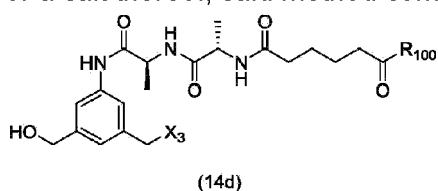




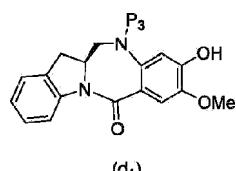
**[0012]** In a first aspect, the present invention provides a method of preparing a compound of formula (17d),



or a salt thereof, said method comprising reacting a compound of formula (14d)

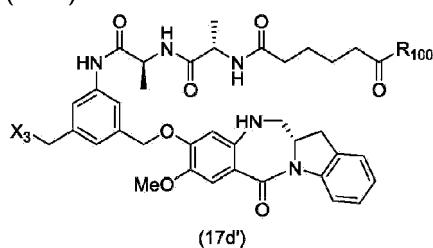


with a monomer compound of formula (d1),

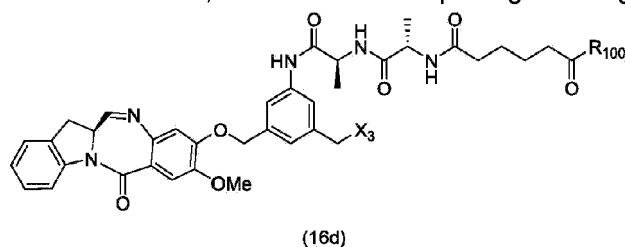


wherein  $X_3$  is  $-Cl$ ;  $P_3$  is H or an amine protecting group; and  $R_{100}$  is  $(C_1-C_3)alkoxy$ .

**[0013]** In a sixth disclosure, there is provided a method of preparing a compound of formula (17d''):



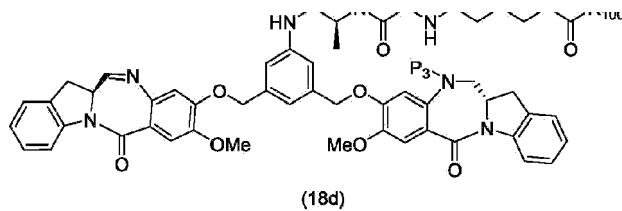
or a salt thereof, said method comprising reacting a compound of formula (16d)



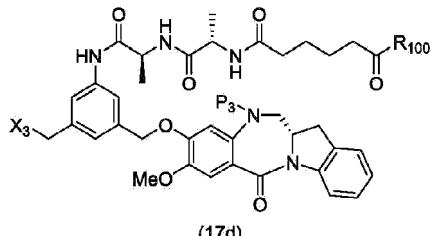
with an imine reducing agent, wherein  $X_3$  is  $-Cl$ ; and  $R_{100}$  is  $(C_1-C_3)alkoxy$ .

**[0014]** In a second aspect, the present invention provides a method of preparing a compound of formula (18d),

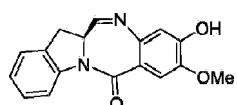




or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula of (17d):



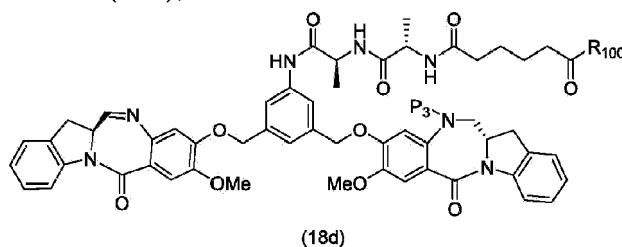
with a monomer of formula (a<sub>1</sub>):



(a<sub>1</sub>)

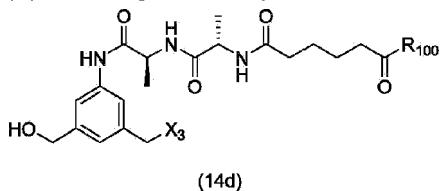
wherein X<sub>3</sub> is -Cl; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0015]** In a third aspect, the present invention provides a method of preparing a compound of formula (18d),

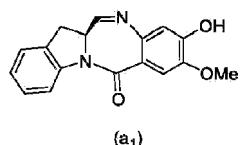


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

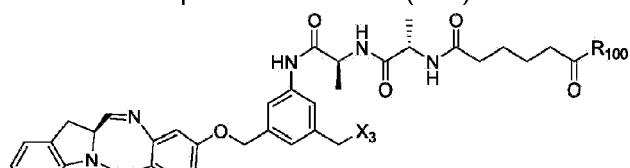
1. (1) reacting the compound of formula (14d):

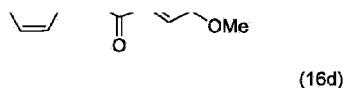


or a salt thereof, with a monomer compound of formula (a<sub>1</sub>),



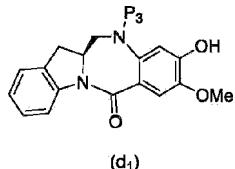
to form a compound of formula (16d):





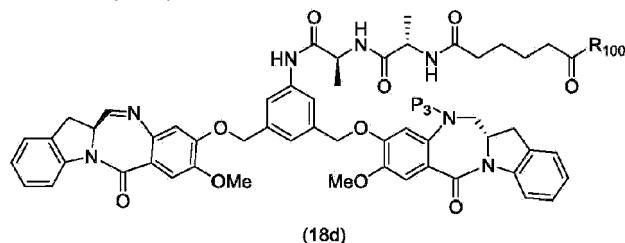
or a salt thereof; and

2. (2) reacting the compound of formula of (16d) with a reduced monomer of formula (d<sub>1</sub>):



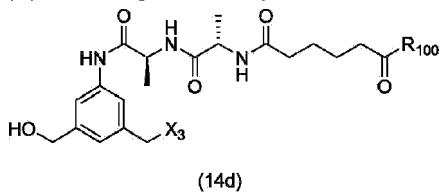
to form a compound of formula (18d), or a pharmaceutically acceptable salt thereof, wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0016]** In a fourth aspect, the present invention provides method of preparing a compound of formula (18d),

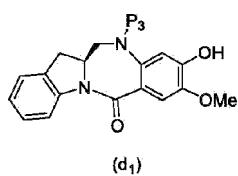


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

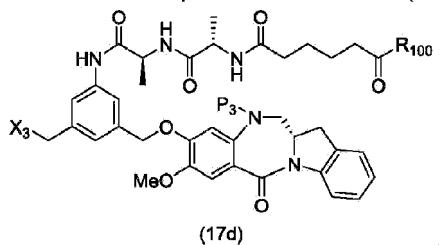
1. (1) reacting the compound of formula (14d):



or a salt thereof, with a reduced monomer compound of formula (d<sub>1</sub>),

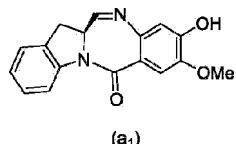


to form a compound of formula (17d):



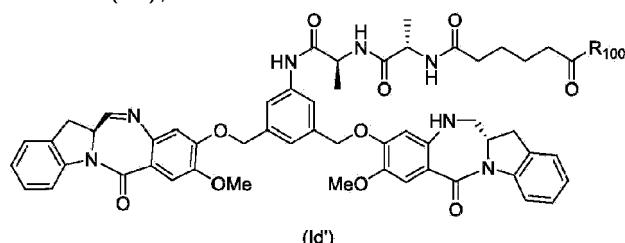
or a salt thereof; and

2. (2) reacting the compound of formula of (17d) with a monomer of formula (a<sub>1</sub>):



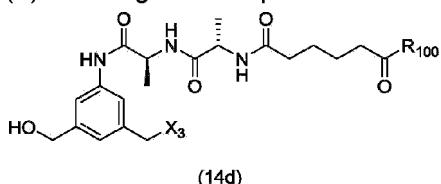
to form a compound of formula (18d), or a pharmaceutically acceptable salt thereof, wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0017]** In a fifth aspect, the present invention provides a method of preparing a compound of formula (Id'),

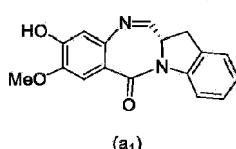


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

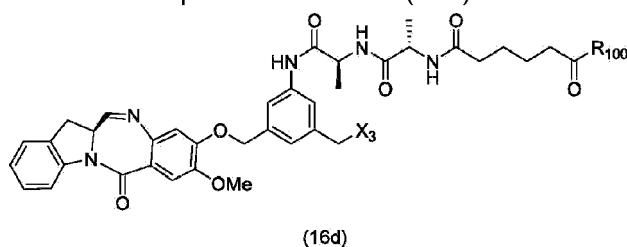
1. (1) reacting the compound of formula (14d):



or a salt thereof, with a monomer compound of formula (a<sub>1</sub>),

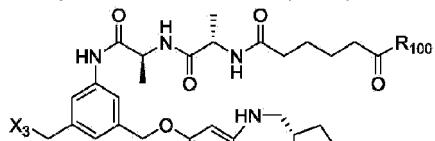


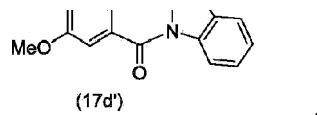
to form a compound of formula (16d):



or a salt thereof;

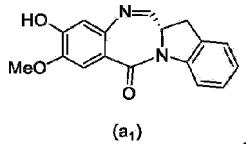
2. (2) reacting the compound of formula (16d) with an imine reducing agent to form a compound of formula (17d'):





or a salt thereof; and

3. (3) reacting the compound of formula (17d') with a monomer of formula (a<sub>1</sub>):



to form the compound of formula (Id'); wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

## BRIEF DESCRIPTION OF THE FIGURES

[0018] FIGs. 1-13 show exemplary schemes for the methods of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

[0019] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention.

[0020] It should be understood that any of the embodiments described herein can be combined with one or more other embodiments of the invention, unless explicitly disclaimed or improper. Combination of embodiments are not limited to those specific combinations claimed via the multiple dependent claims.

## DEFINITIONS

[0021] "Alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twenty carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, 2-butyl, 2-methyl-2-propyl, 1-pentyl, 2-pentyl 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-

butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, 1-heptyl, 1-octyl, and the like. Preferably, the alkyl has one to ten carbon atoms. More preferably, the alkyl has one to four carbon atoms.

**[0022]** "Aryl" means a monovalent aromatic hydrocarbon radical of 6-18 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar." Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Preferably, aryl is phenyl group.

**[0023]** The term "halo" or "halogen" refers to F, Cl, Br or I. In one embodiment, the halogen is Br or I.

**[0024]** The term "**compound**" or "**cytotoxic compound**," "**cytotoxic dimer**" and "**cytotoxic dimer compound**" are used interchangeably. They are intended to include compounds for which a structure or formula or any derivative thereof has been disclosed in the present invention. The term also includes, stereoisomers, geometric isomers, tautomers, solvates, metabolites, salts (e.g., pharmaceutically acceptable salts) and prodrugs, and prodrug salts of a compound of all the formulae disclosed in the present invention. The term also includes any solvates, hydrates, and polymorphs of any of the foregoing. The specific recitation of "stereoisomers," "geometric isomers," "tautomers," "solvates," "metabolites," "salt" "prodrug," "prodrug salt," "conjugates," "conjugates salt," "solvate," "hydrate," or "polymorph" in certain aspects of the invention described in this application shall not be interpreted as an intended omission of these forms in other aspects of the invention where the term "compound" is used without recitation of these other forms.

**[0025]** The term "**precursor**" of a given group refers to any group which may lead to that group by any deprotection, a chemical modification, or a coupling reaction.

**[0026]** The term "**chiral**" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "**achiral**" refers to molecules which are superimposable on their mirror image partner.

**[0027]** The term "**stereoisomer**" refers to compounds which have identical chemical constitution and connectivity, but different orientations of their atoms in space that cannot be interconverted by rotation about single bonds.

**[0028]** "**Diastereomer**" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of

diastereomers may separate under high resolution analytical procedures such as crystallization, electrophoresis and chromatography.

**[0029]** "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

**[0030]** Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

**[0031]** The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

**[0032]** As used herein, the term "imine reducing reagent" refers to a reagent that is capable of reducing an imine functional group to an amine functional group. In certain embodiments, the imine reducing reagent is a hydride reducing reagent. Examples of such imine reducing reagents include, but are not limited to, borohydrides (e.g., sodium borohydride, sodium triacetoxy borohydride, sodium cyanoborohydride, lithium borohydride (LiBH<sub>4</sub>), potassium borohydride (KBH<sub>4</sub>)), hydrogen gas, and lithium aluminum hydride, ammonium formate, borane, 9-borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminium hydride (DIBAL), and sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al). In certain embodiments, the imine reducing reagent is sodium triacetoxy borohydride.

**[0033]** The term "protecting group" or "protecting moiety" refers to a substituent that is

commonly employed to block or protect a particular functionality while reacting other functional groups on the compound, a derivative thereof, or a conjugate thereof. For example, an "amine protecting group" or an "amino-protecting moiety" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Such groups are well known in the art (see for example P. Wuts and T. Greene, 2007, Protective Groups in Organic Synthesis, Chapter 7, J. Wiley & Sons, NJ) and exemplified by carbamates such as methyl and ethyl carbamate, FMOC, substituted ethyl carbamates, carbamates cleaved by 1,6- $\beta$ -elimination (also termed "self immolative"), ureas, amides, peptides, alkyl and aryl derivatives. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc), 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, or 2,2,2-trichloroethoxycarbonyl. For a general description of protecting groups and their use, see P. G.M. Wuts & T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 2007.

**[0034]** An "alcohol protecting group" or an "alcohol-protecting moiety" is a substituent attached to an alcohol group that blocks or protects the alcohol functionality in the compound. Such groups are well known in the art (see for example, P. Wuts and T. Greene, 2007, Protective Groups in Organic Synthesis, Chapter 2, J. Wiley & Sons, NJ). Suitable alcohol protecting group include, but are not limited to, pivaloyl, methoxymethyl, 2-methoxyethoxymethyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, diphenylmethyl, benzyloxymethyl, 2,2,2-trichloroethoxycarbonyl, tetrahydrofuranyl, tetrahydropyranyl, benzyl, benzoyl, *para*-phenylbenzoyl, 2,4,6-trimethylbenzoyl, *para*-bromobenzoyl, *para*-nitro benzoyl, picolinoyl, nicotinoyl, 5-dibenzosuberyl, trityl/triphenylmethyl, or tris(4-*tert*-butylphenyl)methyl and various silyl protecting groups (for example, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl). In certain embodiments, the alcohol protecting group is sterically hindered. In certain embodiments, the alcohol protecting group is preferably methoxymethyl, tetrahydropyranyl, 2-methoxyethoxymethyl, *p*-methoxybenzyl, benzyloxymethyl, or 2,2,2-trichloroethoxycarbonyl. More preferably, the alcohol protecting group is 2,2,2-trichloroethoxycarbonyl. In certain embodiments, the alcohol protecting group is a silyl protecting group, preferably, triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl. More preferably, the alcohol protecting group is *tert*-butyldimethylsilyl.

**[0035]** An "alcohol protecting reagent" as used herein refers to a reagent that introduces an alcohol protecting group onto an alcohol group.

**[0036]** An "acid labile alcohol protecting group" is an alcohol protecting group that is not stable under acidic condition and releases the alcohol protecting group to form free alcohol. Examples of an acid labile alcohol protecting group include, but are not limited to, acetate, allyl, methoxymethyl, tetrahydrofuranyl, tetrahydropyranyl, 5-dibenzosuberyl, 1-ethoxyethyl, 1-

methyl-1methoxylethyl, 2-(phenylselenyl)ethyl, trityl/triphenylmethyl, tris(4-*tert*-butylphenyl)methyl, and various silyl protecting group (for example, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl). In certain embodiments, the alcohol protecting group is a silyl protecting group, preferably, triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl. More preferably, the alcohol protecting group is *tert*-butyldimethylsilyl.

**[0037]** As used herein, the term "**alcohol deprotecting reagent**" refers to a reagent that is capable of cleaving an alcohol protecting group to form free alcohol. Such reagents are well known in the art (see for example P. Wuts and T. Greene, 2007, Protective Groups in Organic Synthesis, Chapter 2, J. Wiley & Sons, NJ). Examples of such alcohol deprotecting reagents include, but are not limited to, tetra-*n*-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethylsilicate, hydrogen fluoride or a solvate thereof, hydrogen fluoride pyridine, silicon tetrafluoride, hexafluorosilicic acid, cesium fluoride, hydrochloric acid, acetic acid, trifluoroacetic acid, pyridinium p-toluenesulfonate, p-toluenesulfonic acid (p-TsOH), formic acid, periodic acid. In certain embodiments, the alcohol deprotecting reagent is hydrochloric acid or tetra-*n*-butylammonium fluoride (TBAF). In certain embodiments, the alcohol deprotecting agent is hydrogen fluoride-pyridine (HF-pyridine).

**[0038]** As used herein, "**amine deprotecting group**" refers a reagent that is capable of cleaving an amine protecting group to form free amine. Such reagents are well known in the art (see for example P. Wuts and T. Greene, 2007, Protective Groups in Organic Synthesis, Chapter 7, J. Wiley & Sons, NJ). Examples of such amine deprotecting reagents include, but are not limited to, tetra-*n*-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

**[0039]** As used herein, "**alcohol activating agent**" refers a reagent that increases the reactivity of a hydroxyl group thereby making the hydroxyl group a better leaving group. Examples of such alcohol activating agents include p-toluenesulfonyl chloride, thionyl chloride, triflic anhydride, mesyl chloride, mesyl anhydride, triphenylphosphine, acyl chloride, 4-dimethylaminopyridine, and others. In certain embodiments, the alcohol activating agent is thionyl chloride. In certain embodiment, the alcohol activating agent is triphenylphosphine.

**[0040]** The phrase "**pharmaceutically acceptable salt**" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate," ethanesulfonate, benzenesulfonate, p-toluenesulfonate, pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts, alkali metal (*e.g.*, sodium and potassium) salts, alkaline earth metal (*e.g.*, magnesium) salts, and ammonium salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an

acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

**[0041]** If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

**[0042]** If the compound of the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

**[0043]** The phrase "**pharmaceutically acceptable**" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

**[0044]** The term "**leaving group**" refers to a group of charged or uncharged moiety that departs during a nucleophilic substitution or displacement. Such leaving groups are well known in the art and include, but not limited to, halogens, esters, alkoxy, hydroxyl, tosylates, triflates, mesylates, nitriles, azide, carbamate, disulfides, thioesters, thioethers and diazonium compounds.

**[0045]** As used herein, the term "**halogenating reagent**" refers to a reagent that converts an alcohol group to a halide group. A "**brominating reagent**" is a reagent that converts an alcohol group to a bromide group. A "**iodinating reagent**" is a reagent that converts an alcohol group to a iodide group. A "**chlorinating reagent**" is a reagent that converts an alcohol group to a chloride group. Exemplary brominating reagents include, but are not limited to, bromine, hydrobromic acid, carbon tetrabromide, phosphorus tribromide, and potassium bromide. Exemplary iodinating reagent include, but are not limited to, hydroiodic acid, iodine, carbon tetr碘ide, phosphorus triiodide, sodium iodide, or potassium iodide. Exemplary chlorinating

reagent include, but are not limited to, carbon tetrachloride, methanesulfonyl chloride, sulfonyl chloride, thionyl chloride, cyanuric chloride, *N*-chlorosuccinimide, phosphorus(V) oxychloride, phosphorus pentachloride, and phosphorus trichloride. In a specific embodiment, the chlorinating reagent is methanesulfonyl chloride.

**[0046]** As used herein, a "sulfonating reagent" refers to a reagent that converts an alcohol group to a sulfonate ester group. Preferably, the sulfonating reagent is a sulfonic anhydride, such as methanesulfonic anhydride, or a sulfonic chloride, such as methanesulfonyl chloride (MsCl).

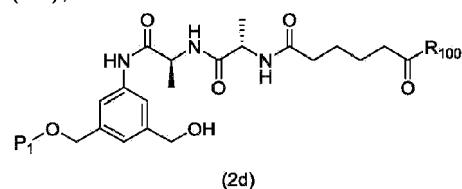
**[0047]** As used herein, an "activated ester" refers to an ester group that is readily displaced by a hydroxyl or an amine group. Exemplary activated esters include, but are not limited to nitrophenyl (e.g., 2 or 4-nitrophenyl) ester, dinitrophenyl (e.g., 2,4-dinitrophenyl) ester, sulfo-tetrafluorophenyl (e.g., 4-sulfo-2,3,5,6-tetrafluorophenyl) ester, pentafluorophenyl ester, nitropyridyl (e.g., 4-nitropyridyl) ester, trifluoroacetate, and acetate.

**[0048]** As used herein, an "esterification reagent" refers to a reagent that converts an alcohol group to an ester group. Exemplary esterification reagent include, but are not limited to, nitrobenzoid acid (e.g., 2 or 4-nitrobenzoic acid), dinitrobenzoid acid (e.g., 2,4-dinitrobenzoic acid), sulfo-tetrafluorobenzoid acid (e.g., 4-sulfo-2,3,5,6-tetrafluorobenzoic acid), pentafluorobenzoic acid, nitropyridine carboxylic acid (e.g., 4-nitro-2-pyridine carboxylic acid, trifluoroacetic acid, and acetic acid, or acyl chloride, acid anhydride or other activated carboxylic acid derivatives thereof.

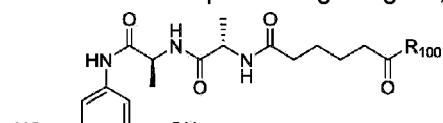
## METHODS OF THE PRESENT INVENTION

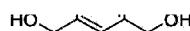
**[0049]** The present invention provides novel methods for preparing indolinobenzodiazepine dimer compounds that have one imine functionality and one amine functionality. As compared to the methods known in the art, the present methods can produce the desired dimer compounds with higher yield and without the use of HPLC purification.

**[0050]** In the first disclosure, there is provided a method of preparing a compound of formula (2d),



or a salt thereof, said method comprising introducing an alcohol protecting group onto one of the primary alcohols of a compound of formula (1d) by reacting the compound of formula (1d) with an alcohol protecting reagent,





(1d)

wherein P<sub>1</sub> is the alcohol protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0051]** Specific methods of preparing compound of formula (2d) described above the alcohol protecting group is sterically hindered.

**[0052]** In another specific method, the alcohol protecting group is pivaloyl, methoxymethyl, 2-methoxyethoxymethyl, *p*-methoxybenzyl, 3,4-dimethyoxybenzyl, 2,6-dimethyoxybenzyl, diphenylmethyl, benzyloxymethyl, 2,2,2-trichloroethoxycarbonyl, tetrahydrofuranyl, tetrahydropyranyl, benzyl, benzoyl, *para*-phenylbenzoyl, 2,4,6-trimethylbenzoyl, *para*-bromobenzoyl, *para*-nitrobenzoyl, picolinoyl, nicotinoyl, 5-dibenzosuberyl, trityl/triphenylmethyl, or tris(4-*tert*-butylphenyl)methyl. Preferably, the alcohol protecting group is methoxymethyl, tetrahydropyranyl, 2-methoxyethoxymethyl, *p*-methoxybenzyl, benzyloxymethyl, or 2,2,2-trichloroethoxycarbonyl. Even more preferably, the alcohol protecting group is 2,2,2-trichloroethoxycarbonyl.

**[0053]** In another specific method, the alcohol protecting group is a silyl protecting group. For example, the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethylethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl. Preferably, the silyl protecting group is triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl. More preferably, the silyl protecting group is *tert*-butyldimethylsilyl.

**[0054]** The silyl protecting group can be introduced by reacting the compound of formula (1d) with R<sup>3</sup>-Cl, R<sup>3</sup>-Br, R<sup>3</sup>-I or R<sup>3</sup>-OSO<sub>2</sub>CF<sub>3</sub> (collectively the alcohol protecting reagent) in the presence of a base, wherein R<sup>3</sup> is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or [2-(trimethylsilyl)ethoxy]methyl. The molar ratio of the alcohol protecting reagent to the compound of formula (1d) may be between 0.8-1.2, between 1 to 5, between 1 to 2, between 1 to 1.5, between 1 to 1.4, between 1 to 1.3, between 1 to 1.2, or between 1 to 1.1. Less than 2 molar equivalents of the alcohol protecting reagent may be used relative to the compound of formula (1d). Preferably, 1.5, 1.4, 1.3, 1.2, 1.1 or 1.0 molar equivalent of the alcohol protecting reagent relative to the compound of formula (1d) is used.

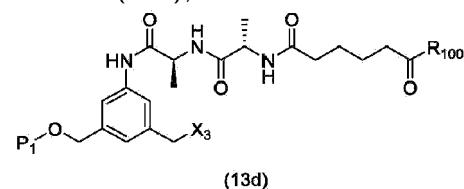
**[0055]** The base may be a non-nucleophilic base. Examples of non-nucleophilic base include, but are not limited to, imidazole, triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, 1,8-diazabicycloundec-7-ene, or tetramethylpiperidine. Preferably, the non-nucleophilic base is imidazole. Molar excess amount of the base can be used. More than 2 molar equivalents of the base (e.g., non-nucleophilic base) may be used relative to the compound of formula (1d).

**[0056]** The reaction between the compound of formula (1d) and R<sup>3</sup>-Cl, R<sup>3</sup>-Br, R<sup>3</sup>-I or R<sup>3</sup>-OSO<sub>2</sub>CF<sub>3</sub> may be carried out in the presence of a catalyst that facilitates the introduction of the silyl protecting group. Any suitable catalysts known in the art (see, for example, P. Wuts and T. Greene, 2007, Protective Groups in Organic Synthesis, Chapter 2, J. Wiley & Sons, NJ) can be used in the reaction. Exemplary catalysts include, but are not limited to, 4-dimethylaminopyridine (DMAP), 1,1,3,3-tetramethylguanidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

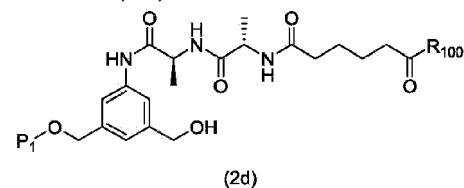
**[0057]** Any suitable organic solvents can be used for the methods of the first disclosure. Exemplary solvents include, but are not limited to, DMF, CH<sub>2</sub>Cl<sub>2</sub>, dichloroethane, THF, dimethylacetamide, etc. In certain methods, DMF is used as the solvent.

**[0058]** In another specific method, the method of preparing the compound of formula (2d) comprises reacting the compound of (1d) with TBSCl in the presence of a non-nucleophilic base. The base may be imidazole or DIPEA. In a specific method, the base is imidazole. In another specific method, the base is DIPEA.

**[0059]** In the second disclosure, there is provided a method of preparing a compound of formula (13d),



or a salt thereof, said method comprising reacting a chlorinating reagent with a compound of formula (2d),



wherein P<sub>1</sub> is an alcohol protecting group; X<sub>3</sub> is -Cl; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0060]** In specific methods of the second disclosure, the alcohol protecting group is pivaloyl, methoxymethyl, 2-methoxyethoxymethyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, diphenylmethyl, benzyloxymethyl, 2,2,2-trichloroethoxycarbonyl, tetrahydrofuranyl, tetrahydropyranyl, benzyl, benzoyl, para-phenylbenzoyl, 2,4,6-trimethylbenzoyl, para-bromobenzoyl, para-nitrobenzoyl, picolinoyl, nicotinoyl, 5-dibenzosuberyl, trityl/triphenylmethyl, or tris(4-*tert*-butylphenyl)methyl. Preferably, the alcohol protecting group is methoxymethyl, tetrahydropyranyl, 2-methoxyethoxymethyl, p-methoxybenzyl, benzyloxymethyl, or 2,2,2-trichloroethoxycarbonyl. Even more preferably, the alcohol protecting group is 2,2,2-trichloroethoxycarbonyl.

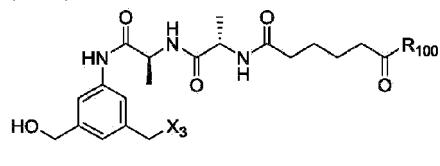
**[0061]** In another specific method, the alcohol protecting group is a silyl protecting group. For example, the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl,

dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, 2-trimethyethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl. Preferably, the silyl protecting group is triethylsilyl, triisopropylsilyl, or *tert*-butyldimethylsilyl. More preferably, the silyl protecting group is *tert*-butyldimethylsilyl.

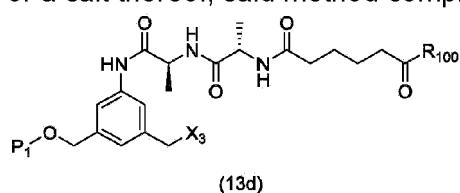
**[0062]** In one method, the base is used. The base can be a non-nucleophilic base. Examples of non-nucleophilic base include, but are not limited to, triethylamine, imidazole, diisopropylethylamine (DIPEA), pyridine, 2,6-lutidine, dimethylformamide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or tetramethylpiperidine. Preferably, the non-nucleophilic base is pyridine.

**[0063]** Any suitable organic solvents can be used for the methods of the second disclosure. Exemplary solvents include, but are not limited to, DMF,  $\text{CH}_2\text{Cl}_2$ , dichloroethane, THF, dimethylacetamide, etc. In certain methods, DMF is used as the solvent.

**[0064]** In the third disclosure, there is provided a method of preparing a compound of formula (14d),



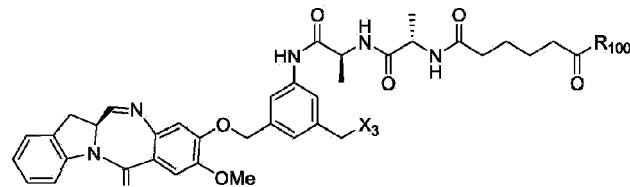
or a salt thereof, said method comprising reacting a compound of formula (13d)



with an alcohol deprotecting reagent, wherein  $P_1$  is an alcohol protecting group;  $X_3$  is -Cl; and  $R_{100}$  is ( $C_1-C_3$ )alkoxy.

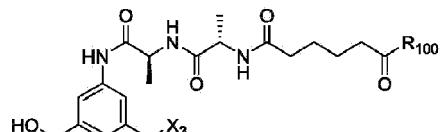
**[0065]** In a specific method of the third disclosure, the alcohol deprotecting reagent is tetra-*n*-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethylsilicate, hydrogen fluoride or a solvate thereof, hydrogen fluoride pyridine, silicon tetrafluoride, hexafluorosilicic acid, cesium fluoride, hydrochloric acid, acetic acid, trifluoroacetic acid, pyridinium p-toluenesulfonate, p-toluenesulfonic acid (p-TsOH), formic acid, or periodic acid. Preferably, the alcohol deprotecting reagent is hydrogen fluoride pyridine.

**[0066]** In the fourth disclosure, there is provided a method of preparing a compound of formula (16d),

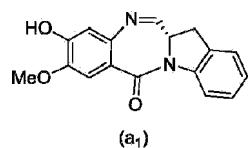




or a salt thereof, said method comprising reacting a compound of formula (14d)



with a monomer compound of formula (a<sub>1</sub>),



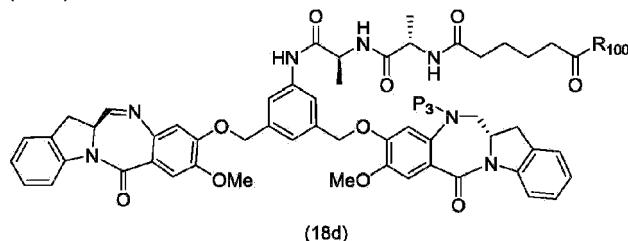
wherein X<sub>3</sub> is -Cl; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0067]** In a specific method of the fourth disclosure, the compound of formula (14d) is reacted with a monomer of formula (a<sub>1</sub>) in the presence of an alcohol activating agent. In one method, the alcohol activating agent is a trialkylphosphine, triarylphosphine, or triheteroarylphosphine. In a specific method, the alcohol activating agent is trimethylphosphine, tributylphosphine, tri(o-tolyl)phosphine, tri(m-tolyl)phosphine, tri(p-tolyl)phosphine, tri(2-pyridyl)phosphine, tri(3-pyridyl)phosphine, tri(4-pyridyl)phosphine, or [4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecyl)phenyl] diphenylphosphine. In another method, the alcohol activating agent can be a phosphine-like reagent, such as (tributylphosphoranylidene)acetonitrile, (cyanomethylene)tributylphosphorane (CMBP), or (cyanomethylene)trimethylphosphorane (CMMP). In a more specific method, the alcohol activating agent is triphenylphosphine. In one method, the alcohol activating agent can be polymer-bound or polymer-supported, such as polymer-bound or polymer-supported trialkyl phosphine, triarylphosphine (e.g., triphenylphosphine), or triheteroarylphosphine.

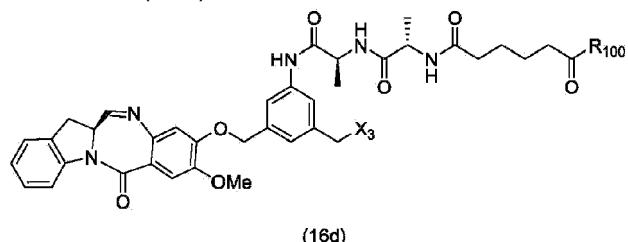
**[0068]** In another specific method of the fourth disclosure, the compound of formula (14d) is reacted with a monomer of formula (a<sub>1</sub>) in the presence of an azodicarboxylate. In one method, the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), ditertbutyl azodicarboxylate (DTAD), 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD), di-(4-chlorobenzyl)azodicarboxylate (DCAD), azodicarboxylic dimorpholide, N,N,N',N'-tetramethylazodicarboxamide (TMAD), N,N,N',N'- tetraisopropylazodicarboxamide (TIPA), 4,4'-azopyridine, bis (2,2,2-trichloroethyl) azodicarboxylate, o-(tert-Butyldimethylsilyl)-N-tosylhydroxylamine, di-(4-chlorobenzyl)azodicarboxylate, cyclic 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD), dimethyl acetylenedicarboxylate (DMAD), di-2-methoxyethyl azodicarboxylate, di-(4-chlorobenzyl)azodicarboxylate and bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoronyl) azodicarboxylate. More specifically, the azodicarboxylate is DIAD. In one method, the azodicarboxylate is polymer-bound or polymer supported, such as polymer-supported alkylazodicarboxylate (e.g. polymer-bound DEAD, DIAD, DTAD or ADDP).

**[0069]** In yet other specific methods of the fourth disclosure, the compound of formula (14d) is reacted with a monomer of formula (a<sub>1</sub>) in the presence of triphenylphosphine and an azodicarboxylate. In one method, the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and ditertbutyl azodicarboxylate (DTAD). More specifically, the azodicarboxylate is DIAD.

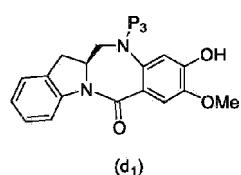
**[0070]** In the fifth disclosure, there is provided a method of preparing a compound of formula (18d):



a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of formula of (16d):



with a reduced monomer of formula (d<sub>1</sub>):

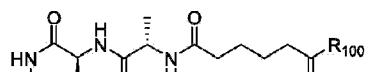


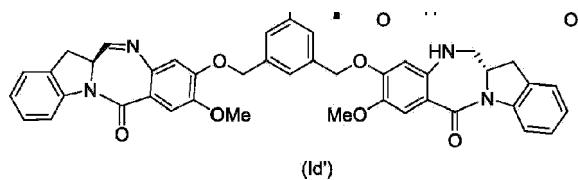
wherein X<sub>3</sub> is -Cl; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0071]** In one method of the fifth disclosure, the reaction between the compound of formula (16d) and the reduced monomer of formula (d<sub>1</sub>) is carried out in the presence of a base. In specific method, the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride. Preferably, the base is potassium carbonate.

**[0072]** Any suitable organic solvents can be used for the methods of the fifth disclosure. In one method, the solvent is a polar aprotic solvent. Exemplary solvents include, but are not limited to, dimethylformamide (DMF), CH<sub>2</sub>Cl<sub>2</sub>, dichloroethane, THF, dimethylacetamide, etc. In certain methods, dimethylformamide or dimethylacetamide is used as the solvent.

**[0073]** In a specific method of the fifth disclosure, the compound of formula (16d) is reacted with reduced monomer of formula (d<sub>1</sub>), wherein P<sub>3</sub> is H, to form a compound of formula (Id'):



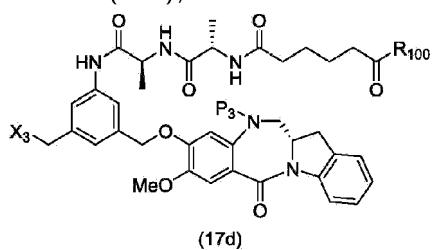


**[0074]** In another method of the fifth disclosure,  $P_3$  is an amine protecting group. Any suitable amine protecting group can be used in the method described above. In one method, the amine protecting group is 2-trimethylsilylethyl, (2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, or 2, 2,2,2-trichloroethoxycarbonyl.

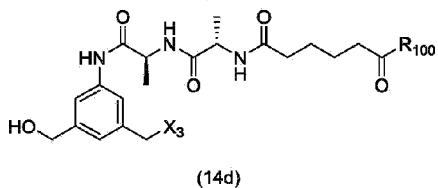
**[0075]** When  $P_3$  is an amine protecting group, the compound of formula (18d) is further reacted with an amine deprotecting reagent to form a compound of formula (Id').

**[0076]** Examples of suitable amine deprotecting reagents include, but are not limited to, those selected from the group consisting of tetra-n-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

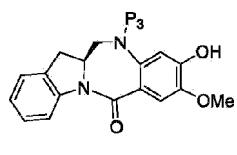
**[0077]** The first aspect of the present invention provides a method of preparing a compound of formula (17d),



or a salt thereof, said method comprising reacting a compound of formula (14d)



with a monomer compound of formula (d<sub>1</sub>),



wherein  $X_3$  is -Cl;  $P_3$  is H or an amine protecting group; and  $R_{100}$  is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

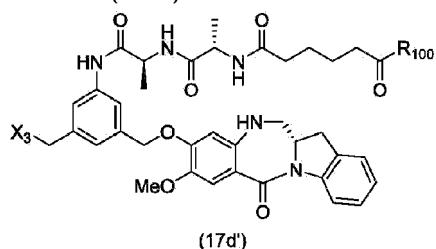
**[0078]** In a specific embodiment, for methods of the first aspect, the compound of formula (14d) is reacted with a monomer of formula (d<sub>1</sub>) in the presence of an alcohol activating agent. In a specific embodiment, the alcohol activating agent is trimethylphosphine, tributylphosphine, tri(o-tolyl)phosphine, tri(m-tolyl)phosphine, tri(p-tolyl)phosphine, tri(2-pyridyl)phosphine, tri(3-

pyridyl)phosphine, tri(4-pyridyl)phosphine, or [4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)phenyl] diphenylphosphine. In another embodiment, the alcohol activating agent can be a phosphine-like reagent, such as (tributylphosphoranylidene)acetonitrile, (cyanomethylene)tributylphosphorane (CMBP), or (cyanomethylene)trimethylphosphorane (CMMP). In a more specific embodiment, the alcohol activating agent is triphenylphosphine. In one embodiment, the alcohol activating agent can be polymer-bound or polymer-supported, such as polymer-bound or polymer-supported trialkyl phosphine, triarylphosphine (e.g., triphenylphosphine), or triheteroarylphosphine.

**[0079]** In another specific embodiment, for methods of the first aspect, the compound of formula (14d) is reacted with a monomer of formula (d<sub>1</sub>) in the presence of an azodicarboxylate. In one embodiment, the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), ditertbutyl azodicarboxylate (DTAD), 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD), di-(4-chlorobenzyl)azodicarboxylate (DCAD), azodicarboxylic dimorpholide, N,N,N',N'-tetramethylazodicarboxamide (TMAD), N,N,N',N'-tetraisopropylazodicarboxamide (TIPA), 4,4'-azopyridine, bis (2,2,2-trichloroethyl) azodicarboxylate, o-(tert-Butyldimethylsilyl)-N-tosylhydroxylamine, di-(4-chlorobenzyl)azodicarboxylate, cyclic 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD), dimethyl acetylenedicarboxylate (DMAD), di-2-methoxyethyl azodicarboxylate, di-(4-chlorobenzyl)azodicarboxylate and bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoronyl) azodicarboxylate, . More specifically, the azodicarboxylate is DIAD. In one embodiment, the azodicarboxylate is polymer-bound or polymer supported, such as polymer-supported alkylazodicarboxylate (e.g. polymer-bound DEAD, DIAD, DTAD or ADDP).

**[0080]** In yet another specific embodiment, for methods of the first aspect, the compound of formula (14d) is reacted with a monomer of formula (d<sub>1</sub>) in the presence of triphenylphosphine and an azodicarboxylate. In one embodiment, the azodicarboxylate is selected from the group consisting of: diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and ditertbutyl azodicarboxylate (DTAD). More specifically, the azodicarboxylate is DIAD.

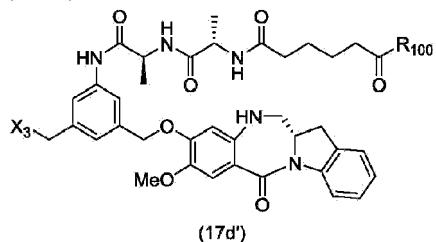
**[0081]** In yet another specific embodiment of the first aspect, P<sub>3</sub> is H and the compound of formula (14d) is reacted with the monomer compound of formula (d<sub>1</sub>) to form a compound of formula (17d'):



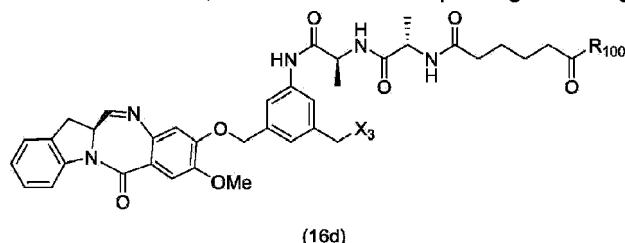
**[0082]** In another specific embodiment of the first aspect,  $P_3$  is an amine protecting group and the method further comprises the step of reacting the compound of formula (17d) with an amine deprotecting reagent to form a compound of formula (17d').

**[0083]** Examples of suitable amine deprotecting reagent include, but are not limited to, the amine deprotecting reagent is selected from the group consisting of tetra-n-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

**[0084]** In the sixth disclosure, there is provided a method of preparing a compound of formula (17d'):



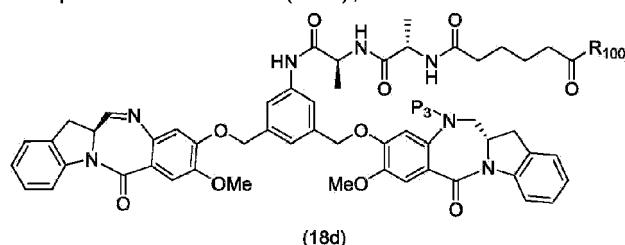
or a salt thereof, said method comprising reacting a compound of formula (16d)



with an imine reducing agent, wherein  $X_3$  is  $-Cl$ ; and  $R_{100}$  is  $(C_1-C_3)alkoxy$ .

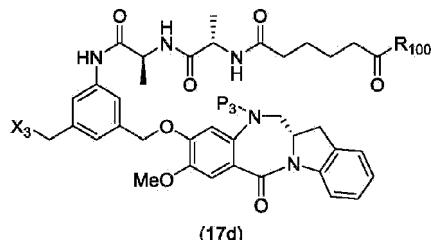
**[0085]** In one specific method, for methods of the sixth disclosure, the imine reducing agent is a hydride reducing agent. Examples of suitable hydride reducing agents include, but are not limited to, sodium borohydride, sodium triacetoxy borohydride, sodium cyanoborohydride, lithium aluminum hydride, hydrogen gas, ammonium formate, borane, 9-borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminium hydride (DIBAL), lithium borohydride ( $LiBH_4$ ), potassium borohydride ( $KBH_4$ ), or sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al). In one particular method, the hydride reducing agent is sodium triacetoxy borohydride ( $NaBH(OAc)_3$ ).

**[0086]** In the second aspect, the present invention provides a method of preparing a compound of formula (18d),

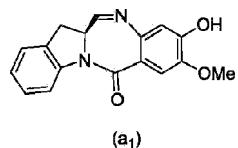


or a pharmaceutically acceptable salt thereof, said method comprising reacting a compound of

formula of (17d):



with a monomer of formula (a<sub>1</sub>):



wherein X<sub>3</sub> is -Cl; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0087]** In one embodiment, for methods of the second aspect, the reaction between the compound of formula (17d) and the monomer of formula (a<sub>1</sub>) is carried out in the presence of a base. In specific embodiment, the base is sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, or potassium hydride. Preferably, the base is potassium carbonate.

**[0088]** Any suitable organic solvents can be used for the methods of the second aspect. In one embodiment, the solvent is a polar aprotic solvent. Exemplary solvents include, but are not limited to, dimethylformamide (DMF), CH<sub>2</sub>Cl<sub>2</sub>, dichloroethane, THF, dimethylacetamide, etc. In certain embodiments, dimethylformamide or dimethylacetamide is used as the solvent.

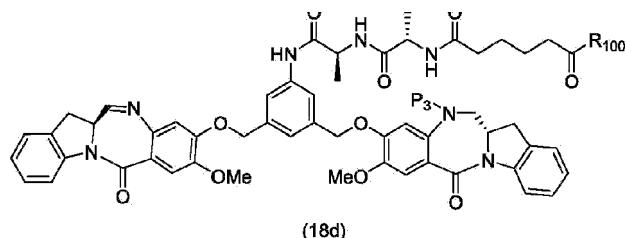
**[0089]** In a specific embodiment of the second aspect, the compound of formula (17d) is reacted with the monomer of formula (a<sub>1</sub>), wherein P<sub>3</sub> is H, to form a compound of formula (Id').

**[0090]** In another specific embodiment of the second aspect, P<sub>3</sub> is an amine protecting group. Any suitable amine protecting group can be used in the method described above. In one embodiment, the amine protecting group is 2-trimethylsilylethyl,(2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, or 2, 2,2,2-trichloroethoxycarbonyl.

**[0091]** When P<sub>3</sub> is an amine protecting group, the compound of formula (18d) is further reacted with an amine deprotecting reagent to form a compound of formula (Id').

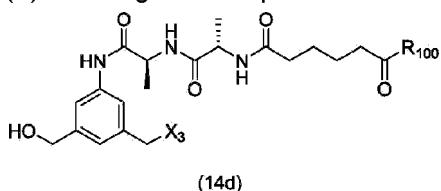
**[0092]** Examples of suitable amine deprotecting reagent include, but are not limited to, the amine deprotecting reagent is selected from the group consisting of tetra-n-butylammonium fluoride, acetic acid, hydrogen fluoride pyridine, cesium fluoride, piperidine, morpholine, or trifluoroacetic acid.

**[0093]** In the third aspect, the present invention provides a method of preparing a compound of formula (18d),

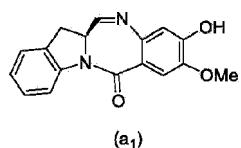


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

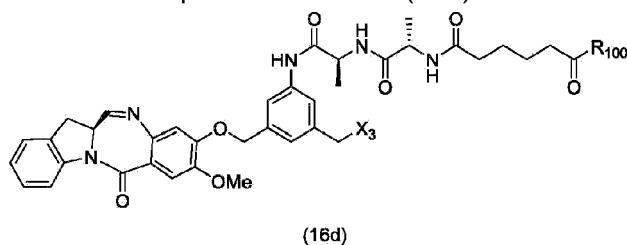
1. (1) reacting the compound of formula (14d):



, or a salt thereof, with a monomer compound of formula (a<sub>1</sub>),

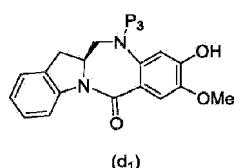


to form a compound of formula (16d):



, or a salt thereof; and

2. (2) reacting the compound of formula of (16d) with a reduced monomer of formula (d<sub>1</sub>):

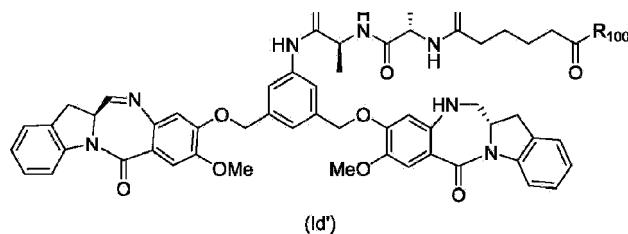


to form a compound of formula (18d), or a pharmaceutically acceptable salt thereof, wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

**[0094]** The conditions and reagents for the method of the third aspect are as described above in the fourth, and/or fifth disclosure(s) and any specific methods described therein.

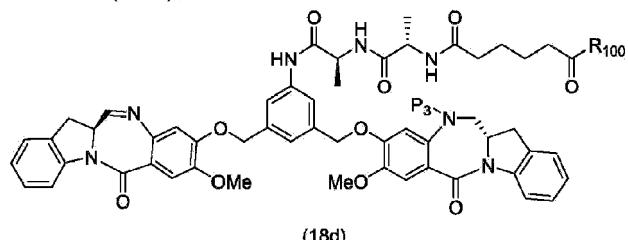
**[0095]** In a specific embodiment, for the method of the third aspect, P<sub>3</sub> is H, the compound of formula (16d) is reacted with reduced monomer of formula (d<sub>1</sub>) to form a compound of formula (Id'):





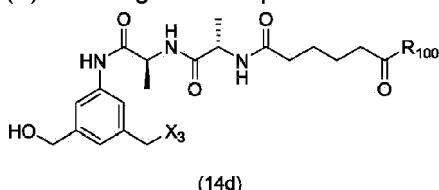
**[0096]** In another specific embodiment, for the method of the third aspect,  $P_3$  is an amine protecting group and the method further comprises reacting the compound of formula (18d) with an amine deprotecting reagent to form a compound of formula (Id').

**[0097]** In the fourth aspect, the present invention provides method of preparing a compound of formula (18d),

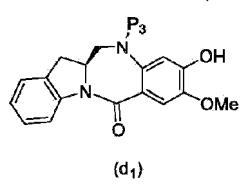


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

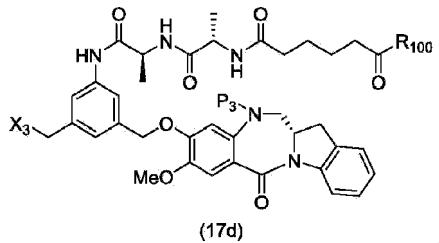
1. (1) reacting the compound of formula (14d):



or a salt thereof, with a reduced monomer compound of formula (d<sub>1</sub>),

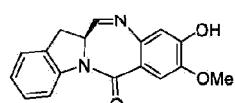


to form a compound of formula (17d):



or a salt thereof; and

2. (2) reacting the compound of formula (17d) with a monomer of formula (a<sub>1</sub>):

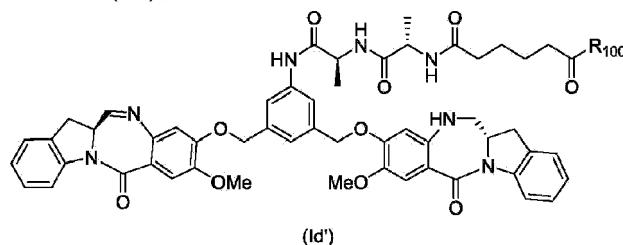


(a<sub>1</sub>)

to form a compound of formula (18d), or a pharmaceutically acceptable salt thereof, wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; P<sub>3</sub> is H or an amine protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

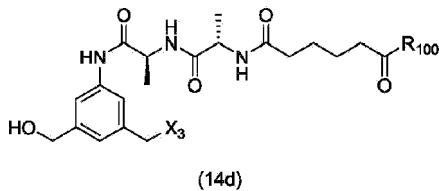
**[0098]** The conditions and reagents for the method of the fourth aspect are as described above in the first and/or second aspect(s) and any specific embodiments described therein.

**[0099]** In the fifth aspect, the present invention provides a method of preparing a compound of formula (Id'),

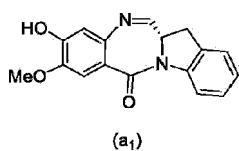


or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

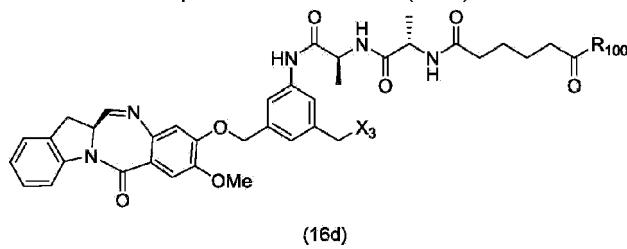
1. (1) reacting the compound of formula (14d):



or a salt thereof, with a monomer compound of formula (a<sub>1</sub>),

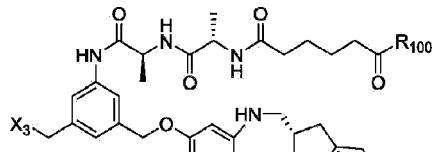


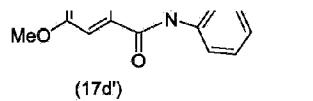
to form a compound of formula (16d):



or a salt thereof;

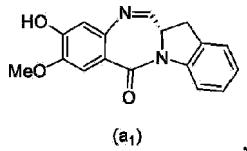
2. (2) reacting the compound of formula (16d) with an imine reducing agent to form a compound of formula (17d'):





or a salt thereof; and

3. (3) reacting the compound of formula (17d') with a monomer of formula (a<sub>1</sub>):

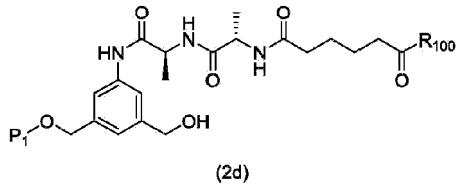


to form the compound of formula (Id'); wherein X<sub>3</sub> is -Cl; P<sub>1</sub> is an alcohol protecting group; and R<sub>100</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

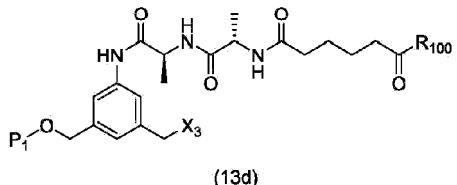
**[0100]** The conditions and reagents for the method of the fifth aspect are as described above in the fifth disclosure, sixth disclosure and/or second aspect and any specific methods therein.

**[0101]** In one embodiment, for methods of the third, fourth or fifth aspects described above, the compound (14d) of a salt thereof is prepared a method comprising the following steps:

1. (1) reacting a chlorinating reagent with a compound of formula (2d),



to form a compound a compound of formula (13d),



or a salt thereof; and

2. (2) reacting the compound of formula (13d) with an alcohol deprotecting reagent to form the compound of formula (14d) or a salt thereof, wherein X<sub>3</sub> is -Cl; and P<sub>1</sub> is an alcohol protecting group.

**[0102]** The conditions and reagents for the method of preparing compound of formula (14d) above are as described above in the second and/or third disclosure(s) and any specific methods described therein.

**[0103]** In another embodiment, for the methods described above, the compound of formula (2d) is prepared by reacting a compound of formula (1d) with an alcohol protecting reagent.

**[0104]** The conditions and reagents for the method of preparing compound of formula (2d) above are as described above in the first disclosure and any specific methods described therein.

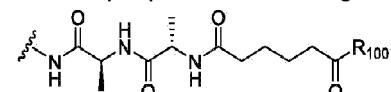
**[0105]** In one embodiment, for methods described above, R<sub>100</sub> is methoxy.

**[0106]** The method of the present invention can also be any combination of the methods described above (e.g., methods in the first, second, third, fourth and fifth aspects. The variable definitions described in any of the specific embodiments below also apply to any combination of methods described above.

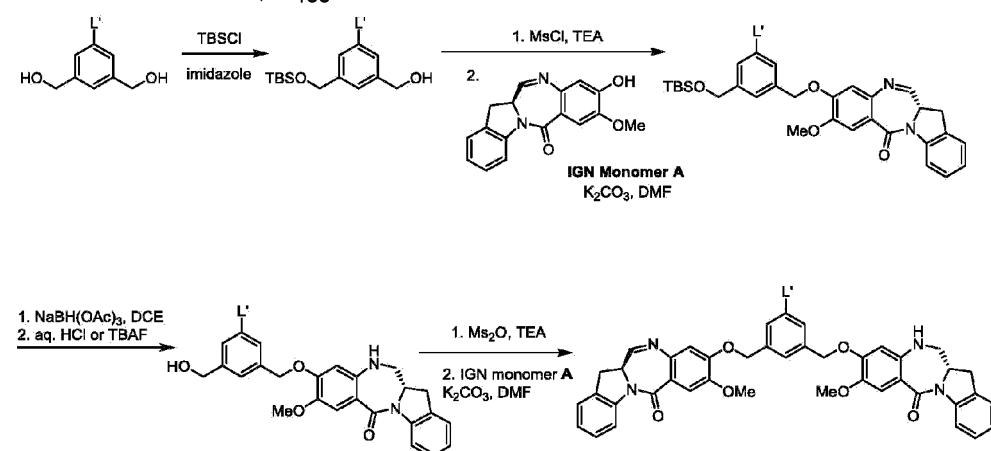
**[0107]** The reactions described herein in the methods of the present invention can be carried out in any suitable solvent(s). In one embodiment, the solvent is an organic solvent. Exemplary organic solvents include, but are not limited to, dichloromethane, dichloroethane, DMF, DMA, acetone, acetonitrile, THF, DMSO, ethyl acetate etc., or a combination thereof.

**[0108]** The reactions described herein in the methods of the present invention can be carried out at any suitable temperature. In one embodiment, the reaction can be carried out at room temperature. In another embodiment, the reaction can be carried out at a low temperature, such as 0°C. In yet another embodiment, the reaction can be carried out at an elevated temperature, such as about 40°C, about 50 °C etc.

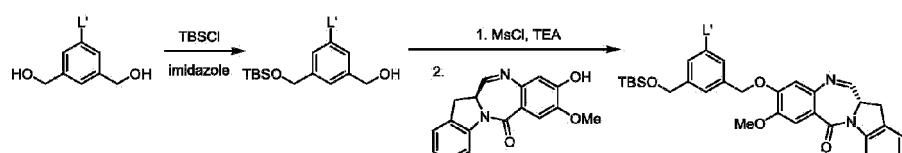
**[0109]** In certain embodiment, the indolinobenzodiazepine dimer compound of formula (Id') can be prepared according to Schemes 1 -10 shown below, wherein L' is

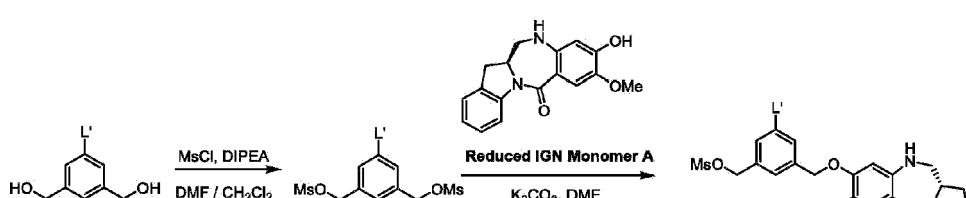
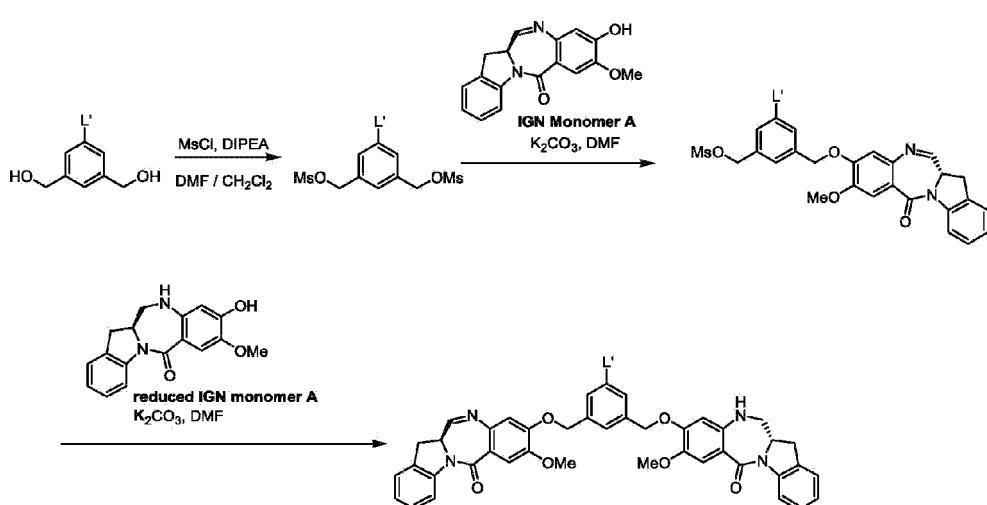
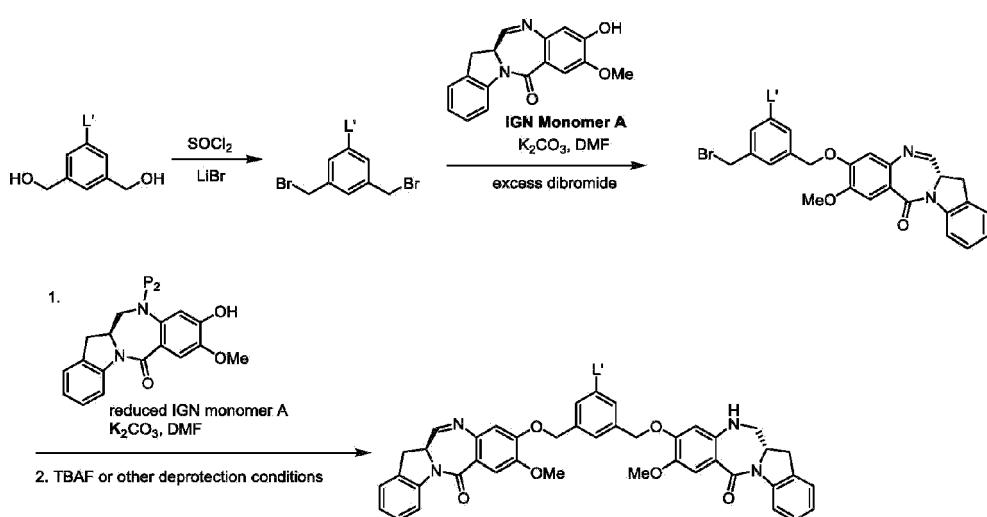
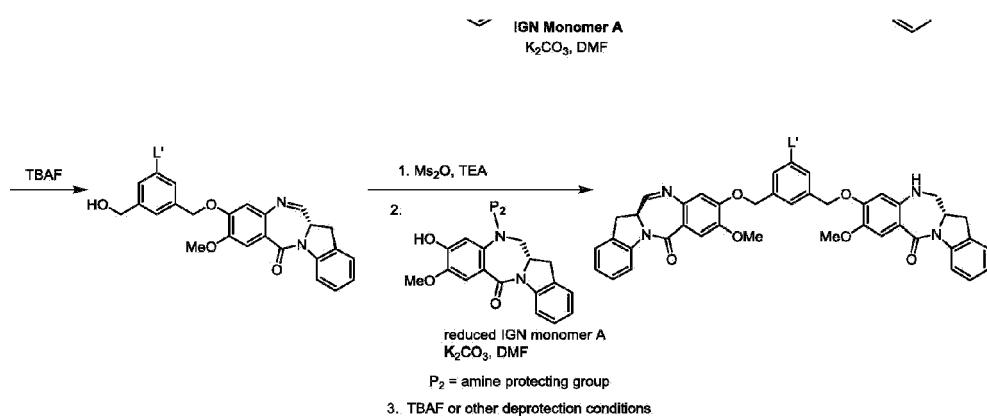


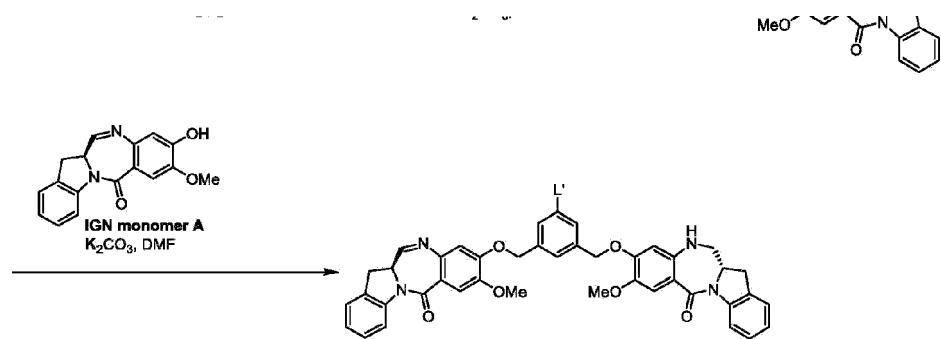
In one embodiment, R<sub>100</sub> is -OMe.



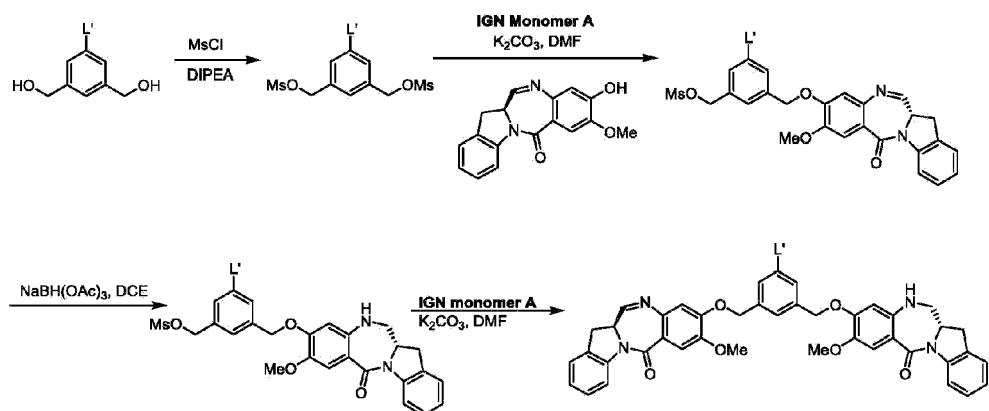
**Scheme 1**



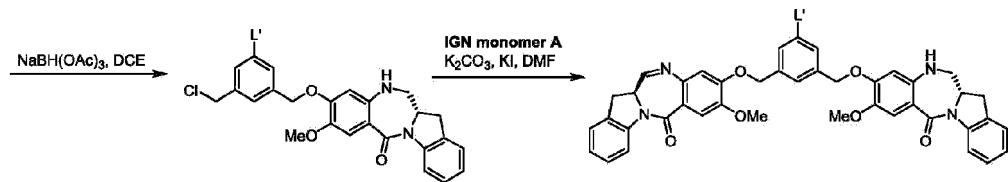
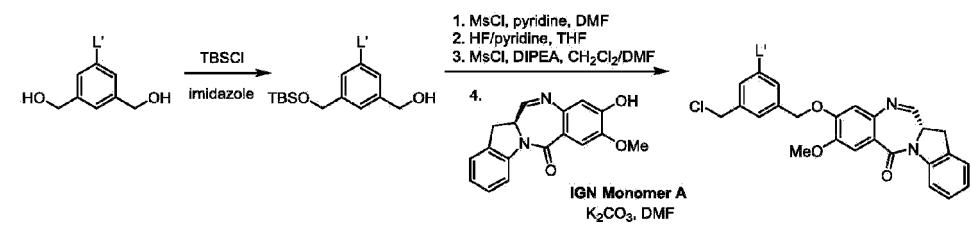




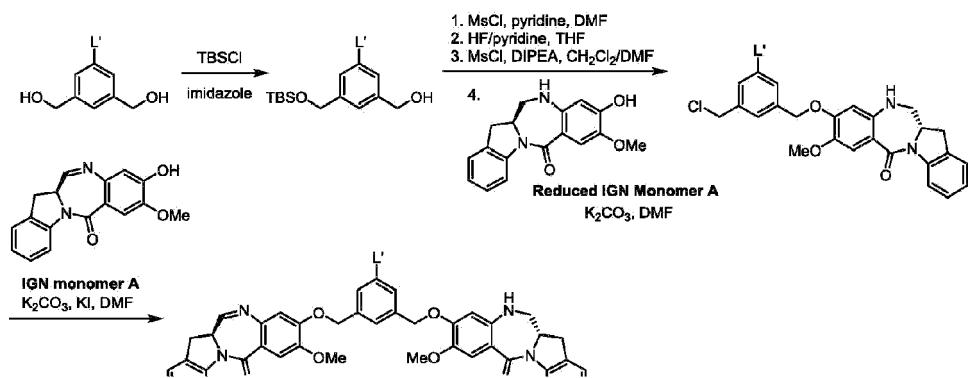
Scheme 5



Scheme 6

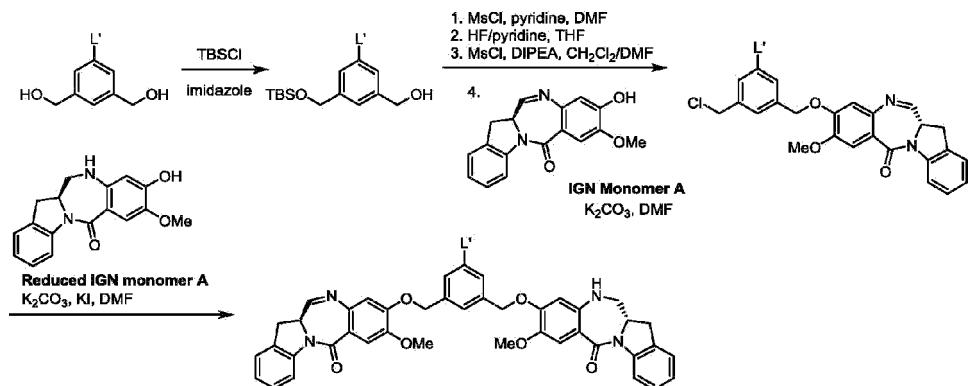


Scheme 7

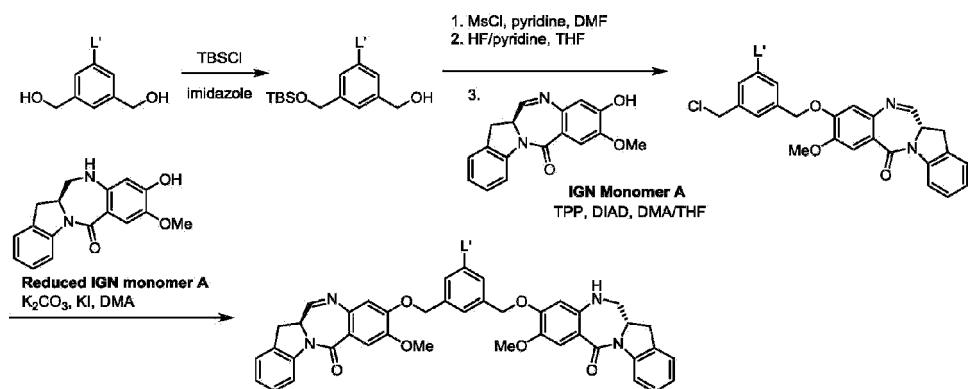




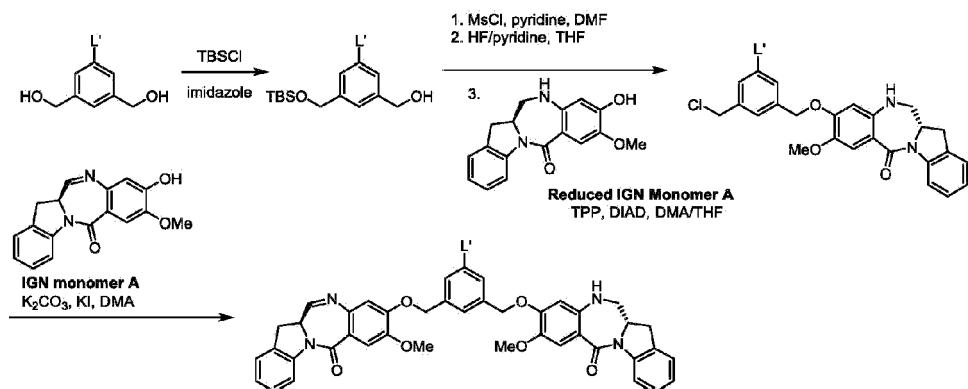
Scheme 8



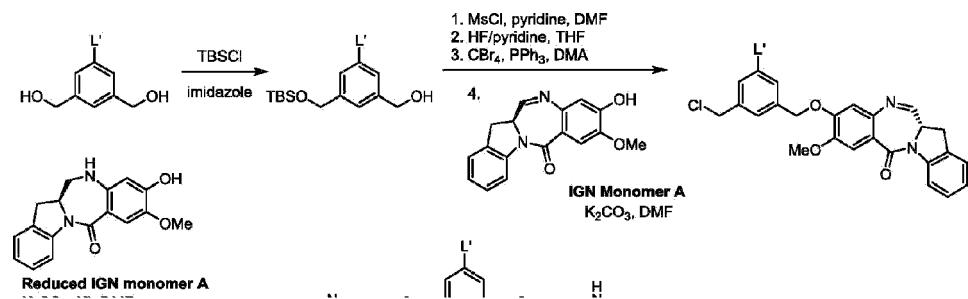
Scheme 9

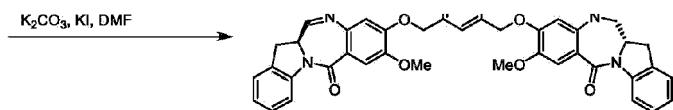


Scheme 10



Scheme 11



**Scheme 12**

**[0110]** In a 1<sup>st</sup> specific disclosure, for compounds of formula (1d), (2d), (13d), (14d), (16d), (17d), (17d'), (18d), or (Id'), R<sub>100</sub> is -OMe.

**[0111]** In a 2<sup>nd</sup> specific disclosure, for compound of formula (2d) and (13d), P<sub>1</sub> is a silyl protecting group; and the remaining variables are as described in first to fifth aspects or first to sixth disclosures or the 1<sup>st</sup> specific disclosure above. More specifically, the silyl protecting group is dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, trimethylsilyl, triisopropylsilyl, tribenzylsilyl, triphenylsilyl, 2-norbornyldimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, 2-trimethyethylsilyl (TEOC), or [2-(trimethylsilyl)ethoxy]methyl. Even more specifically, the silyl protecting group is triethylsilyl, triisopropylsilyl, or tert-butyldimethylsilyl. Even more specifically still, the silyl protecting group is tert-butyldimethylsilyl.

**[0112]** In a 3<sup>rd</sup> specific disclosure, for the compound of formula (13d), (14d), (16d), (17d) or (17d'), X<sub>3</sub> is chlorine; and the remaining variables are as described above in the first to fifth aspects or first to sixth disclosures or in the 1<sup>st</sup> or 2<sup>nd</sup> specific disclosures.

**[0113]** In a 4<sup>th</sup> specific disclosure, for the compound of formula (d<sub>1</sub>), (17d) or (18d), P<sub>3</sub> is H or an amine protecting group selected from 2-trimethylsilylethyl,(2-phenyl-2-trimethylsilyl)ethyl, triisopropylsiloxy, 2-(trimethylsilyl)ethoxymethyl, allyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, or 2, 2,2,2-trichloroethoxycarbonyl; and the remaining variables are as described above in the first to fifth aspects or first to sixth disclosures or in the 1<sup>st</sup> or 3<sup>rd</sup> specific disclosures.

## EXAMPLES

**[0114]** The invention will now be illustrated by reference to non-limiting examples. Unless otherwise stated, all percents, ratios, parts, etc. are by weight. All reagents were purchased from the Aldrich Chemical Co., New Jersey, or other commercial sources. Nuclear Magnetic Resonance (<sup>1</sup>H NMR) spectra were acquired on a Bruker 400 MHz instrument. Mass spectra were acquired on a Bruker Daltonics Esquire 3000 instrument and LCMS were acquired on an Agilent 1260 Infinity LC with an Agilent 6120 single quadrupole MS using electrospray ionization and UPLC were acquired on a Waters, Acquity system with a single quadrupole MS Zspray™ (column: Acquity BEH C18, 2.1 x 50 mm, 1.7 µm, method: 2.5 min, flow rate 0.8 mL/min, solvent A: water, solvent B: MeCN, 5 to 95% of MeCN over 2.0 min and 95% MeCN for 0.5 min).

**[0115]** The following solvents, reagents, protecting groups, moieties and other designations may be referred to by their abbreviations in parenthesis:

Me = methyl; Et = ethyl; Pr = propyl; *i*-Pr = isopropyl; Bu = butyl; *t*-Bu = tert-butyl; Ph = phenyl, and Ac = acetyl

AcOH or HOAc = acetic acid

ACN or CH<sub>3</sub>CN = acetonitrile

Ala = alanine

Ar = argon

aq = aqueous

Bn = benzyl

Boc or BOC = tert-butoxycarbonyl

CBr<sub>4</sub> = carbontetrabromide

Cbz or Z = benzyloxycarbonyl

DCM or CH<sub>2</sub>Cl<sub>2</sub> = dichloromethane

DCE = 1,2-dichloroethane

DMAP = 4-dimethylaminopyridine

DI water = deionized water

DIBAL = diisobutylaluminum hydride

DIEA or DIPEA = N,N-diisopropylethylamine

DMA = N,N-dimethylacetamide

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DTT = dithiothreitol

EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EEDQ = N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

ESI or ES = electrospray ionization

EtOAc = ethylacetate

Gly = glycine

g = grams

h = hour

HATU = N,N,N'N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexaphosphate

HPLC = high-performance liquid chromatography

HOBt or HOBT = 1-hydroxybenzotriazole

LAH = lithium aluminum hydride

LC = liquid chromatography

LCMS = liquid chromatography mass spectrometry

min = minutes

mg = miligrams

mL = mililiters

mmol = milimoles

$\mu$ g = micrograms

$\mu$ L = microliters

$\mu$ mol = micromoles

Me = methyl

MeOH = methanol

MeI = methyliodide

MS = mass spectrometry

MsCl = methanesulfonyl chloride (mesyl chloride)

Ms<sub>2</sub>O = methanesulfonic anhydride

MTBE = Methyl *tert*-butyl ether

NaBH(OAc)<sub>3</sub> = sodium triacetoxyborohydride

NHS = N-hydroxysuccinamide

NMR = nuclear magnetic resonance spectroscopy

PPh<sub>3</sub> = triphenylphosphine

PTLC = preparative thin layer chromatography

*rac* = racemic mixture

R<sub>f</sub> = retardation factor

RPHPLC or RP-HPLC = reverse phase high-performance liquid chromatography

RT or rt = room temperature (ambient, about 25 °C)

sat or sat'd = saturated

STAB = sodium triacetoxyborohydride (NaBH(OAc)<sub>3</sub>)

TBSCl or TBDMSCl = *tert*-butyldimethylsilyl chloride

TBS = *tert*-butyldimethylsilyl

TCEPHCl = *tris*(2-carboxyethyl)phosphine hydrochloride salt

TEA = triethylamine (Et<sub>3</sub>N)

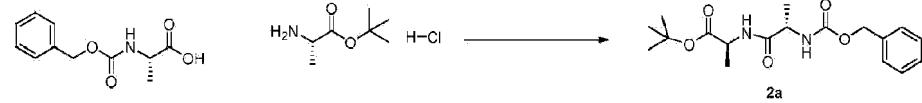
TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

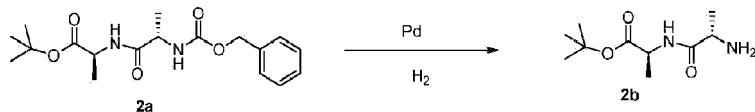
### Example 1.

[0116]

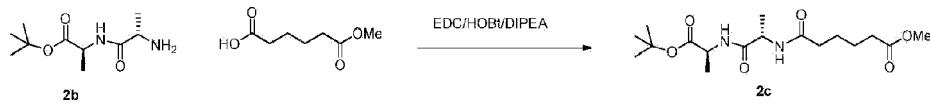


[0117] (S)-2-((benzyloxy)carbonyl)amino propanoic acid (5 g, 22.40 mmol) and (S)-*tert*-butyl 2-aminopropanoate hydrochloride (4.48 g, 24.64 mmol) were dissolved in anhydrous DMF (44.8 mL). EDC·HCl (4.72 g, 24.64 mmol), HOEt (3.43 g, 22.40 mmol), and DIPEA (9.75 mL, 56.0 mmol) were added. The reaction stirred under argon, at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed with saturated ammonium chloride, saturated sodium bicarbonate, water, and brine. The organic layer was dried over

sodium sulfate and concentrated. The crude oil was purified by silica gel chromatography (Hexanes/Ethyl Acetate) to yield compound **2a** (6.7 g, 85% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38-7.31 (m, 5H), 6.53-6.42 (m, 1H), 5.42-5.33 (m, 1H), 5.14 (s, 2H), 4.48-4.41 (m, 1H), 4.32-4.20 (m, 1H), 1.49 (s, 9H), 1.42 (d, 3H,  $J$  = 6.8 Hz), 1.38 (d, 3H,  $J$  = 7.2 Hz).



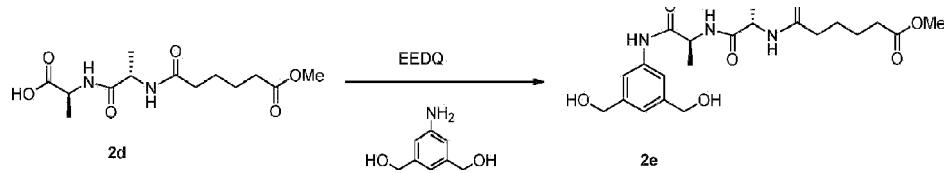
**[0118]** Compound **2a** (6.7 g, 19.12 mmol) was dissolved in methanol (60.7 mL) and water (3.03 mL). The solution was purged with argon for five minutes. Palladium on carbon (wet, 10%) (1.017 g, 0.956 mmol) was added slowly. The reaction was stirred overnight under an atmosphere of hydrogen. The solution was filtered through Celite, rinsed with methanol and concentrated. It was azeotroped with methanol and acetonitrile and the resulting oil was placed directly on the high vacuum to give compound **2b** (4.02 g, 97% yield) which was used directly in the next step.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78-7.63 (m, 1H), 4.49-4.42 (m, 1H), 3.55-3.50 (m, 1H), 1.73 (s, 2H), 1.48 (s, 9H), 1.39 (d, 3H,  $J$  = 7.2 Hz), 1.36 (d, 3H,  $J$  = 6.8 Hz).



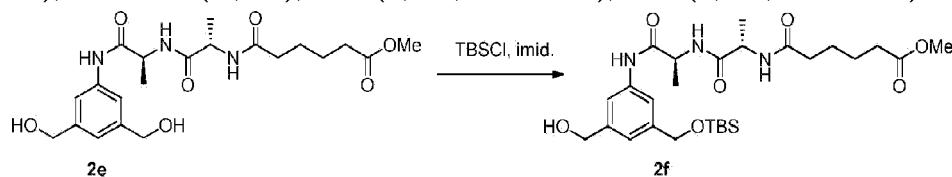
**[0119]** Compound **2b** (4.02 g, 18.59 mmol) and mono methyladipate (3.03 mL, 20.45 mmol) were dissolved in anhydrous DMF (62.0 mL). EDC·HCl (3.92 g, 20.45 mmol), HOEt (2.85 g, 18.59 mmol) and DIPEA (6.49 mL, 37.2 mmol) were added. The mixture was stirred overnight at room temperature. The reaction was diluted with dichloromethane/methanol (150 mL, 5:1) and washed with saturated ammonium chloride, saturated sodium bicarbonate, and brine. It was dried over sodium sulfate, filtered and concentrated. The compound was azeotroped with acetonitrile (5x), then pumped on the high vacuum at 35 °C to give compound **2c** (6.66 g, 100% yield). The crude material was taken onto next step without purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.75 (d, 1H,  $J$  = 6.8 Hz), 6.44 (d, 1H,  $J$  = 6.8 Hz), 4.52-4.44 (m, 1H), 4.43-4.36 (m, 1H), 3.65 (s, 3H), 2.35-2.29 (m, 2H), 2.25-2.18 (m, 2H), 1.71-1.60 (m, 4H), 1.45 (s, 9H), 1.36 (t, 6H,  $J$  = 6.0 Hz).



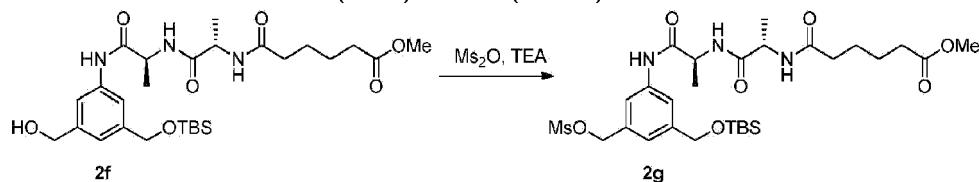
**[0120]** Compound **2c** (5.91 g, 16.5 mmol) was stirred in TFA (28.6 mL, 372 mmol) and deionized water (1.5 mL) at room temperature for three hours. The reaction mixture was concentrated with acetonitrile and placed on high vacuum to give crude compound **2d** as a sticky solid (5.88 g, 100% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.21 (d, 1H,  $J$  = 6.8 Hz), 6.81 (d, 1H,  $J$  = 7.6 Hz), 4.69-4.60 (m, 1H), 4.59-4.51 (m, 1H), 3.69 (s, 3H), 2.40-2.33 (m, 2H), 2.31-2.24 (m, 2H), 1.72-1.63 (m, 4H), 1.51-1.45 (m, 3H), 1.42-1.37 (m, 3H).



**[0121]** Compound **2d** (5.6 g, 18.52 mmol) was dissolved in anhydrous dichloromethane (118 mL) and anhydrous methanol (58.8 mL). (5-amino-1,3-phenylene)dimethanol (2.70 g, 17.64 mmol) and EEDQ (8.72 g, 35.3 mmol) were added and the reaction was stirred at room temperature overnight. The solvent was concentrated and ethyl acetate was added. The resulting slurry was filtered, washed with ethyl acetate and dried under vacuum/N<sub>2</sub> to give compound **2e** (2.79 g, 36% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*6):  $\delta$  9.82 (s, 1H), 8.05, (d, 1H, *J* = 9.2 Hz), 8.01 (d, 1H, *J* = 7.2 Hz), 7.46 (s, 2H), 6.95 (s, 1H), 5.21-5.12 (m, 2H), 4.47-4.42 (m, 4H), 4.40-4.33 (m, 1H), 4.33-4.24 (m, 1H), 3.58 (s, 3H), 2.33-2.26 (m, 2H), 2.16-2.09 (m, 2H), 1.54-1.46 (m, 4H), 1.30 (d, 3H, *J* = 7.2 Hz), 1.22 (d, 3H, *J* = 4.4 Hz).

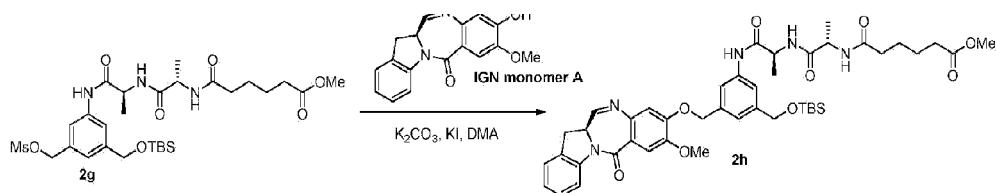


**[0122]** Diol **2e** (1.0 g, 2.286 mmol) was dissolved in anhydrous DMF (7.6 mL). TBSCl (0.482 g, 3.20 mmol) and imidazole (0.467 g, 6.86 mmol) were added and the reaction was stirred at room temperature for 2 hrs. The reaction was quenched with saturated ammonium chloride and diluted with water and EtOAc. The aqueous layer was extracted once with EtOAc and the combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel flash chromatography (DCM/MeOH) to obtain compound **2f** (360 mg, 28% yield). LCMS (8 min method, 40-98%) = 2.35 min. Mass observed (ESI<sup>+</sup>): 574.4 (M+Na)<sup>+</sup>.

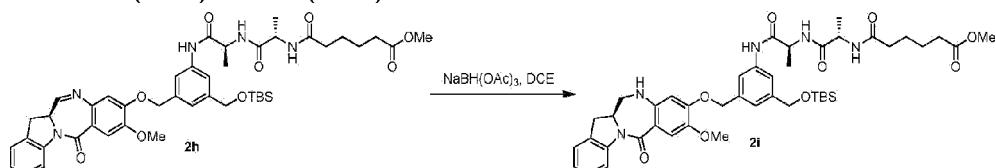


**[0123]** Compound **2f** (360 mg, 0.652 mmol) was dissolved in anhydrous dichloromethane (6.52 mL) and cooled in an acetone/ice bath. Triethylamine (227  $\mu$ L, 1.631 mmol) and methanesulfonic anhydride (146 mg, 0.816 mmol) were added. The reaction stirred at -10°C in the acetone/ice bath for 1 hr. The reaction was diluted with cold EtOAc and quenched with ice water. The organic layer was washed with ice water and then dried over sodium sulfate and magnesium sulfate, filtered and concentrated to give crude compound **2g** as a fluffy solid (390 mg, 95% yield). LCMS (8 min method, 40-98%) = 2.81 min; 5.86 min (8 min method, 5-98%).

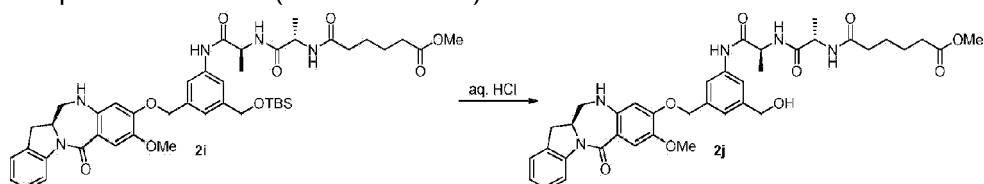
Mass observed (ESI<sup>-</sup>): 628.0 (M-H)<sup>-</sup>.



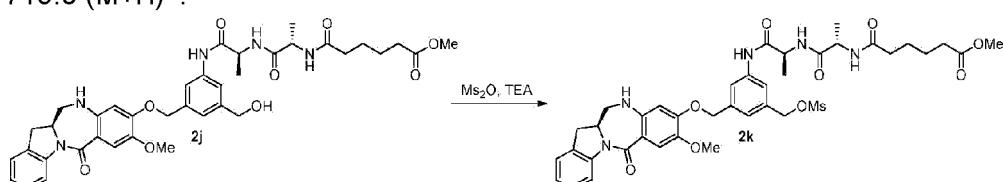
**[0124]** Mesylate **2g** (390 mg, 0.619 mmol) and IGN monomer **A** (264 mg, 0.897 mmol) were dissolved in anhydrous DMA (7.47 mL). Potassium carbonate (207 mg, 1.495 mmol) and potassium iodide (51.4 mg, 0.310 mmol) were added and the reaction was stirred overnight at room temperature. The reaction was precipitated with water, filtered and the filter cake washed with water. The solid was redissolved in DCM, washed with water, dried over magnesium sulfate and concentrated to give crude compound **2h** (568 mg, 111% yield). The product was carried on without further purification. LCMS (8 min method, 5-98%) = 6.23 min. Mass observed (ESI<sup>+</sup>): 827.8 (M+H)<sup>+</sup>.



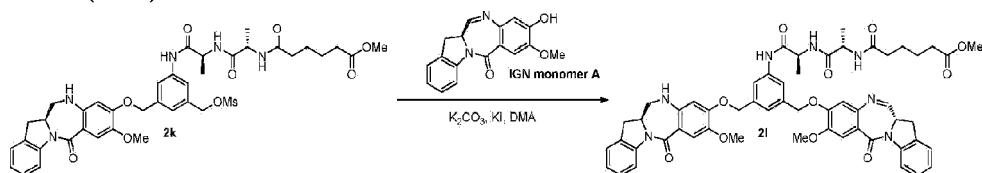
**[0125]** Compound **2h** (0.513 g, 0.619 mmol) was dissolved in DCE (7.74 mL). NaBH(OAc)<sub>3</sub> (0.276 g, 1.239 mmol) was added and the mixture stirred at room temperature for 1.5 h. The reaction was diluted with DCM, quenched with saturated ammonium chloride and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to give compound **2i**. LCMS (15 min method) = 9.93 min.



**[0126]** Compound **2i** (514 mg, 0.619 mmol) was dissolved in THF (3.44 mL). 5 M aqueous HCl (1.24 mL, 6.19 mmol) was added at room temperature and the reaction stirred for 1 h. The reaction mixture was diluted with DCM/MeOH (20:1) and the organic layer was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (DCM/MeOH) to give compound **2j** (210 mg, 47% yield). LCMS (8 min method, 5-98%) = 4.56 min. Mass observed (ESI<sup>+</sup>): 715.8 (M+H)<sup>+</sup>.



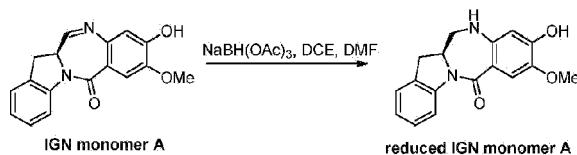
**[0127]** Compound **2j** (210 mg, 0.293 mmol) was dissolved in DCM (3.95 mL) and DMF (500  $\mu$ L) and cooled to -10°C (ice-acetone bath). TEA (57.2  $\mu$ L, 0.411 mmol) and methanesulfonic anhydride (46.6 mg, 0.260 mmol) were added and the reaction was stirred for 3 h under Ar. The reaction was quenched with cold water at -5°C and diluted with EtOAc. The aqueous layer was extracted with cold EtOAc (2 $\times$ ) and the combined organics were washed with cold water (2 $\times$ ). The organic layer was dried over anhydrous sodium/magnesium sulfate, filtered and concentrated. The crude product **2k** was pumped on the high vacuum and taken onto next step without purification. LCMS (8 min method, 5-98%) = 5.06 min. Mass observed (ESI $^-$ ): 791.8 (M-H) $^-$ .



**[0128]** Compound **2k** (233 mg, 0.293 mmol) was dissolved in DMA (1.95 mL). **IGN monomer A** (103 mg, 0.352 mmol) and potassium carbonate (60.7 mg, 0.440 mmol) were added at room temperature and the reaction stirred overnight. DI water was added to the reaction mixture and the resulting solid was filtered and washed with water. The solid was redissolved in DCM/MeOH (20:1), washed with water, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by RP-HPLC (ACN/H<sub>2</sub>O) to give **2l** (44 mg, 15% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI $^+$ ): 991.7 (M+H) $^+$ .

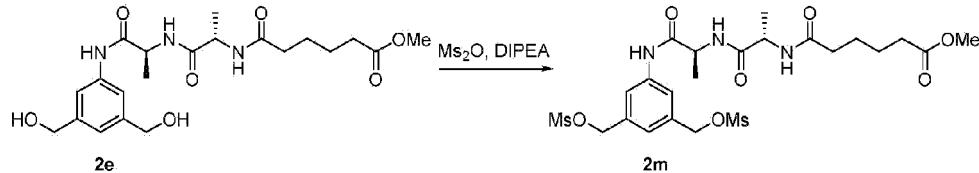
### Example 2.

#### [0129]

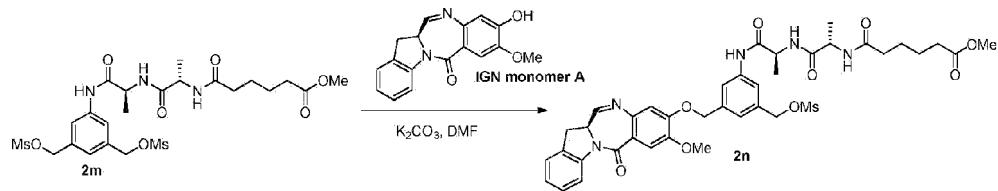


**[0130]** To a solution of **IGN monomer A** (1.0 g, 3.4 mmol) in DCE (10 mL) and DMF (4 mL) was added sodium triacetoxyborohydride (1.1 g, 5.1 mmol, 1.5 equiv) and the reaction was stirred until completion of starting material. Upon completion of the starting material after 2h at room temperature, the reaction was quenched with sat. ammonium chloride (10 mL), and then the layers were separated. The aqueous layer was extracted once with dichloromethane (10 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed in vacuo to give a white/brown powder. The powder was washed with EtOAc (2 x 10 mL) and dried under vacuum to give **reduced IGN monomer A** as a white solid (0.87 g, 2.9 mmol, 87%

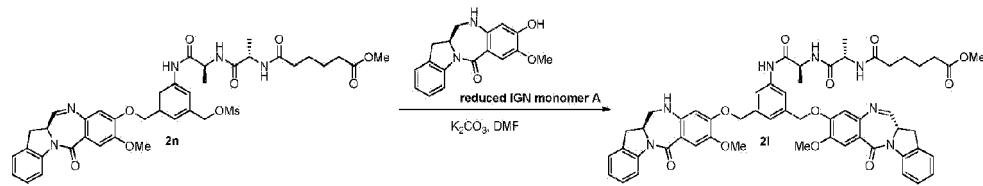
yield) which was used in the next step without further purification. UPLCMS (2.5 min method) = 1.34 min. Mass observed (ESI<sup>+</sup>): 297.4 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.44 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.30 - 7.23 (m, 2H), 7.22 - 7.12 (m, 1H), 7.01 (td, *J* = 7.4, 1.1 Hz, 1H), 6.21 (s, 1H), 6.17 (d, *J* = 6.6 Hz, 1H), 4.37 (tdd, *J* = 10.1, 4.4, 1.9 Hz, 1H), 3.70 (s, 3H), 3.58 - 3.39 (m, 2H), 3.31 - 3.15 (m, 2H), 2.88 (dd, *J* = 16.9, 4.4 Hz, 1H).



**[0131]** A solution of **2e** (5.53 g, 12.6 mmol) in DCM (81 mL) and DMF (64.9 mL) was cooled down to 0 °C and then DIPEA (6.13 mL, 37.9 mmol, 3.0 equiv.) was added followed by a solution of methanesulfonic anhydride (5.06 g, 29.1 mmol, 2.3 equiv.) in DCM (15 mL) / DMF (1 mL) dropwise. The reaction was stirred for 1h before quenching with cold water. After washing with water and brine the solution was dried over magnesium sulfate, filtered, and the solvent was removed in vacuo to give an orange oil which was triturated in diethyl ether to give bis mesylate **2m** (6.4 g, 10.8 mmol, 85% yield). LCMS (8 min method) = 4.019 min. Mass observed (ESI<sup>+</sup>): 594.8 (M+H)<sup>+</sup>. The crude material was carried on to the next step without further purification.



**[0132]** To a solution of **2m** (0.52 g, 0.88 mmol) and **IGN monomer A** (0.18 g, 0.61 mmol, 0.7 equiv.) in DMF (7 mL) was added potassium carbonate (0.24 g, 1.75 mmol, 2.0 equiv.) and the reaction was stirred at room temperature for 12 h. The reaction was quenched with water (30 mL) and was extracted with DCM (3 x 15 mL). The organic layers were combined and washed with water (3 x 60 mL), brine (60 mL), dried over magnesium sulfate, filtered and the solvent was removed in vacuo to give a crude yellow oil. The material was purified by silica gel chromatography (DCM/(MeCN/MeOH (4/1) from 100/0 to 65/35) to give desired product **2n** (0.09 g, 0.12 mmol, 13% yield). UPLCMS (2.5 min method) = 1.46 min. Mass observed (ESI<sup>+</sup>): 792.6 (M+H)<sup>+</sup>.

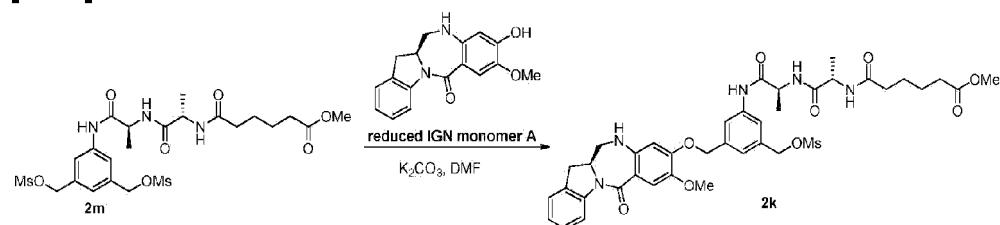


**[0133]** To a solution of **2n** (0.05 g, 0.06 mmol) in DMF (0.48 mL, 6.2 mmol) was added

potassium carbonate (0.02 g, 0.12 mmol, 2.0 equiv.) followed by **reduced IGN monomer A** (0.02 g, 0.07 mmol, 1.1 equiv.). The reaction was stirred at room temperature for 12 h. The reaction was quenched with water and the resulting solid was filtered and washed with water. The solid was redissolved in DCM/MeOH (20:1), washed with water, dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **21** (0.03 g, 0.04 mmol, 55% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI+): 991.7 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, reported as a mixture of water adducts):  $\delta$  10.10 (d, *J* = 3.7 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.21 - 8.10 (m, 1H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.78 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.43 - 7.13 (m, 7H), 7.16 - 6.98 (m, 2H), 6.49 (s, 1H), 6.36 (d, *J* = 13.1 Hz, 0.4H), 6.16 (d, *J* = 6.2 Hz, 0.4H), 5.80 (s, 0.4H), 5.67 (s, 0.4H), 5.57 (d, *J* = 5.6 Hz, 0.4H), 5.35 - 5.09 (m, 2H), 5.03 (t, *J* = 5.9 Hz, 2H), 4.81 - 4.72 (m, 0.4H), 4.60 (dt, *J* = 9.7, 5.0 Hz, 0.2H), 4.51 - 4.36 (m, 2H), 4.39 - 4.23 (m, 1H), 4.17 (td, *J* = 9.7, 2.9 Hz, 0.4H), 3.93 (s, 0.4H), 3.83 - 3.74 (m, 5H), 3.62 (s, 2H), 3.75 - 3.44 (m, 2H), 3.32 (d, *J* = 11.6 Hz, 1H), 3.19 - 3.07 (m, 1H), 2.95 (dd, *J* = 17.1, 4.3 Hz, 1H), 2.38 - 2.29 (m, 1H), 2.18 (m, 1H), 1.56 (m, *J* = 3.9 Hz, 4H), 1.41 - 1.31 (m, 3H), 1.30 - 1.14 (m, 3H).

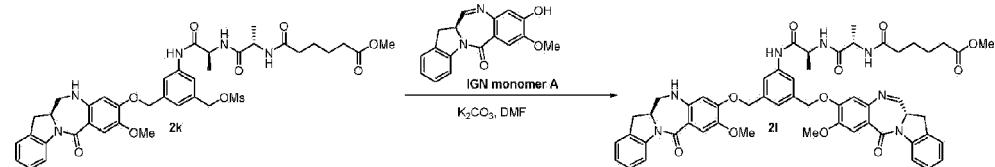
### Example 3.

〔0134〕



[0135] To a solution of **2m** (0.88 g, 1.47 mmol) in DMF (11 mL) was added **reduced IGN monomer A** (0.26 g, 0.88 mmol, 0.6 equiv.) followed by potassium carbonate (0.41 mg, 2.95 mmol, 2.0 equiv.). After the reaction was stirred for 12 h, the reaction was diluted with water (50 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and filtered. The solvent was removed and the crude mixture was purified by silica gel chromatography (DCM/MeOH) to give desired product **2k** (0.11 g, 0.14 mmol, 10% yield).

LCMS (8 min method) = 5.013 min. Mass observed (ESI<sup>+</sup>): 794.3 (M+H)<sup>+</sup>.

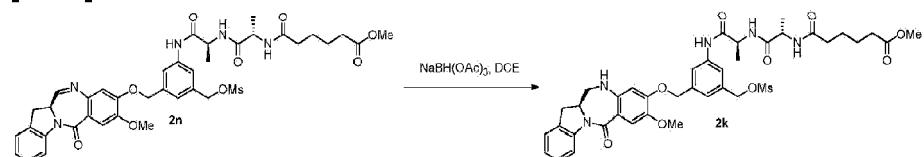


[0136] To a solution of **2k** (0.11 g, 0.14 mmol) in DMF (2 mL) was added potassium carbonate (0.04 g, 0.29 mmol, 2.0 equiv.) **IGN monomer A** (0.04 g, 0.14 mmol, 1.0 equiv.) was added

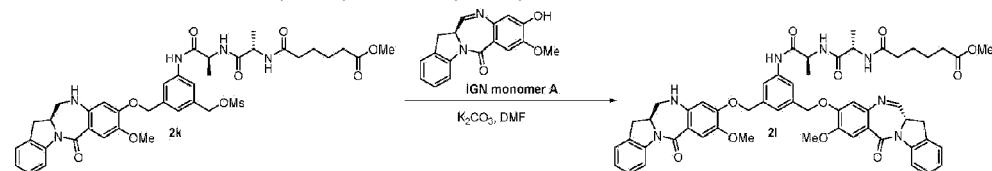
and the reaction was stirred at rt for 12 h. The reaction was quenched with water (10 mL) and the resulting solid was filtered and washed with water. The solid was redissolved in DCM/MeOH (20:1), washed with water (10 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **21** (0.08 g, 0.09 mmol, 59% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

**Example 4.**

**[0137]**



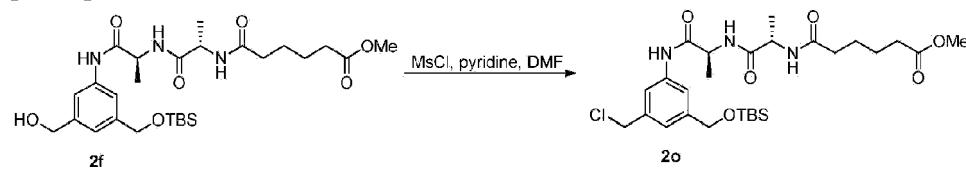
**[0138]** To a solution of **2n** (0.1 g, 0.13 mmol) in DCE (2 mL) was added sodium triacetoxyborohydride (0.03g , 0.13 mmol, 1.0 equiv.) and the reaction was stirred at rt for 2 h. The reaction was quenched with saturated ammonium chloride (2 mL) and the layers were separated. The aqueous layer was extracted with DCM (5 mL) and the combined organic layers were washed with water, brine, dried over magnesium sulfate and filtered. The crude yellow solid was purified using silica gel chromatography (EtOAc/MeOH (95/5)) to afford the desired reduced product **2k** (0.035 g, 0.044 mmol, 35% yield). LCMS (8 min method) = 5.021 min. Mass observed (ESI<sup>+</sup>): 794.3 (M+H)<sup>+</sup>.



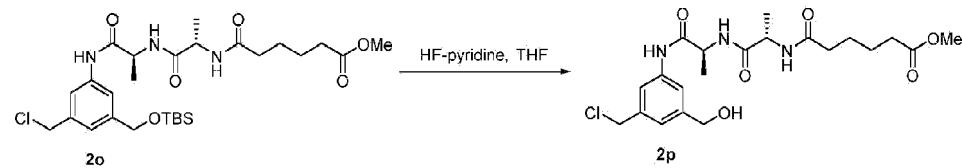
**[0139]** To a solution of **2k** (0.035 g, 0.044 mmol) in DMF (1.0 mL) was added potassium carbonate (0.013 g, 0.09 mmol, 2.0 equiv.). **IGN monomer A** (0.013 g, 0.04 mmol, 1.0 equiv.) was added and the reaction was stirred at room temperature for 12 h. The reaction was quenched with water (10 mL) and the resulting solid was filtered and washed with water. The solid was redissolved in DCM/MeOH (20:1, 20 mL), washed with water (20 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **2l** (0.017 g, 0.01 mmol, 38% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

**Example 5.**

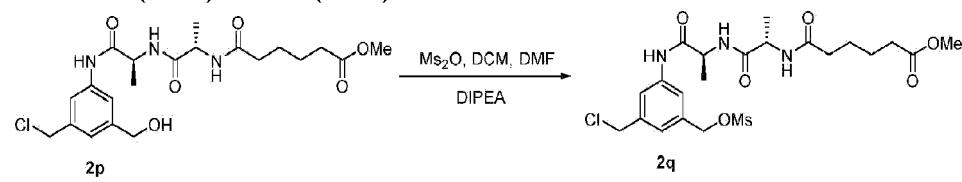
[0140]



[0141] To a solution of **2f** (8.8 g, 16.0 mmol) in  $\text{DMF}$  (100 mL) was added pyridine (4.51 ml, 55.8 mmol, 3.5 equiv.). The reaction was cooled down to 0 °C then methanesulfonyl chloride (2.5 mL, 31.9 mmol, 2.0 equiv.) was added dropwise and reaction stirred for 2 h. The mixture was quenched with sat. sodium bicarbonate (30 mL),  $\text{EtOAc}$  was added and the layers were separated. The aqueous layer was extracted with  $\text{EtOAc}$  (3 x 50 mL) and the combined organic layers were washed with water, brine, dried over magnesium sulfate and filtered. The solvent was removed and the crude white solid **2o** was used in the next step without purification (6.2 g, 10.9 mmol, 68%). UPLCMS (2.5 min method) = 1.96 min. Mass observed (ESI $^+$ ): 570.7 ( $\text{M}+\text{H}$ ) $^+$ .

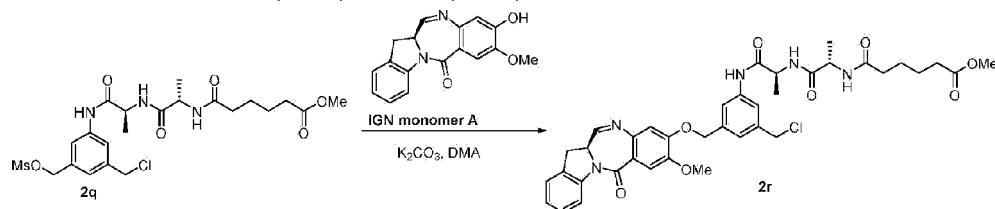


[0142] To a solution of **2o** (1.7 g, 2.98 mmol) in  $\text{THF}$  (36.6 mL) was added DIPEA (2.1 mL, 11.9 mmol, 4.0 equiv.) followed by HF-pyridine (0.84 mL, 6.0 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 3 h. The reaction was quenched with sat. sodium bicarbonate (20 mL) and then the layers were separated. The aqueous layer was extracted with  $\text{EtOAc}$  (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate, filtered and the solvent removed in vacuo to give a crude white oil which was purified by silica gel chromatography (DCM/MeOH) to give desired product **2p** as a white solid (0.75 g, 1.6 mmol, 55% yield). UPLCMS (2.5 min method) = 1.23 min. Mass observed (ESI $^+$ ): 456.4 ( $\text{M}+\text{H}$ ) $^+$ .

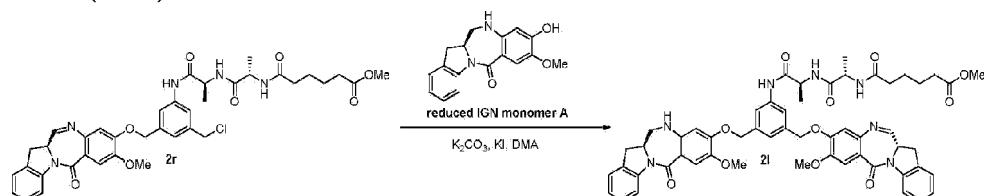


[0143] To a solution of **2p** (0.65 g, 1.43 mmol) in  $\text{DCM}$  (10 mL) and  $\text{DMF}$  (2 mL) was added DIPEA (0.51 mL, 2.85 mmol, 2.0 equiv.) and the reaction was cooled down to 0 °C. A solution of methanesulfonic anhydride (0.3 g, 1.71 mmol) in  $\text{DCM}$  (2 mL) was added slowly. The reaction was completed after 30 min, quenched with water (20 mL), the layers were extracted, aqueous layer washed with  $\text{DCM}$  (2 x 10 mL). Organic layers were combined, washed with water (20 mL), brine (10 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give desired product **2q** (0.76 g, 1.42 mmol, 100% yield) which was

carried crude into the next step without further purification. UPLCMS (2.5 min method) = 1.37 min. Mass observed (ESI<sup>+</sup>): 534.4 (M+H)<sup>+</sup>.



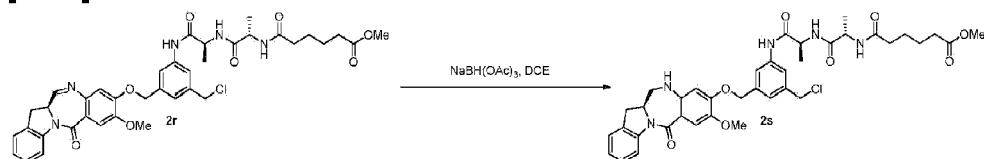
**[0144]** To a solution of **2q** (0.76 g, 1.42 mmol) in DMA (13 mL) was added potassium carbonate (0.59 g, 4.27 mmol) followed by a solution of **IGN monomer A** (0.5 g, 1.71 mmol) in DMA (1 mL). The reaction was stirred at room temperature for 12 h. The reaction was quenched with water (30 mL) and the mixture was stirred for 10 min. The solid was filtered and then dissolved in DCM/MeOH (9/1, 20 mL) and washed with brine (10 mL). The organic layer was separated and dried over magnesium sulfate, filtered and concentrated in vacuo to give a crude yellow solid **2r** (0.76 g, 1.04 mmol, 73% yield) which was carried crude into the next step without further purification. UPLCMS (2.5 min method) = 1.55 min. Mass observed (ESI<sup>+</sup>): 732.9 (M+H)<sup>+</sup>.



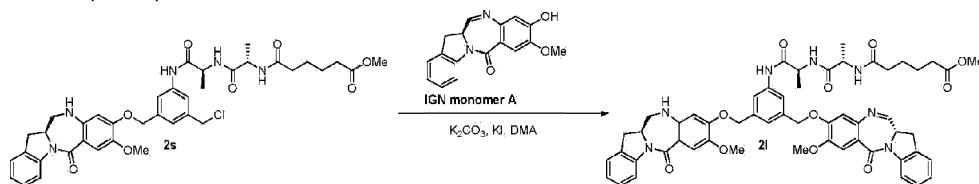
**[0145]** To a solution of **2r** (0.26 g, 0.36 mmol) in DMA (10 mL) was added potassium iodide (0.06 g, 0.355 mmol, 1.0 equiv.), **reduced IGN monomer A** (0.1 g, 0.37 mmol, 1.05 equiv.) and potassium carbonate (0.15 g, 1.06 mmol, 3.0 equiv.). The reaction was warmed up to 40 °C and stirred for 4 h. The reaction was quenched with water (20 mL) and the mixture stirred for 10 min. The resulting solid was filtered. The solid was redissolved in DCM/MeOH (20:1, 20 mL), washed with water (20 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **2l** (0.097 g, 0.097 mmol, 28% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

### Example 6.

#### [0146]



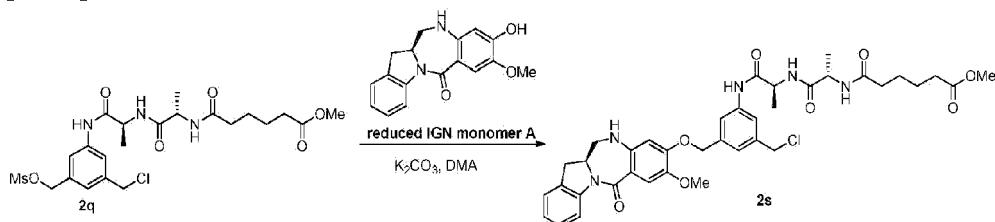
**[0147]** To a solution of **2r** (0.76 g, 1.04 mmol) in DCE (10 mL) was added DMF (3.0 mL) followed by addition of sodium triacetoxyborohydride (0.33 g, 1.56 mmol) at 0 °C. The reaction was stirred at room temperature for 4 h. The reaction was quenched with sat. ammonium chloride (20 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried over magnesium sulfate, filtered and the solvent removed in vacuo to give the desired crude material **2s** as an oil (0.65 g, 0.88 mmol, 85% yield) which was used in the next step without further purification. UPLCMS (2.5 min method) = 1.80 min. Mass observed (ESI<sup>+</sup>): 735.3 (M+H)<sup>+</sup>.



**[0148]** To a solution of **2s** (0.65 g, 0.88 mmol) in DMA (15 mL) was added potassium carbonate (0.25 g, 1.78 mmol, 2.0 equiv.) followed by potassium iodide (0.073 g, 0.44 mmol, 0.5 equiv.) and a solution of **IGN monomer A** (0.29 g, 0.974 mmol, 1.1 equiv.) in DMA (2 mL) was added to the reaction mixture at room temperature. The reaction was heated at 40 °C for 5 h. The reaction was quenched with water (30 mL) and then solid was filtered off. The solid was redissolved in DCM/MeOH (20:1, 30 mL), washed with water (20 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue (0.78 g) was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **21** (0.43 g, 0.43 mmol, 49% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

### Example 7.

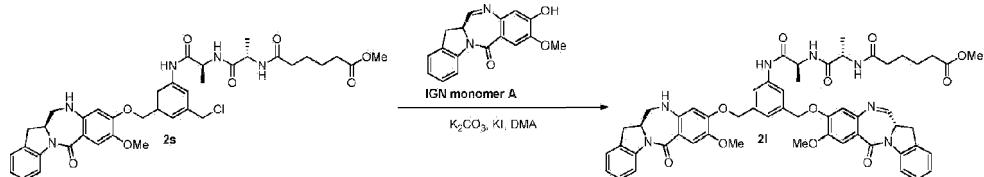
**[0149]**



**[0150]** To a solution of **2q** (0.14 g, 0.27 mmol) in DMA (3 mL) was added potassium carbonate (0.11 g, 0.81 mmol) followed by a solution of **reduced IGN monomer A** (0.084 g, 0.28 mmol) in DMA (1 mL). The reaction was stirred at room temperature for 12 h. The reaction was quenched with water (20 mL) and the mixture stirred for 10 min. The solid was filtered and then dissolved in DCM/MeOH (9/1, 20 mL) and washed with brine (10 mL). The organic layer was separated and dried over magnesium sulfate, filtered and solvent removed in vacuo. The

crude material was purified by silica gel chromatography using DCM (MeOH/EtOAc, 1/4) to give desired product **2s** (0.08 g, 0.11 mmol, 40% yield). UPLCMS (2.5 min method) = 1.63 min.

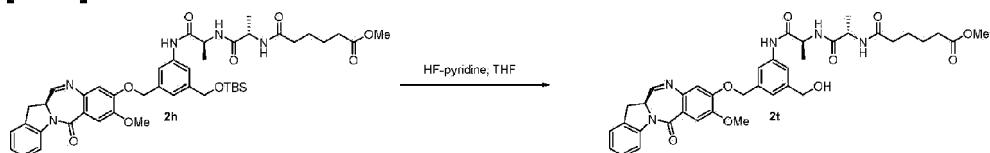
Mass observed (ESI<sup>+</sup>): 735.2 (M+H)<sup>+</sup>



**[0151]** To a solution of **2s** (0.06 g, 0.09 mmol) in DMA (2 mL) was added potassium carbonate (0.025 g, 0.18 mmol) followed by potassium iodide (0.007 g, 0.044 mmol). A solution of **IGN monomer A** (0.03 g, 0.097 mmol) in DMA (1 mL) was added to the reaction mixture at room temperature. The reaction was heated at 40 °C for 5h., The reaction was cooled down and quenched with water (20 mL) and the solid was filtered off. The solid was redissolved in DCM/MeOH (20:1, 20 mL), washed with water (10 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue (0.07 g) was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **2l** (0.035 g, 0.035 mmol, 51% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

#### Example 8.

#### [0152]

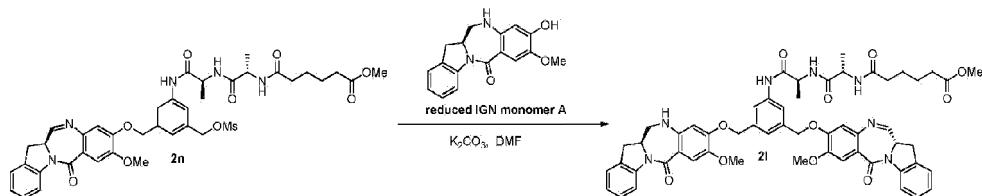


**[0153]** To a solution of **2h** (0.85 g, 1.027 mmol) in THF (9 mL) was added DIPEA (0.54 mL, 3.1 mmol, 3.0 equiv.) followed by HF-pyridine (0.3 mL, 2.053 mmol, 2.0 equiv.) at room temperature. The reaction was stirred for 3 h at room temperature. The reaction was quenched with sat. sodium bicarbonate (10 mL), the layers were separated and the aqueous layer extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and filtered. The solvent was removed in vacuo to give crude product as a solid which was washed with EtOAc to give the desired product **2t** (0.64 g, 0.89 mmol, 87% yield). UPLCMS (2.5 min method) = 1.36 min. Mass observed (ESI<sup>+</sup>): 714.6 (M+H)<sup>+</sup>.



**[0154]** To a solution of **2t** (0.23 g, 0.322 mmol) in dichloromethane (3 mL) was added DIPEA (0.11 ml, 0.644 mmol, 2.0 equiv.) followed by methanesulfonic anhydride (0.084 g, 0.48 mmol, 1.5 equiv.) as a solution in DCM (1 mL) at 0 °C. The reaction was stirred for 1 h. The reaction was quenched with water (3 mL) and diluted with DCM (3 mL). The layers were separated and the organic layer was washed with brine (3 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo and the crude material **2n** (0.25 g, 0.31 mmol, 98% yield) was used in the next step without further purification. UPLCMS (2.5 min method) = 1.45 min.

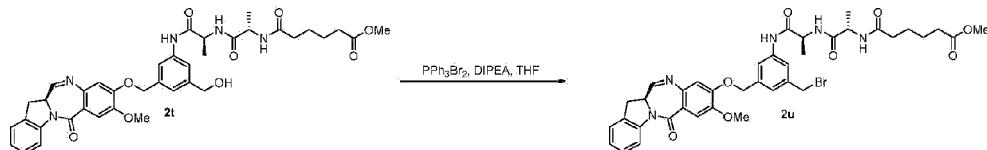
Mass observed (ESI<sup>+</sup>): 792.5 (M+H)<sup>+</sup>.



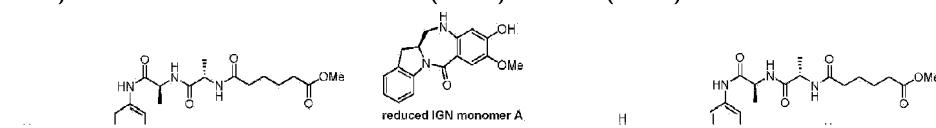
**[0155]** To a solution of **2n** (0.02 g, 0.027 mmol) in DMF (0.2 ml) was added potassium carbonate (0.007g, 0.053 mmol, 2.0 equiv.) followed by **reduced IGN monomer A** (0.009g, 0.029 mmol, 1.1 equiv.) and the reaction was stirred at room temperature for 18 h. Water (3 mL) was added to the reaction mixture and the resulting solid was filtered. The solid was redissolved in DCM/MeOH (20:1, 5 mL), washed with water (5 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **21** (0.005 g, 0.005 mmol, 19% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

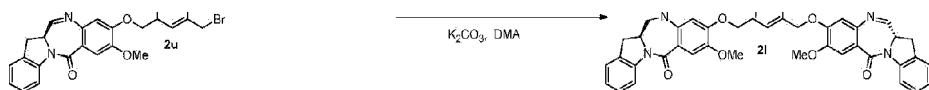
#### Example 9.

#### [0156]



**[0157]** To a solution of **2t** (0.02 g, 0.031 mmol) in THF (2 mL) was added DIPEA (0.016 mL, 0.092 mmol, 3.0 equiv.) followed by a solution of dibromotriphenylphosphorane (0.03 g, 0.062 mmol, 2.0 equiv.) in THF (0.5 mL). The reaction was stirred at room temperature for 12 h., The reaction was stopped by evaporation of solvent and then the crude material was purified by silica gel chromatography to give **2u** (0.006 g, 0.007 mmol, 25% yield). UPLCMS (2.5 min method) = 1.56 min. Mass observed (ESI<sup>+</sup>): 778.2 (M+H)<sup>+</sup>.





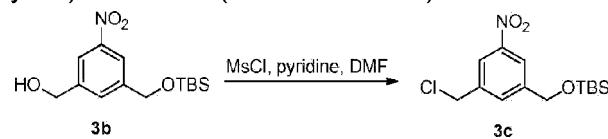
**[0158]** To a solution of **2u** (0.006 g, 7.73  $\mu$ mol) in DMA (1 mL) was added **reduced IGN monomer A** (0.003 g, 9.27  $\mu$ mol) followed by potassium carbonate (0.002 g, 0.015 mmol) and the reaction was stirred at room temperature for 18 h. Water (3 mL) was added to the reaction mixture and the resulting solid was filtered and washed with water. The solid was redissolved in DCM/MeOH (20:1, 5 mL), washed with water (5 mL), dried with magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **21** (0.001 g, 0.001 mmol, 13% yield). LCMS (8 min method, 5-98%) = 5.4 min. Mass observed (ESI<sup>+</sup>): 991.7 (M+H)<sup>+</sup>.

#### Example 10.

**[0159]**

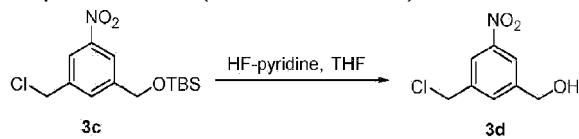


**[0160]** To a solution of (5-nitro-1,3-phenylene)dimethanol **3a** (4.0 g, 21.84 mmol) in DCM (40 mL) and DMF (5 mL) was added DIPEA (3.86 mL, 21.84 mmol, 1.0 equiv.) followed by TBSCl (3.29 g, 21.84 mmol, 1.0 equiv.) as a solution in DMF (5 mL). The reaction was stirred at 0 °C for 1 h.. The reaction was quenched with sat. ammonium chloride (20 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic layers were washed with water (2 x 50 mL), brine, dried over magnesium sulfate, filtered and solvent was removed in vacuo to give a crude yellow oil. The crude product was purified by silica gel chromatography (DCM/MeOH) to give desired product **3b** (3.69 g, 12.41 mmol, 57% yield). UPLCMS (2.5 min method) = 1.96 min. Mass observed (ESI<sup>+</sup>): 298.5 (M+H)<sup>+</sup>.

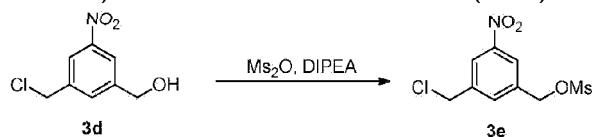


**[0161]** To a solution of **3b** (2.0 g, 6.72 mmol) in DMF (50 mL) was added pyridine (1.6 ml, 20.17 mmol, 3.0 equiv.) followed by methanesulfonyl chloride (1.1 mL, 13.45 mmol, 2.0 equiv.) at 0 °C. The reaction was warmed to rt and was stirred for 3 h. The reaction was quenched with sat. sodium bicarbonate (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), dried over magnesium sulfate and filtered. The solvent removed in vacuo and the crude material **3c** (2.0g, 6.7 mmol, 94% yield) was carried crude onto the next

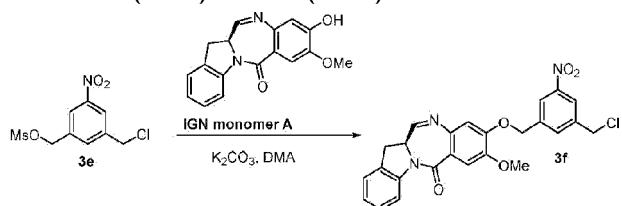
step. UPLCMS (2.5 min method) = 2.22 min. Mass observed (ESI<sup>+</sup>): 316.7 (M+H)<sup>+</sup>.



[0162] To a solution of **3c** (2.0 g, 6.33 mmol) in THF (38.9 mL) was added DIPEA (5.5 mL, 31.6 mmol, 5.0 equiv.) followed by HF-pyridine (2.7 mL, 19.0 mmol, 3.0 equiv.) and the reaction was stirred at room temperature for 2 h. The reaction was then quenched with sat. sodium bicarbonate (100 mL). The layers were separated and then the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were then washed with water (30 mL), brine (30 mL), dried over magnesium sulfate and filtered. The excess of solvent was removed in vacuo to give desired product **3d** (1.1g, 5.46 mmol, 86% yield). UPLCMS (2.5 min method) = 1.31 min. Mass observed (ESI<sup>+</sup>): 202.4 (M+H)<sup>+</sup>.

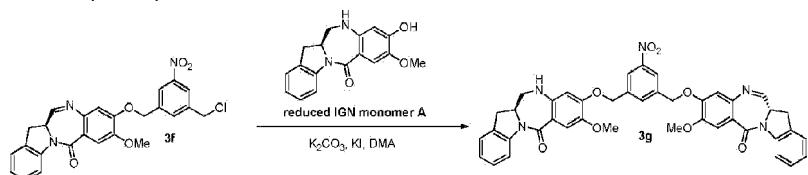


[0163] To a solution of **3d** (1.0 g, 4.96 mmol) in DCM (10 mL) was added DIPEA (2.6 mL, 14.9 mmol, 3.0 equiv.) at 0 °C then a solution of methanesulfonic anhydride (1.1 g, 6.45 mmol, 1.3 equiv.) in DCM was added to the reaction mixture. The reaction was stirred for 1 h. The reaction was quenched with water (10 mL) and the layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with sat. sodium bicarbonate (10 mL), brine (20 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo and the crude material **3e** (1.3 g, 4.65 mmol, 94% yield) was used in the next step without further purification. UPLCMS (2.5 min method) = 1.51 min. Mass observed (ESI<sup>+</sup>): 280.6 (M+H)<sup>+</sup>.



[0164] To a solution of **3e** (0.4 g, 1.43 mmol) and potassium carbonate (0.6 g, 4.29 mmol, 3.0 equiv.) in DMA (13.4 mL) was added a solution of **IGN monomer A** (0.46 g, 1.57 mmol, 1.1 equiv.) in DMA (2 mL) at room temperature and the reaction was stirred for 5 h. The reaction was quenched with water (30 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over magnesium sulfate and the solvent was removed in vacuo. The crude oil was purified over silica gel chromatography using DCM / MeOH to give compound **3f** (0.37g, 0.77 mmol, 54% yield). UPLCMS (2.5 min method) = 1.69 min. Mass observed (ESI<sup>+</sup>):

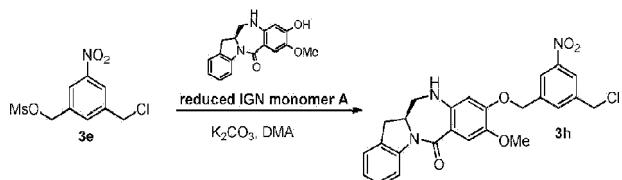
478.3 (M+H)<sup>+</sup>.



**[0165]** To a solution of **3f** (0.11 g, 0.23 mmol) in DMA (3.0 mL) was added potassium carbonate (0.095 g, 0.69 mmol, 3.0 equiv.), followed by potassium iodide (0.02 g, 0.11 mmol, 0.5 equiv.). A solution of **reduced IGN monomer A** (0.07 g, 0.25 mmol, 1.1 equiv.) in DMA (1 mL) was added. The reaction was then gently heated at 35 °C for 5 h. The reaction was quenched with water, and the solid was filtered off. The solid was redissolved in DCM/MeOH (20:1), washed with water, dried with magnesium sulfate, filtered and concentrated. The crude residue (0.13 g) was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **3g** (0.063 g, 0.085 mmol, 36% yield). UPLC/MS (2.5 min method) = 1.79 min. Mass observed (ESI<sup>+</sup>): 738.3 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, reported as a mixture of water adducts) <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.43 - 8.36 (m, 2H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.13 - 8.02 (m, 2H), 7.44 - 7.14 (m, 6H), 7.14 - 6.99 (m, 2H), 6.79 (s, 0.5H), 6.56 (s, 0.5H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.39 (d, *J* = 6.9 Hz, 1H), 6.17 (d, *J* = 6.8 Hz, 0.5H), 5.69 (s, 0.5H), 5.59 (d, *J* = 5.7 Hz, 0.5H), 5.47 - 5.27 (m, 4H), 5.03 (t, *J* = 6.1 Hz, 0.5H), 4.77 (dd, *J* = 9.1, 6.8 Hz, 0.5H), 4.61 (dt, *J* = 9.7, 5.1 Hz, 0.15H), 4.50 - 4.39 (m, 0.5H), 4.27 (dd, *J* = 10.9, 4.2 Hz, 0.5H), 4.16 (td, *J* = 9.6, 2.9 Hz, 0.5H), 3.95 (s, 0.5H), 3.89 - 3.76 (m, 6H), 3.76 - 3.44 (m, 4H), 3.20 - 3.08 (m, 1H), 2.96 (dd, *J* = 17.0, 4.4 Hz, 1H).

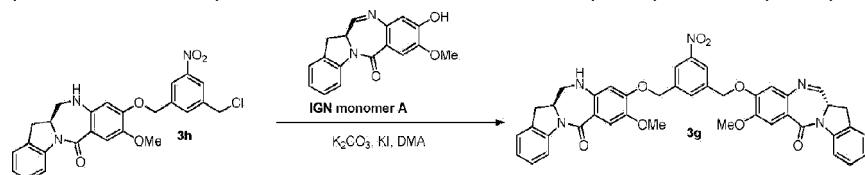
#### Example 11.

**[0166]**



**[0167]** To a solution of **3e** (0.45 g, 1.61 mmol) in DMA (15.1 mL) was added potassium carbonate (0.67 g, 4.83 mmol, 3.0 equiv.) followed by a solution of **reduced IGN monomer A** (0.5 g, 1.69 mmol, 1.1 equiv.) in DMA (2 mL). The reaction was stirred at room temperature for 5h.. The reaction was quenched with water (30 mL) and the mixture was stirred for 10 min. The solid was filtered and then dissolved in DCM/MeOH (9/1, 30 mL) and washed with brine (20 mL). The organic layer was separated and dried over magnesium sulfate, filtered and the solvent removed in vacuo. The crude material was purified by silica gel chromatography using Hexane/EtOAc to give compound **3h** (0.28 g, 0.58 mmol, 36% yield) as colorless oil. UPLC/MS

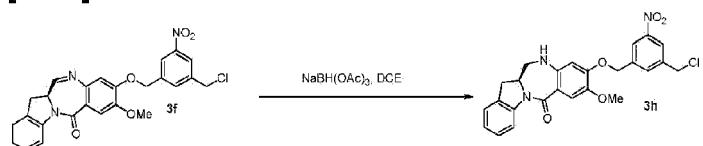
(2.5 min method) = 1.82 min. Mass observed (ESI<sup>+</sup>): 480.3 (M+H)<sup>+</sup>.



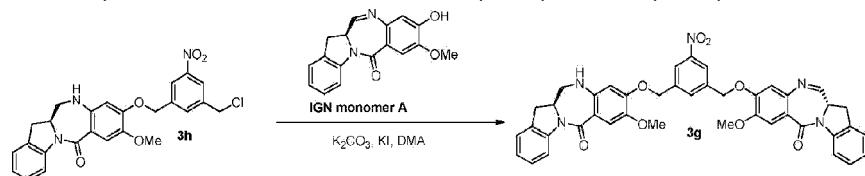
**[0168]** To a solution of **3h** (0.27 g, 0.56 mmol) in DMA (10 mL) was added potassium carbonate (0.16 g, 1.12 mmol, 2.0 equiv.) followed by potassium iodide (0.05 g, 0.28 mmol, 0.05 equiv.). A solution of **IGN monomer A** (0.18 g, 0.62 mmol, 1.1 equiv.) in DMA (2 mL) was added to the reaction mixture at room temperature. The reaction was then stirred at 40 °C for 3h. The reaction was quenched with water (20 mL) and the solid was filtered off and washed with water. The crude yellow solid was dissolved in DCM/MeOH (9/1, 30 mL) and then washed with water (10 mL), dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a crude yellow solid. The crude product was purified by silica gel chromatography using DCM/MeOH (0% to 5% MeOH/DCM) to give the product **3g** as a yellow powder (0.35 g, 0.48 mmol, 86% yield). UPLCMS (2.5 min method) = 1.79 min (2.5 min method). Mass observed (ESI<sup>+</sup>): 738.4 (M+H)<sup>+</sup>.

### Example 12.

**[0169]**



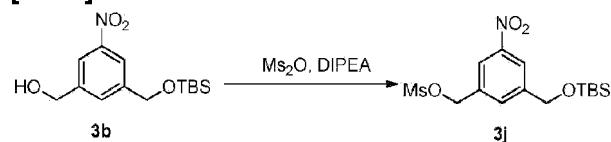
**[0170]** To a solution of **3f** (0.15 g, 0.31 mmol) in DCE (2 mL) was added sodium triacetoxyborohydride (0.067 g, 0.31 mmol, 1.0 equiv.) and the reaction was stirred at room temperature for 1 h. The reaction was quenched with sat. ammonium chloride (1 mL) and then the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent removed in vacuo. The crude brown oil was purified by silica gel chromatography to give desired product **3h** (0.08 g, 0.16 mmol, 52% yield). UPLCMS (2.5 min method) = 1.80 min. Mass observed (ESI<sup>+</sup>): 480.5 (M+H)<sup>+</sup>.



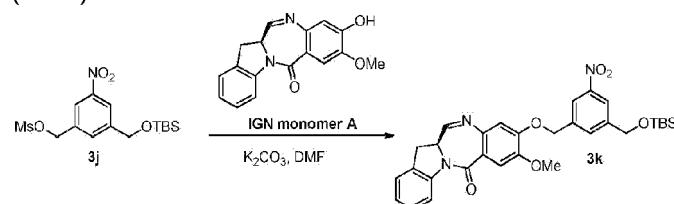
**[0171]** To a solution of **3h** (0.07g, 0.16 mmol) in DMA (2 mL) was added potassium carbonate (0.07 g, 0.47 mmol, 3.0 equiv.) followed by potassium iodide (0.013 g, 0.08 mmol, 0.05 equiv.) and then a solution of **IGN monomer A** (0.05 g, 0.17 mmol, 1.1 equiv.) in DMA (0.5 mL) was added. The reaction was stirred at room temperature for 12h.. Water (20 mL) was added to the mixture and the mixture was stirred for 10 min at which point the solid was filtered. The solid was solubilized in DCM (10 mL) and then washed with brine (10 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent was removed to obtain a yellow oil (0.09 g, 0.12 mmol, 80% yield). UPLCMS (2.5 min method) = 1.79 min (2.5 min method). Mass observed (ESI<sup>+</sup>): 738.5 (M+H)<sup>+</sup>.

**Example 13.**

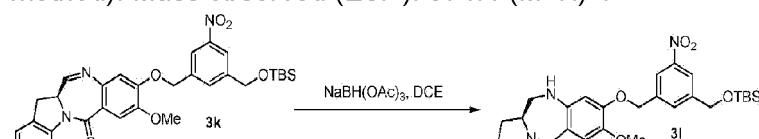
**[0172]**



**[0173]** To a solution of **3b** (1.00 g, 3.4 mmol) in DCM (33 mL) was added DIPEA (1.781 ml, 10.09 mmol, 3.0 equiv.), followed by a solution of methanesulfonic anhydride (0.703 g, 4.03 mmol, 1.2 equiv.) at 0 °C. The reaction was stirred for 1 h. The solvent was evaporated to give the crude product **3j** (1.2 g, 3.2 mmol, 95% yield) which was used in the next step without further purification. UPLCMS (2.5 min method) = 2.04 min. Mass observed (ESI<sup>+</sup>): 376.5 (M+H)<sup>+</sup>.

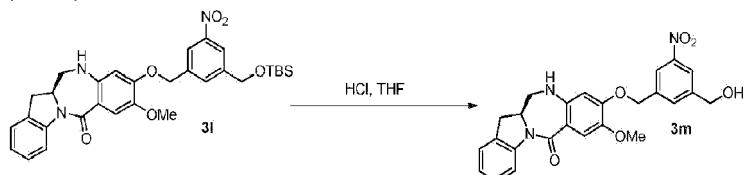


**[0174]** To a solution of **3j** (1.24 g, 3.30 mmol) in DMF (26 mL) was added potassium carbonate (0.91 g, 6.60 mmol, 2.0 equiv.) followed by **IGN monomer A** (0.97 g, 3.30 mmol, 1.0 equiv.) at room temperature for 12 h. The reaction was quenched with water (60 mL) and the solid was filtered off and then dissolved in DCM/MeOH (20/1, 20 mL). The organic layer was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed in vacuo and the crude material was purified over silica gel chromatography to give the desired product **3k** (1.3 g, 2.27 mmol, 69% yield). UPLCMS (2.5 min method) = 2.12 min (2.5 min method). Mass observed (ESI<sup>+</sup>): 574.4 (M+H)<sup>+</sup>.

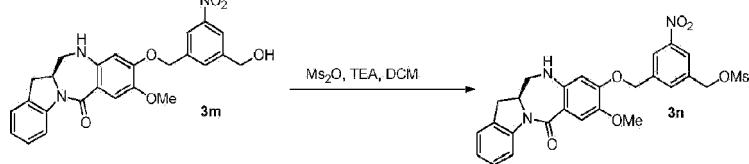




**[0175]** **3k** (0.63 g, 1.1 mmol) was dissolved in anhydrous DCE (11 mL). Sodium triacetoxyborohydride (0.70 g, 3.3 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 1 h at room temperature. The mixture was quenched with sat. ammonium chloride (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to obtain **3l** (0.58 g, 1.0 mmol, 92% yield). UPLCMS (8.0 min method) = 7.797 min (8.0 min method). Mass observed (ESI<sup>+</sup>): 576.3 (M+H)<sup>+</sup>.

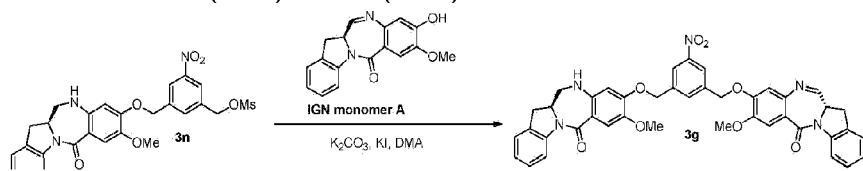


**[0176]** A solution of **3l** (0.58 g, 1.0 mmol) was dissolved in anhydrous THF (5 mL) and 5 M aqueous hydrochloride acid solution (2.01 mL, 10.07 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. sodium bicarbonate (5 mL) and the layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated to give a bright orange solid. The resulting solid was purified by silica gel chromatography (DCM/MeOH) to give compound **3m** (0.33 g, 0.71 mmol, 71% yield). UPLCMS (8.0 min method) = 5.166 min. Mass observed (ESI<sup>+</sup>): 462.1 (M+H)<sup>+</sup>.



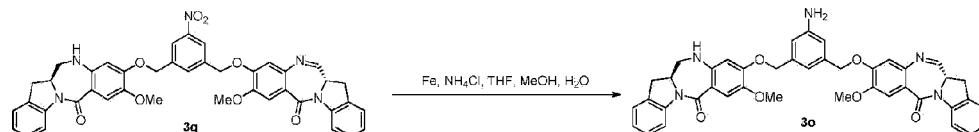
**[0177]** **3m** (0.1 g, 0.22 mmol) was dissolved in anhydrous DCM (1.5 mL) and anhydrous DMF (0.7 mL). The reaction was cooled to 0 °C and triethylamine (0.12 mL, 0.88 mmol) and methanesulfonic anhydride (0.08 g, 0.44 mmol) were added. The reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water (2 x 20 mL), dried over magnesium sulfate, filtered and concentrated. The compound was initially purified by silica gel chromatography (DCM/EtOAc) followed by additional purification by RPPHPLC (MeCN/water) to give the desired product **3n** (0.041 g, 0.076 mmol, 34% yield).

Mass observed (ESI<sup>+</sup>): 540.3 (M+H)<sup>+</sup>.



✓

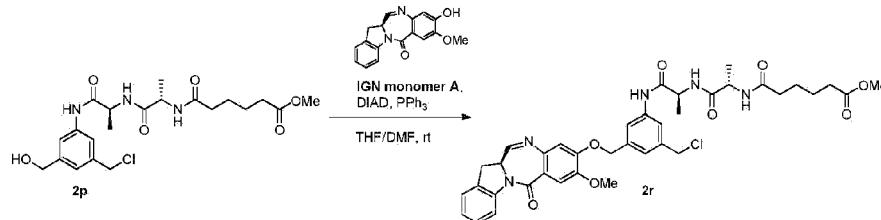
**[0178]** Compound **3n** (0.041 g, 0.076 mmol) and **IGN monomer A** (0.027 g, 0.091 mmol) were dissolved in anhydrous DMA (0.5 mL). Potassium carbonate (0.012 g, 0.091 mmol) and potassium iodide (0.006 g, 0.038 mmol) were added and the mixture stirred for 12 h.. Water (5 mL) was added to the reaction mixture. The solid was filtered off and then redissolved in DCM (20 mL) and washed with water (10 mL). After drying over magnesium sulfate, filtration and concentration, the solid was purified by RPHPLC (ACN/H<sub>2</sub>O) to give **3g** (0.012 g, 0.016 mmol, 21% yield). UPLCMS (2.5 min method) = 1.79 min. Mass observed (ESI<sup>+</sup>): 738.5 (M+H)<sup>+</sup>.



**[0179]** Compound **3g** (0.017 g, 0.023 mmol) was dissolved in anhydrous THF (1 mL), anhydrous MeOH (0.5 mL) and water (0.1 mL). Ammonium chloride (0.012 g, 0.23 mmol, 10.0 equiv.) and iron (0.006 g, 0.115 mmol, 5.0 equiv.) were added. The mixture was stirred at 60 °C for 2 h.. The reaction mixture was cooled to room temp, filtered through Celite and rinsed with 20% MeOH/DCM (10 mL). The filtrate was concentrated and the crude product was purified by silica gel chromatography (DCM/MeOH) to give compound **3o** as a white solid (0.012 g, 0.018 mmol, 76% yield). UPLCMS (2.5 min method) = 1.84 min. Mass observed (ESI<sup>+</sup>): 708.5 (M+H)<sup>+</sup>.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , reported as a mixture of water adducts, T = 330K):  $\delta$  8.26 (d,  $J$  = 7.9 Hz, 1H), 8.17 (d,  $J$  = 7.8 Hz, 1H), 8.03 (d,  $J$  = 4.5 Hz, 1H), 7.49 (s, 1H), 7.42 - 7.33 (m, 2H), 7.36 - 7.08 (m, 4H), 7.09 - 6.95 (m, 2H), 6.76 - 6.64 (m, 3H), 6.47 (s, 1H), 6.15 (d,  $J$  = 6.5 Hz, 1H), 5.11 (m, 2H), 4.98 (m, 2H), 4.58 (dt,  $J$  = 9.9, 4.7 Hz, 1H), 4.47 - 4.36 (m, 1H), 3.87 (m, 1H), 3.76 (s, 3H), 3.71 - 3.46 (m, 4H), 3.39 - 3.28 (m, 1H), 2.93 (dd,  $J$  = 16.8, 4.7 Hz, 1H).

#### Example 14.

**[0180]**

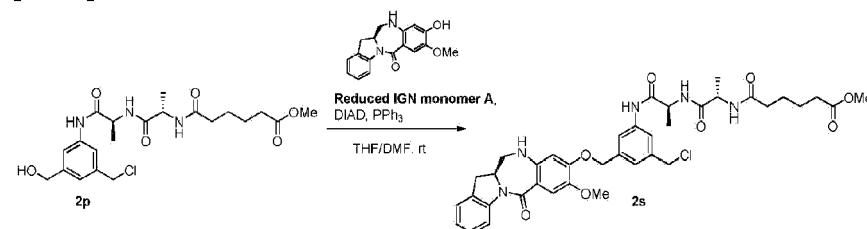


**[0181]** Compound **2p** (0.03 g, 0.066 mmol, 1.0 equiv.) and **IGN monomer A** (0.021 g, 0.072 mmol, 1.1 equiv.) were dissolved in THF (0.65 mL) and DMF (0.3 mL). Triphenylphosphine was added (0.021 g, 0.079 mmol, 1.2 equiv.), followed by a slow addition of DIAD (0.015 mL,

0.079 mmol, 1.2 equiv.). The reaction was stirred at rt under argon for 2 h. The reaction mixture was concentrated and water (~2 mL) was added to triturate the product. The precipitate was filtered and the remaining solid was washed with water. The crude residue was purified by RPHPLC (C18 column, MeCN/water, gradient, 40% to 60%) to give compound **2r** as a white fluffy solid (0.015 g, 0.02 mmol, 31% yield). UPLCMS (2.5 min method) = 1.62 min. Mass observed (ESI<sup>+</sup>) = 732.9 (M+H)<sup>+</sup>.

**Example 15.**

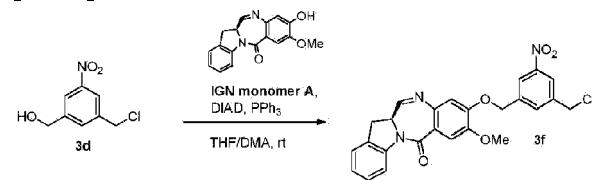
**[0182]**



**[0183]** Compound **2p** (0.03g, 0.066 mmol, 1.0 equiv.) and **reduced IGN monomer A** (0.02g, 0.072 mmol, 1.1 equiv.) were dissolved in THF (0.66 mL) and DMF (0.1 mL). Triphenylphosphine (0.021 g, 0.079 mmol, 1.2 equiv.) was added, followed by a slow addition of DIAD (0.015 mL, 0.079 mmol, 1.2 equiv.). The reaction mixture was stirred at rt under argon for 2 h. The reaction mixture was diluted with DCM and was washed with water (2x). The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by RPHPLC (C18 column, MeCN/water, gradient, 40% to 65%) to yield **2s** as a white fluffy solid (0.017 g, 0.02 mmol, 35% yield). UPLCMS (2.5 min method) = 1.71 min. Mass observed (ESI<sup>+</sup>) = 735.4 (M+H)<sup>+</sup>.

**Example 16.**

**[0184]**

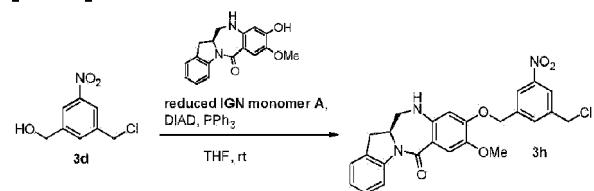


**[0185]** Compound **3d** (0.03 g, 0.149 mmol, 1.0 equiv.) and **IGN monomer A** (0.046 g, 0.156 mmol, 1.05 equiv.) were dissolved in THF (1.5 mL) and DMF (0.3 mL). Triphenylphosphine was added (0.047 g, 0.179 mmol, 1.2 equiv.), followed by a slow addition of DIAD (0.032 mL, 0.164 mmol, 1.1 equiv.). The reaction was stirred at rt under argon for 12 h. The reaction

mixture was concentrated and water (~2 mL) was added to triturate the product. The precipitate was filtered and the remaining solid was washed with water. The crude residue was purified by silica gel chromatography (hexane/EtOAc) to give compound **3f** as a white yellow solid (0.013 g, 0.027 mmol, 18% yield). UPLCMS (2.5 min method) = 1.80 min. Mass observed (ESI<sup>+</sup>) = 478.4 (M+H)<sup>+</sup>.

**Example 17.**

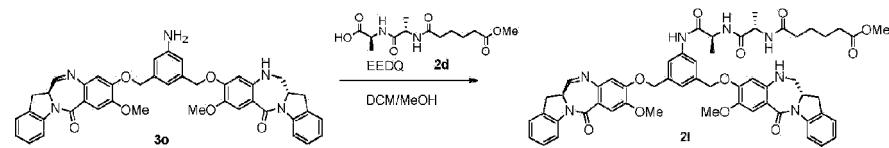
**[0186]**



**[0187]** Compound **3d** (0.03 g, 0.149 mmol, 1.0 equiv.) and **reduced IGN monomer A** (0.046 g, 0.156 mmol, 1.05 equiv.) were dissolved in THF (1.5 mL). Triphenylphosphine was added (0.047 g, 0.179 mmol, 1.2 equiv.), followed by a slow addition of DIAD (0.032 mL, 0.164 mmol, 1.1 equiv.). The reaction was stirred at rt under argon for 2 h. The reaction mixture was concentrated and coevaporated with toluene (2 x). The crude residue was purified by silica gel chromatography (hexane/EtOAc) to give compound **3h** as a orange yellow solid (0.055 g, 0.115 mmol, 77% yield). UPLCMS (2.5 min method) = 1.90 min. Mass observed (ESI<sup>+</sup>) = 480.5 (M+H)<sup>+</sup>.

**Example 18.**

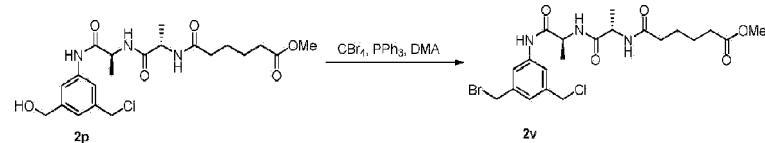
**[0188]**



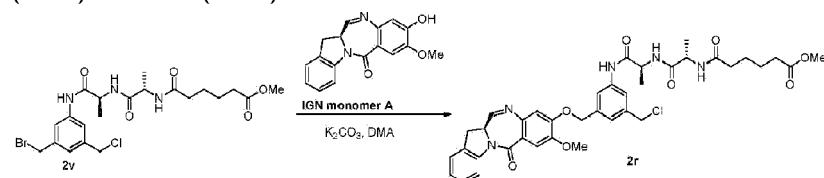
**[0189]** To a solution of **2d** (0.024 g, 0.078 mmol, 1.1 equiv.) in DCM (1 mL) was added EEDQ (0.019 g, 0.078 mmol, 1.1 equiv.). The reaction was stirred for 5 min and MeOH (0.1 mL) was added, followed by a solution of **3o** (0.05 g, 0.071 mmol) in DCM (1 mL). The reaction was stirred at rt for 2 h or until completion of starting material. The reaction was concentrated to form a white precipitate to which MTBE (5 mL) was added and the resulting mixture was stirred for 30 min at room temperature. The solid was filtered off to give compound **21** which was then purified by RPHPLC (C18 column, MeCN/water) to give **21** (0.023 g, 0.023 mmol, 33% yield). UPLCMS (2.5 min method) = 1.75 min. Mass observed (ESI<sup>+</sup>) = 993.2 (M+H)<sup>+</sup>.

## Example 19.

[0190]



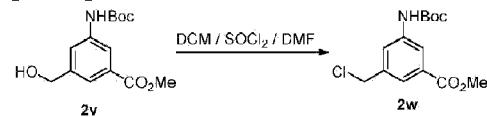
[0191] To a solution of **2p** (0.05 g, 0.110 mmol, 1.0 equiv.) in DMA (1 mL), was added carbon tetrabromide (0.044 g, 0.132 mmol, 1.2 equiv.) followed by triphenylphosphine (0.043 g, 0.164 mmol, 1.5 equiv.) and the reaction was stirred at room temperature for 2 h. The solvent was removed to give a white solid which was triturated with MTBE and the solid was filtered off to give compound **2v**. (0.03 g, 0.058 mmol, 57 % yield, 52% purity), which was carried onto the next step without further purification. UPLCMS (2.5 min method) = 1.59 min. Mass observed ( $\text{ESI}^+$ ) = 518.2 ( $\text{M}+\text{H}$ )<sup>+</sup>.



[0192] To a solution of **2v** (0.03 g, 0.043 mmol, 1.0 equiv.) in DMA (0.5 mL) was added potassium carbonate (0.012 g, 0.087 mmol, 2.0 equiv.) followed by IGN monomer A (0.013 g, 0.046 mmol, 1.05 equiv.). The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with water (5 mL) and the solid was filtered off. The solid was dissolved in DCM/MeOH (9/1, 2 mL). The organic layer was washed with water (10 mL), brine (10 mL), and dried over magnesium sulfate. After filtration and solvent removal, the crude product was purified by RPHPLC (C18 column, MeCN/water) to give **2r** (0.011 g, 0.015 mmol, 35% yield). UPLCMS (2.5 min method) = 1.62 min. Mass observed ( $\text{ESI}^+$ ) = 733.2 ( $\text{M}+\text{H}$ )<sup>+</sup>.

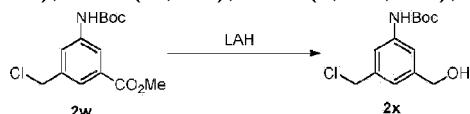
## Example 20

[0193]

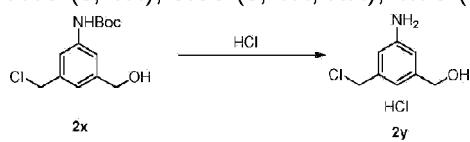


[0194] To a slurry of compound **2v** (14.7 g, 0.052 mol, 1.0 equiv., prepared as described

described in literature, see: Beilstein J. Org. Chem. 2014, 10, 535-543) in DCM and (100 mL) DMF (1 mL), was charged with SOC<sub>12</sub> (12.6 g, 0.104 mol, 2.0 equiv.) in one portion. The resulting solution was stirred at 35 °C overnight resulting in a thick tan slurry. The slurry was filtered and the solid was dried to give 7.5 g as an off-white solid. NMR revealed cleavage of the Boc protecting group. The dark filtrate was charged with solid sodium carbonate (10.6 g, 0.1 mol) followed by buffering to pH ~6-7 by further addition of sodium bicarbonate. To the resulting solution Boc<sub>2</sub>O (12.7 g, 0.058 mol, 1.1 equiv.) was added and was stirred for 0.5 h. The filtered solid (7.5 g) was added to the reaction mixture, followed by the addition of Boc<sub>2</sub>O (6.5 g, 0.030 mol, 1.7 equiv.) (pH~ 6) and continued to stir at rt overnight. Then sat. sodium bicarbonate (10 mL) was added to reach pH 6-7. Additional Boc<sub>2</sub>O (9.3 g, 42.6 mmol), and DMAP (0.2 g, 1.63 mmol) were added and continued to stir overnight. The dark reaction was filtered to remove some precipitate. The DCM layer was washed with 1 N HCl to remove un-Boc product, which was basified and extracted with DCM and recovered 3.0 g colorless crispy solid (un-Boc product). The DCM layer was washed with brine and concentrated to a dark slush. The crude product was purified by silica gel chromatography(EtOAc/Hexanes) to give **2w** as a pale brown solid (9.5 g, 0.031 mmol, 62% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.84 (m, 2H), 7.75 (m, 1H), 6.60 (s, 1H, NH), 4.58 (s, 2H), 3.91 (s, 3H), 1.53 (s, 9H).



**[0195]** A solution of LAH/THF (0.6M, 60 mL, 1.15 equiv.) was stirred at rt for 30 min and then cooled down to -65°C with an acetone-dry ice bath. Compound **2w** (9.3 g, 0.031 mol, 1.0 equiv.) was slowly added in portions (Ti ~-60°C) resulting in a yellow brown slurry which was stirred for 4 h. The reaction was quenched with water (1.3 mL), 15% NaOH (1.3 mL), and water (4 mL) and was stirred for 20 min (Ti ~5°C). The reaction was filtered and rinsed with ethyl acetate (-90 mL). The filtrate was washed with brine, and concentrated to yield **2x** (8.0 g, 0.029 mol, 93% yield) as brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) : δ 7.45 (s, 1H), 7.40 (s, 1H), 7.10 (s, 1H), 6.60 (s, 1H, NH), 4.75 (s, 2H), 4.50 (s, 2H), 1.53 (s, 9H).



**[0196]** Compound **2x** (8.0 g, 0.029 mol, 1.0 equiv.) was dissolved in DCM (20 mL) and cooled in ice-water bath. 4 N HCl/dioxane (15 mL, 1.5 equiv.) was added and the resulting mixture was heated at 50 °C for 1 h and then cooled down to rt. The slurry was concentrated and the solvent switched to heptane. The slurry was filtered, rinsed with hexane, and dried in oven (60 °C) to afford **2y** (5.4 g, 0.026 mol, 88% yield) as light brown solid. <sup>1</sup>H NMR (400 MHz, DMSO-d6): δ 7.45 (s, 1H), 7.25 (s, 2H), 4.76 (s, 2H), 4.52 (s, 2H).



2d HCl 2y 2p

**[0197]** To a solution of **2d** (0.969 g, 3.20 mmol, 1.1 equiv.) in DCM (25 mL) was added EEDQ (0.79 g, 3.2 mmol, 1.1 equiv) at room temperature. After 8 min, a solution of **2y** (0.5 g, 2.91 mmol, 1.0 equiv.), DIPEA (0.51 mL, 2.91 mmol, 1.0 equiv.) in MeOH (5 mL) was added dropwise over 1 minute. The reaction was stirred for 2 h. The reaction mixture was quenched with water (30 mL), the layers were separated and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were washed with sat. sodium bicarbonate (20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated to minimal amount of solvent left. The resulting white solid was diluted in MBTE and was filtered to give the desired product **2p** as a white solid (0.64 g, 1.40 mmol, 48% yield). UPLCMS (2.5 min method) = 1.30 min. Mass observed (ESI<sup>+</sup>) = 456.3 (M+H)<sup>+</sup>.

## REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

### Patent documents cited in the description

- [WO2012128868A \[0002\]](#)
- [WO2016036794A1 \[0003\]](#)
- [WO2016036801A1 \[0004\]](#)

### Non-patent literature cited in the description

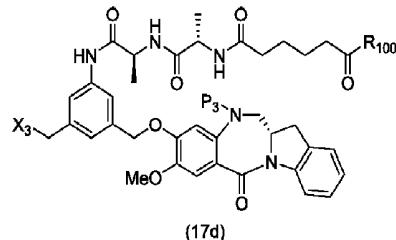
- McGraw-Hill Dictionary of Chemical Terms McGraw-Hill Book Company 1984 0000 [\[0030\]](#)
- ELIEL, E.WILEN, S. Stereochemistry of Organic Compounds John Wiley & Sons, Inc. 1994 0000 [\[0030\]](#)
- P. WUTST. GREENE Protective Groups in Organic Synthesis J. Wiley & Sons 2007 0000 [\[0033\]](#) [\[0034\]](#) [\[0037\]](#) [\[0038\]](#) [\[0056\]](#)
- P. G.M. WUTST. W. GREENE Protective Groups in Organic Synthesis John Wiley & Sons 2007 0000 [\[0033\]](#)

- Beilstein J. Org. Chem., 2014, vol. 10, 535-543 [\[0194\]](#)

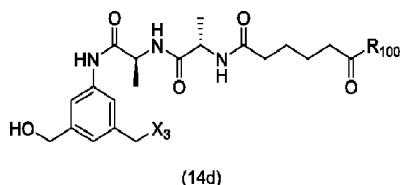
- 1 -

FREMGANGSMÅDER TIL FREMSTILLING AF CYTOKSISKE BENZODIAZEPINDERIVATER  
PATENTKRAV

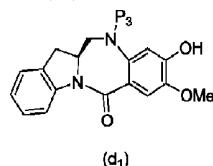
1. Fremgangsmåde til fremstilling af en forbindelse med formlen (17d):



5 eller et salt deraf, hvilken fremgangsmåde omfatter omsætning af en forbindelse med formlen  
(14d)



med en monomerforbindelse med formlen (d<sub>1</sub>),



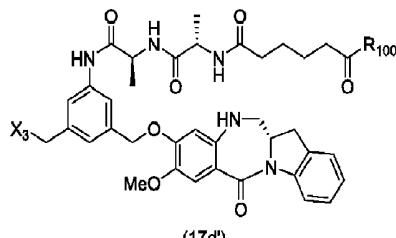
10 hvor X<sub>3</sub> er -Cl; P<sub>3</sub> er H eller en aminbeskyttelsesgruppe; og R<sub>100</sub> er (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

2. Fremgangsmåde ifølge krav 1, hvor forbindelsen med formlen (14d) omsættes med en monomer med formlen (d<sub>1</sub>) i nærvær af et alkoholaktiveringsmiddel og et azodicarboxylat.

3. Fremgangsmåde ifølge krav 2, hvor alkoholaktiveringsmidlet er triphenylphosphin.

4. Fremgangsmåde ifølge krav 2 eller krav 3, hvor azodicarboxylatet er udvalgt fra gruppen  
15 bestående af: diethylazodicarboxylat (DEAD), diisopropylazodicarboxylat (DIAD), 1,1'-(azodicarbonyl)dipiperidin (ADDP) og diterbutylazodicarboxylat (DTAD).

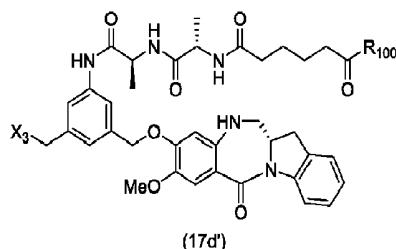
5. Fremgangsmåde ifølge et hvilket som helst af krav 1-4, hvor forbindelsen med formlen (14d) omsættes med monomerforbindelsen med formlen (d<sub>1</sub>), hvor P<sub>3</sub> er H, for at danne en forbindelse med formlen (17d'):



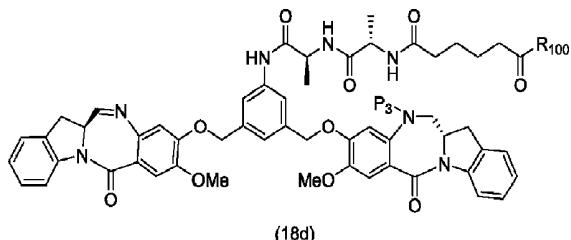
20

6. Fremgangsmåde ifølge et hvilket som helst af krav 1-4, hvor P<sub>3</sub> er en aminbeskyttelsesgruppe og fremgangsmåden endvidere omfatter trinnet med omsætning af forbindelsen med formlen (17d) med et aminafbeskyttelsesreagens for at danne en forbindelse med formlen (17d'):

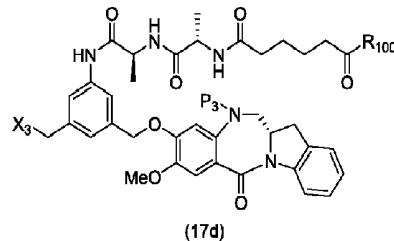
- 2 -



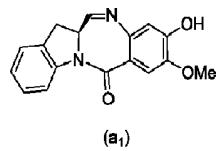
7. Fremgangsmåde til fremstilling af en forbindelse med formlen (18d),



5 eller et farmaceutisk acceptabelt salt deraf, hvilken fremgangsmåde omfatter omsætning af en forbindelse med formlen (17d):



med en monomer med formlen (a<sub>1</sub>):

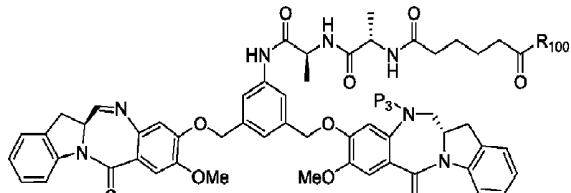


hvor X<sub>3</sub> er -Cl; P<sub>3</sub> er H eller en aminbeskyttelsesgruppe; og R<sub>100</sub> er (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

10 8. Fremgangsmåde ifølge krav 7, hvor forbindelsen med formlen (17d) omsættes med en monomerforbindelse med formlen (a<sub>1</sub>) i nærvær af en base.

9. Fremgangsmåde ifølge krav 8, hvor basen er natriumcarbonat, kaliumcarbonat, cæsiumcarbonat, natriumhydrid eller kaliumhydrid.

10. Fremgangsmåde til fremstilling af en forbindelse med formlen (18d),

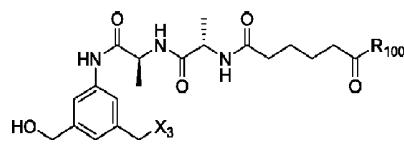


15

eller et farmaceutisk acceptabelt salt deraf, hvilken fremgangsmåde omfatter følgende trin:

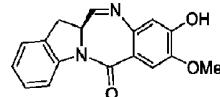
(1) omsætning af forbindelsen med formlen (14d):

- 3 -



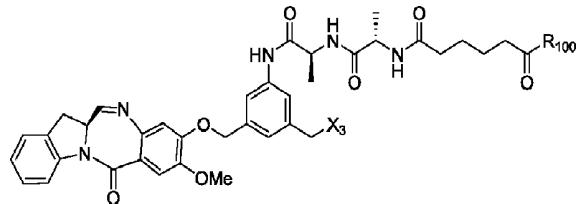
(14d)

,

eller et salt deraf, med en monomerforbindelse med formlen (a<sub>1</sub>),(a<sub>1</sub>)

,

for at danne en forbindelse med formlen (16d):

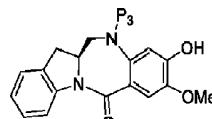


(16d)

,

5

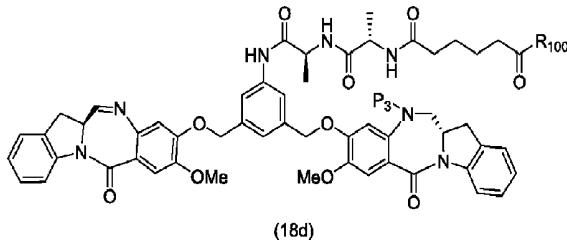
eller et salt deraf; og

(2) omsætning af forbindelsen med formlen (16d) med en reduceret monomer med formlen (d<sub>1</sub>):(d<sub>1</sub>)

for at danne en forbindelse med formlen (18d), eller et farmaceutisk acceptabelt salt deraf, hvor

10 X<sub>3</sub> er -Cl; P<sub>1</sub> er en alkoholbeskyttelsesgruppe; P<sub>3</sub> er H eller en aminbeskyttelsesgruppe; og R<sub>100</sub> er (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

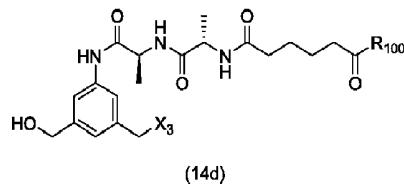
11. Fremgangsmåde til fremstilling af en forbindelse med formlen (18d),



(18d)

eller et farmaceutisk acceptabelt salt deraf, hvilken fremgangsmåde omfatter følgende trin:

15 (1) omsætning af forbindelsen med formlen (14d):

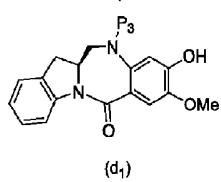


(14d)

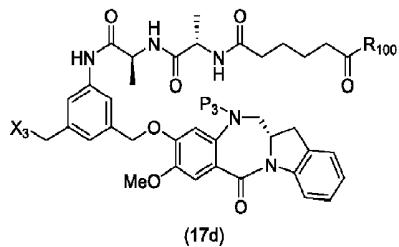
,

eller et salt deraf, med en reduceret monomerforbindelse med formlen (d<sub>1</sub>),

- 4 -

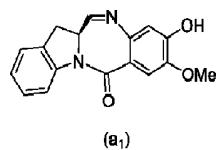


for at danne en forbindelse med formlen (17d):



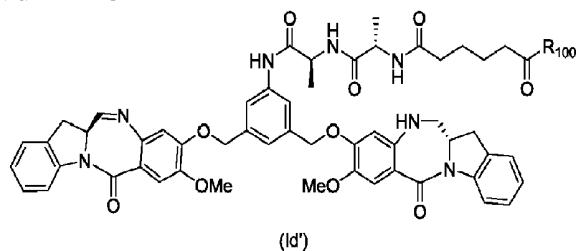
eller et salt deraf; og

5 (2) omsætning af forbindelsen med formlen (17d) med en monomer med formlen (a<sub>i</sub>):

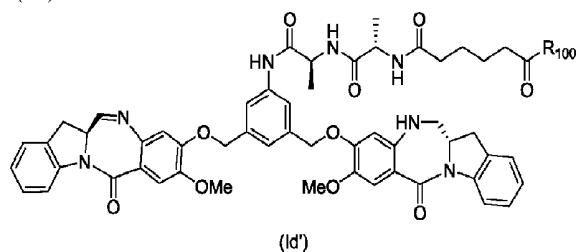


for at danne en forbindelse med formlen (18d), eller et farmaceutisk acceptabelt salt deraf, hvor X<sub>3</sub> er -CI; P<sub>1</sub> er en alkoholbeskyttelsesgruppe; P<sub>3</sub> er H eller en aminbeskyttelsesgruppe; og R<sub>100</sub> er (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

10 12. Fremgangsmåde ifølge krav 7, 8, 9 eller 11, hvor forbindelsen med formlen (17d) omsættes med monomer med formlen (a<sub>1</sub>), hvor P<sub>3</sub> er H, for at danne en forbindelse med formlen (Id'):

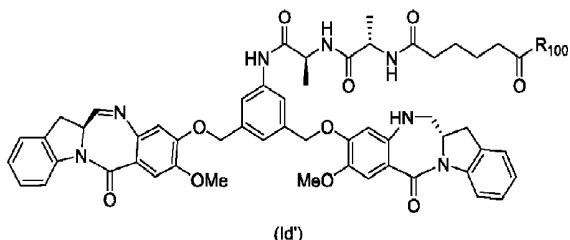


13. Fremgangsmåde ifølge et hvilket som helst af krav 7-11, hvor P<sub>3</sub> er en aminbeskyttelsesgruppe og forbindelsen med formlen (18d) endvidere omsættes med et aminafbeskyttelsesreagens for at danne en 15 forbindelse med formlen (Id'):



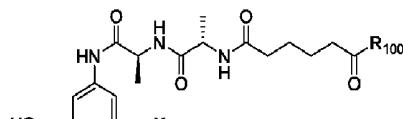
14. Fremgangsmåde til fremstilling af en forbindelse med formlen (Id'),

- 5 -

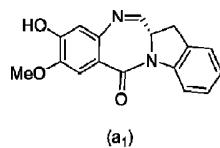


eller et farmaceutisk acceptabelt salt deraf, hvilken fremgangsmåde omfatter følgende trin:

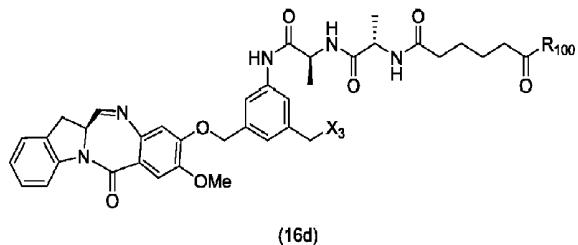
(1) omsætning af forbindelsen med formlen (14d):



eller et salt deraf, med en monomerforbindelse med formlen (a<sub>1</sub>),

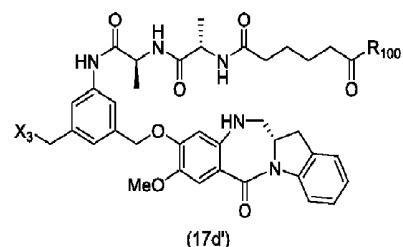


for at danne en forbindelse med formlen (16d):



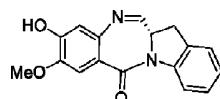
eller et salt deraf;

(2) omsætning af forbindelsen med formlen (16d) med et iminreduktionsmiddel for at danne en forbindelse med formlen (17d'):



eller et salt deraf; og

(3) omsætning af forbindelsen med formlen (17d') med en monomer med formlen (a<sub>1</sub>):



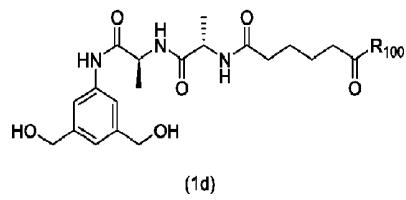
15

for at danne forbindelsen med formlen (Id'); hvor X<sub>3</sub> er -Cl; P<sub>1</sub> er en alkoholbeskyttelsesgruppe; og R<sub>100</sub> er (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

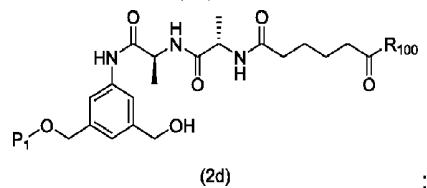
- 6 -

15. Fremgangsmåde ifølge et hvilket som helst af krav 1-6 og 10 til 14, hvor forbindelsen med formlen (14d) eller et salt deraf fremstilles ved en fremgangsmåde, der omfatter følgende trin:

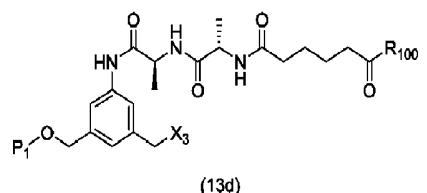
(1) omsætning af en forbindelse med formlen (1d) med et alkoholbeskyttelsesreagens



5 for at danne en forbindelse med formlen (2d):



(2) omsætning af et chloreringsreagens med forbindelsen med formlen (2d) for at danne en forbindelse med formlen (13d),



10 eller et salt deraf;

(3) omsætning af forbindelsen med formlen (13d) med et alkoholafbeskyttelsesreagens for at danne forbindelsen med formlen (14d) eller et salt deraf.

16. Fremgangsmåde ifølge et hvilket som helst af krav 1-15, hvor R100 er methoxy.

## DRAWINGS

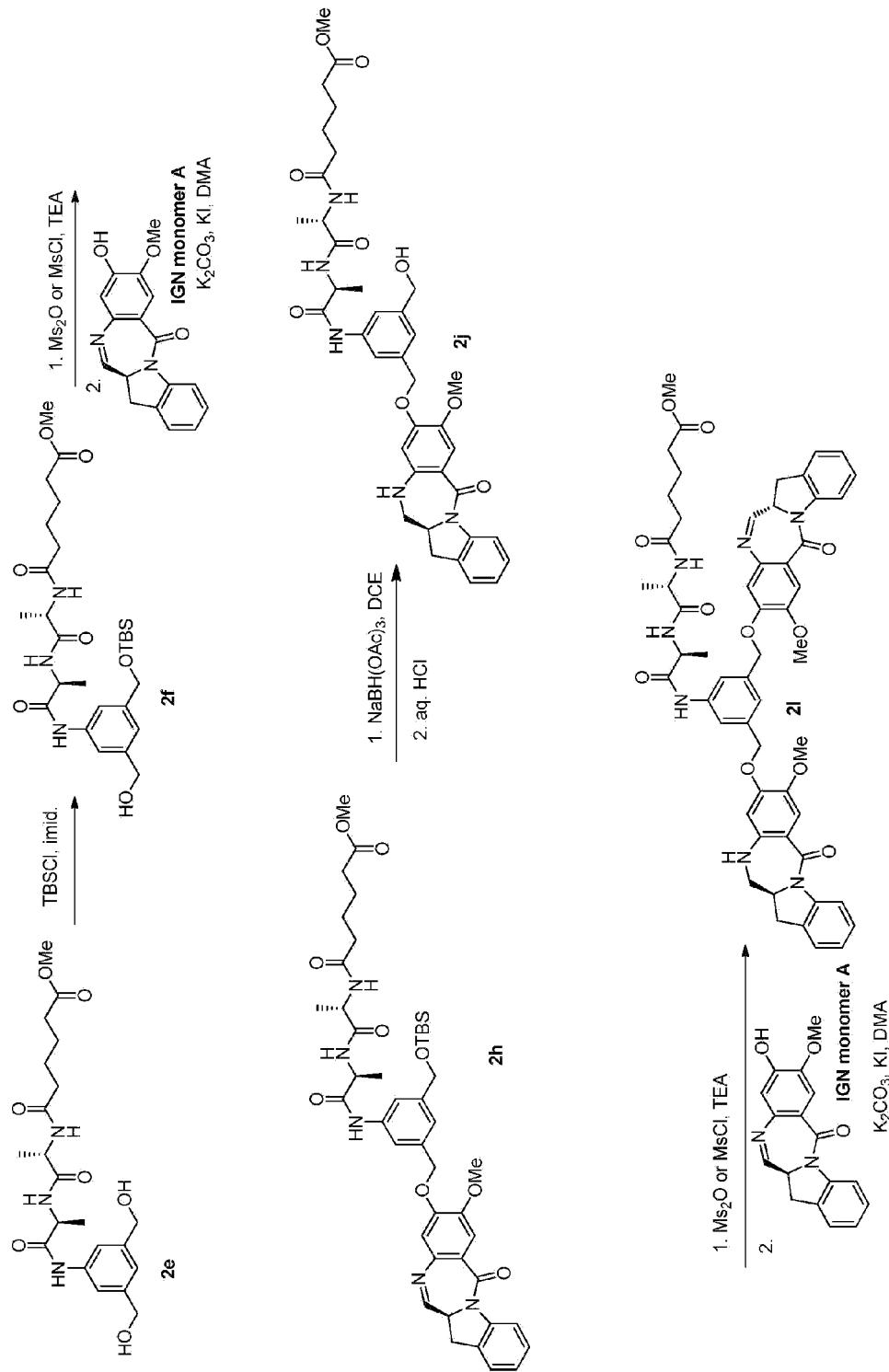


FIG. 1

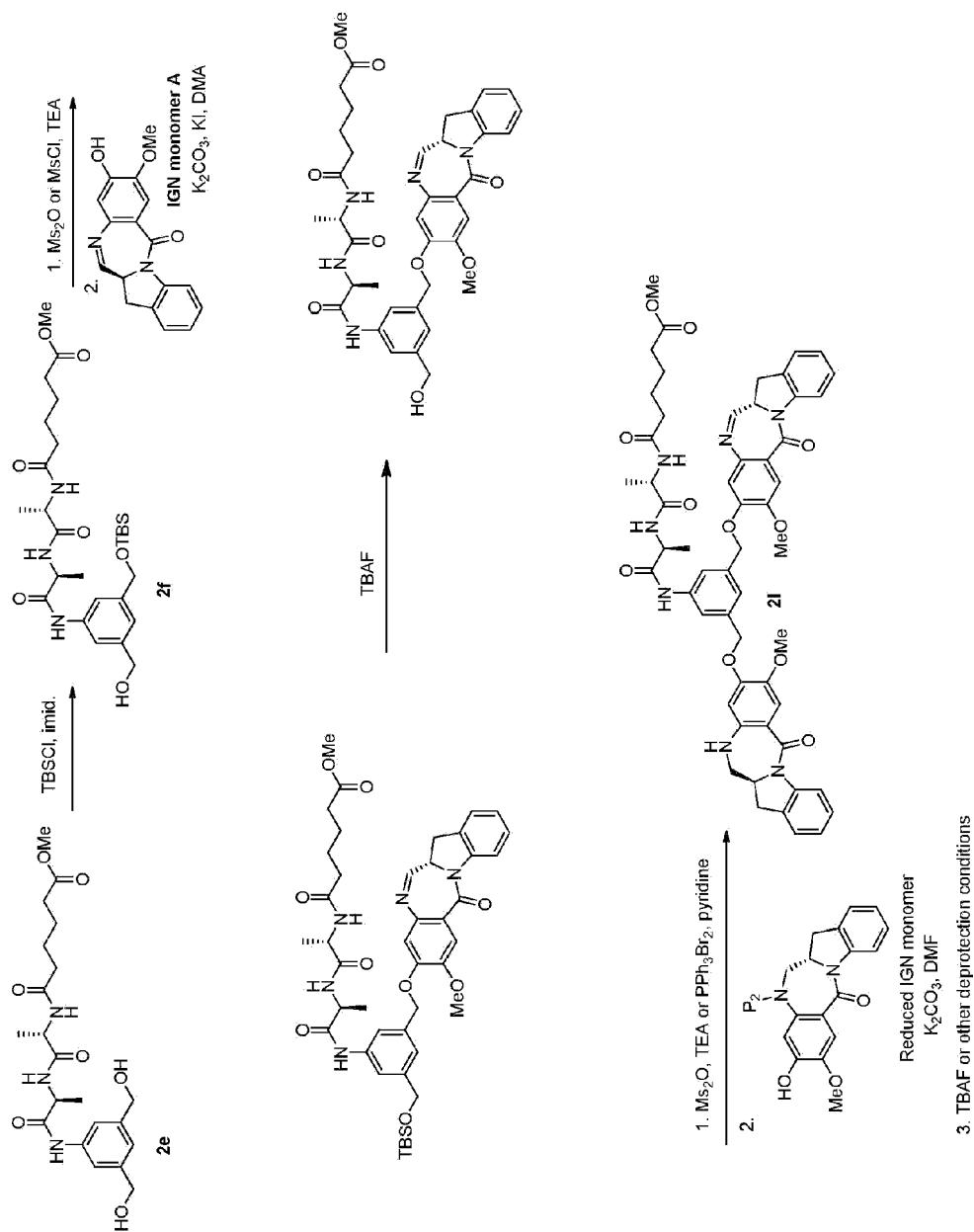


FIG. 2

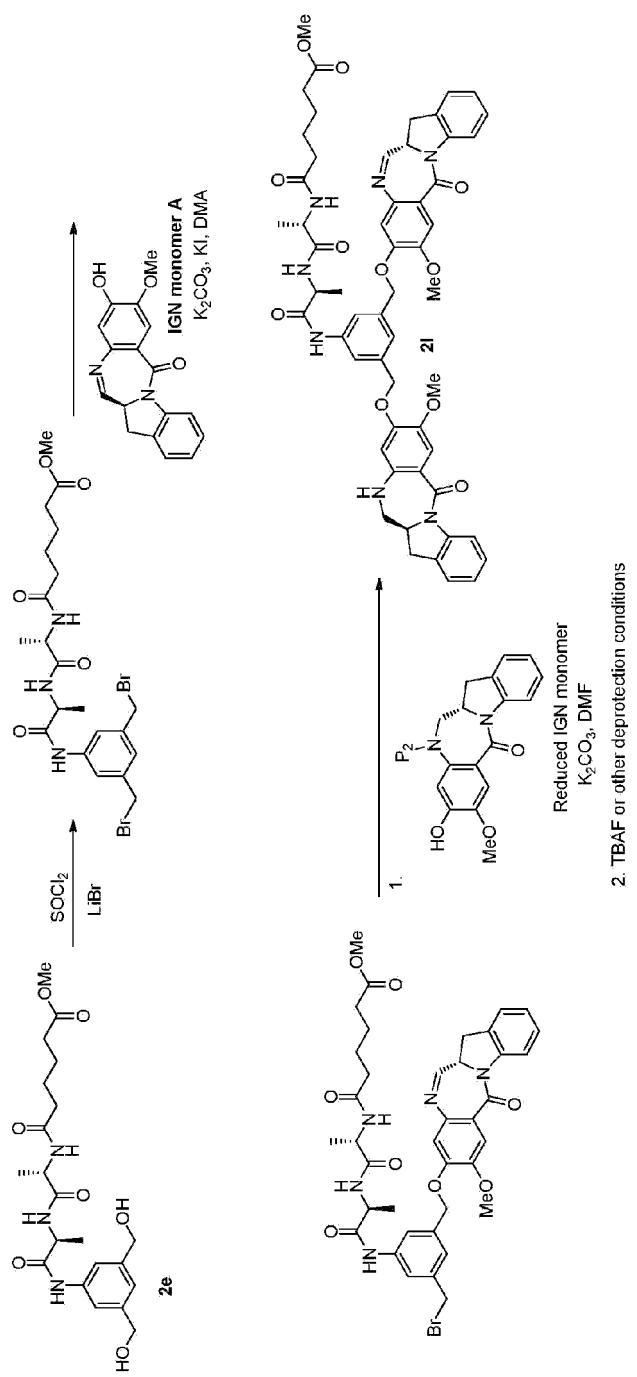


FIG. 3

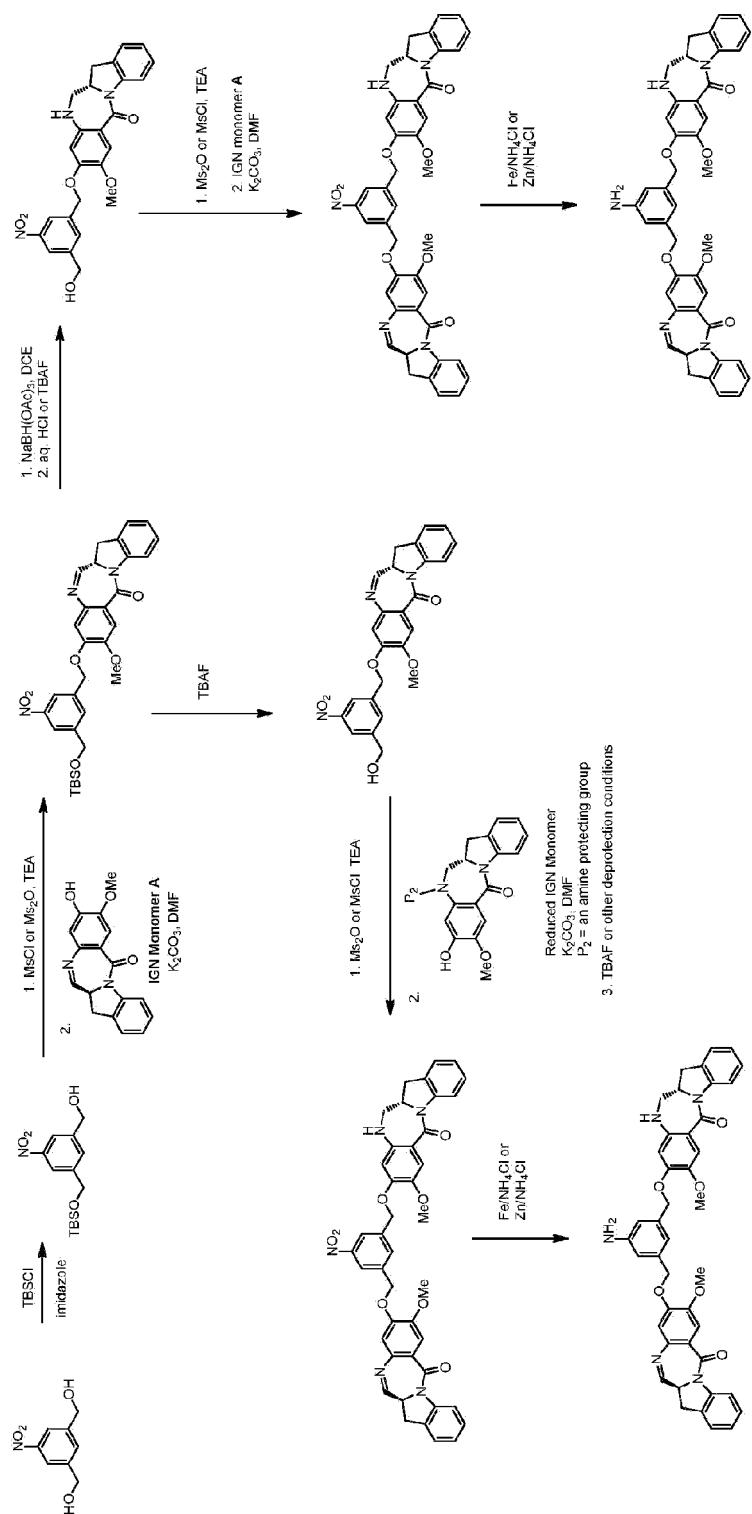


FIG. 4

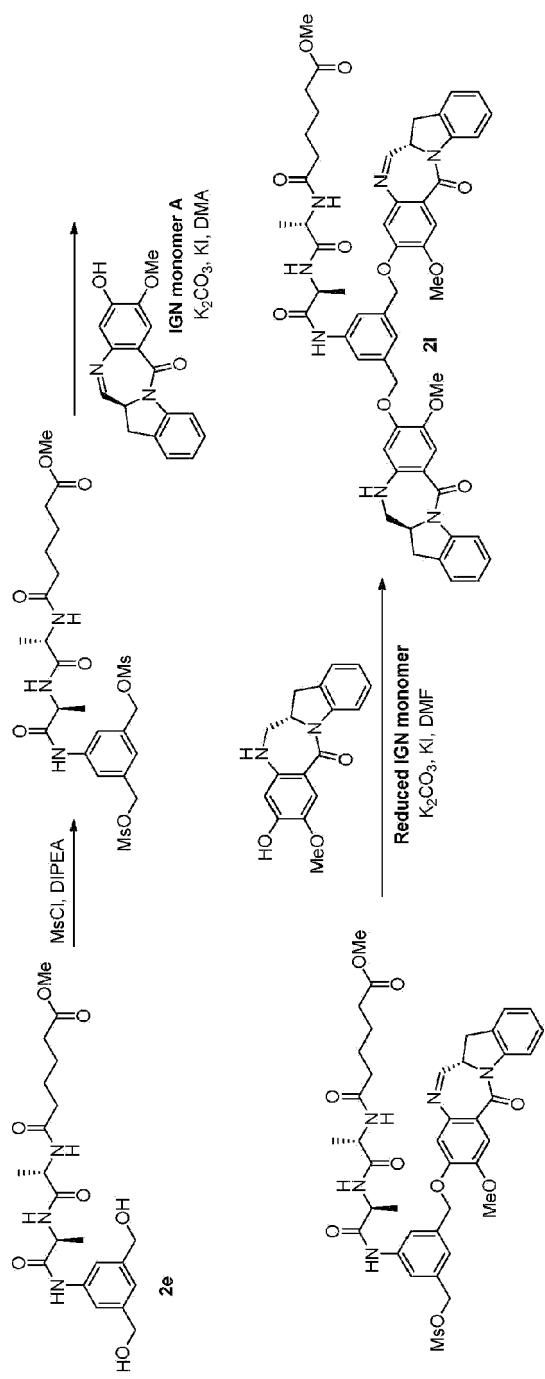


FIG. 5

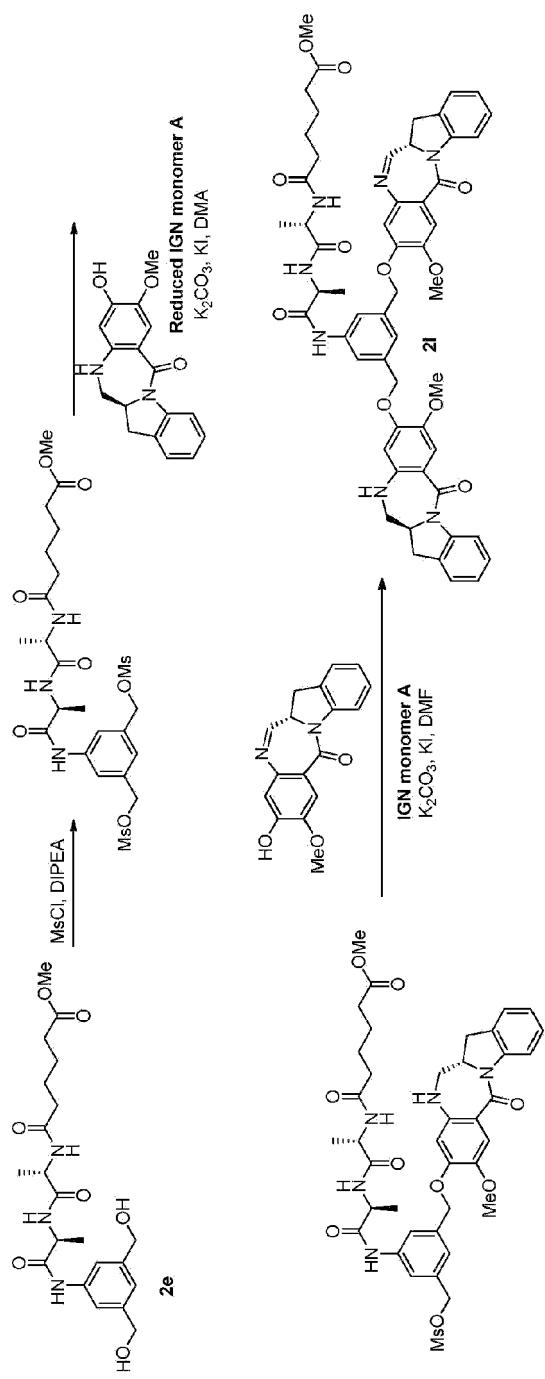


FIG. 6

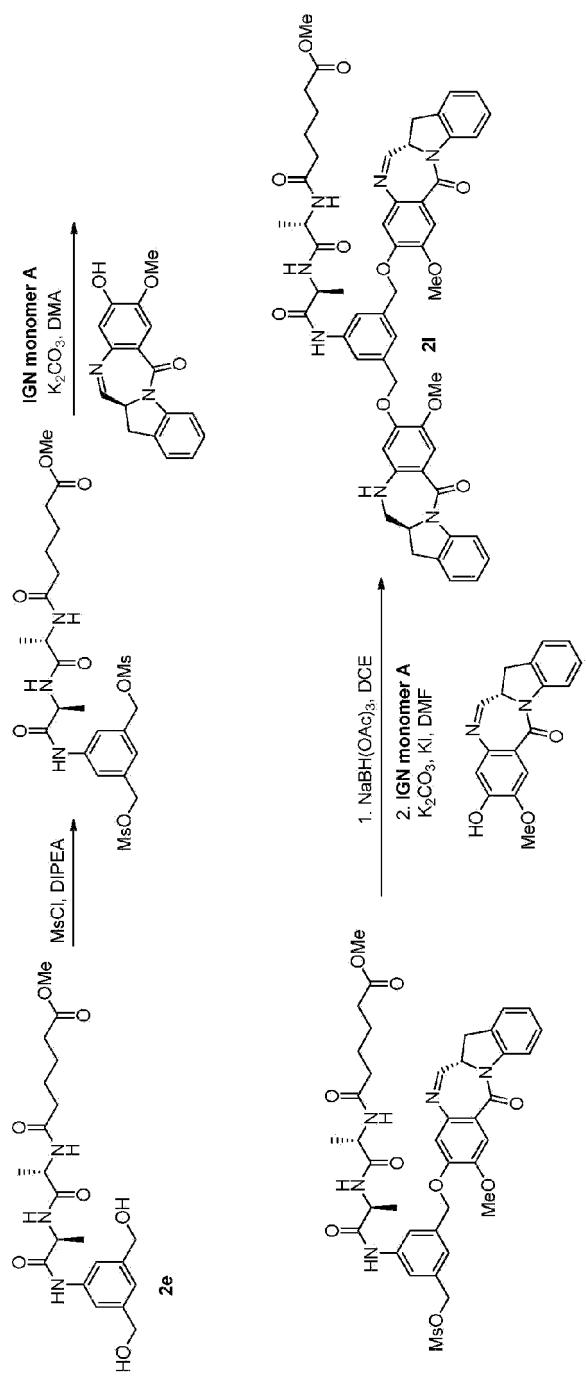


FIG. 7

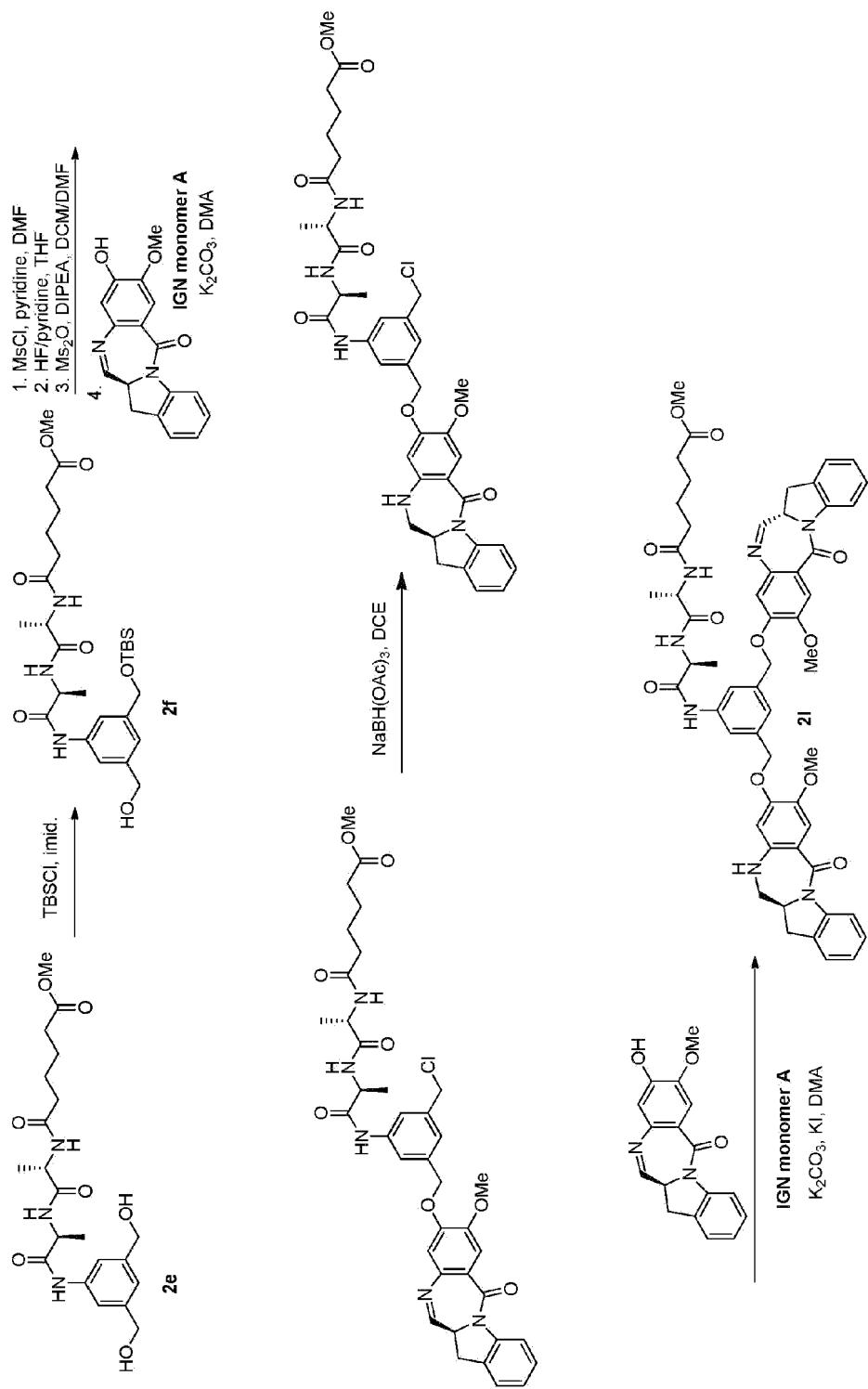


FIG 8

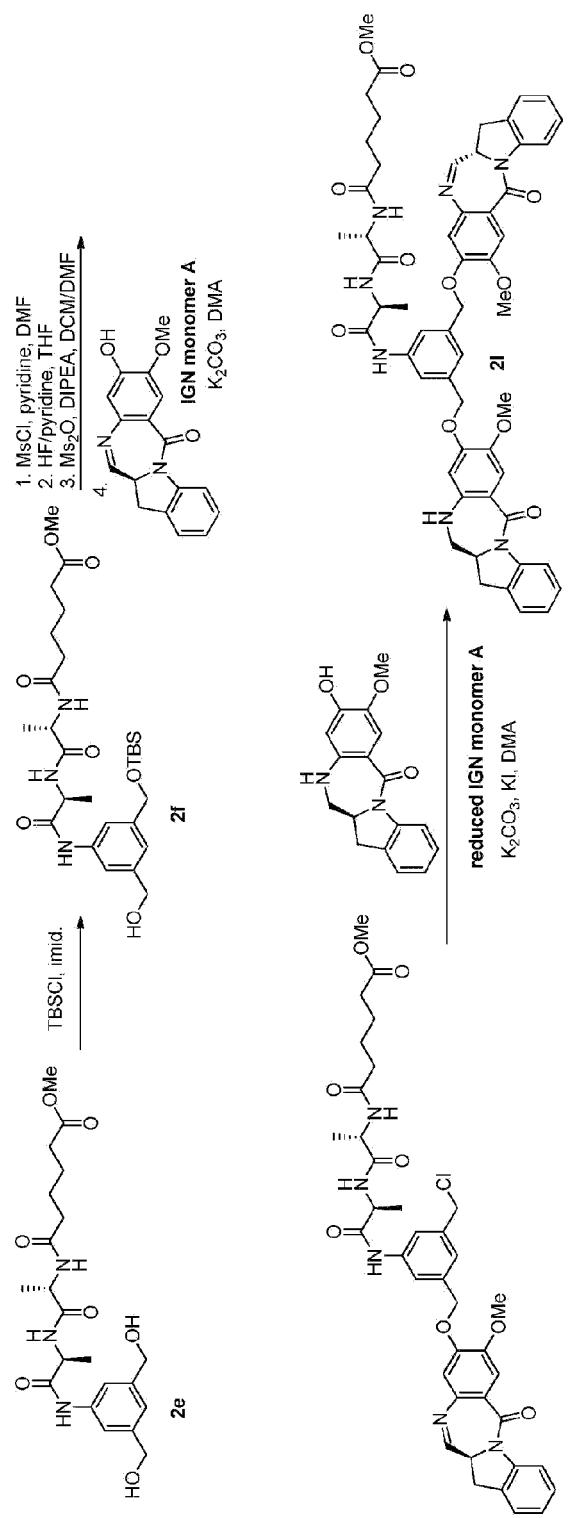


FIG. 9

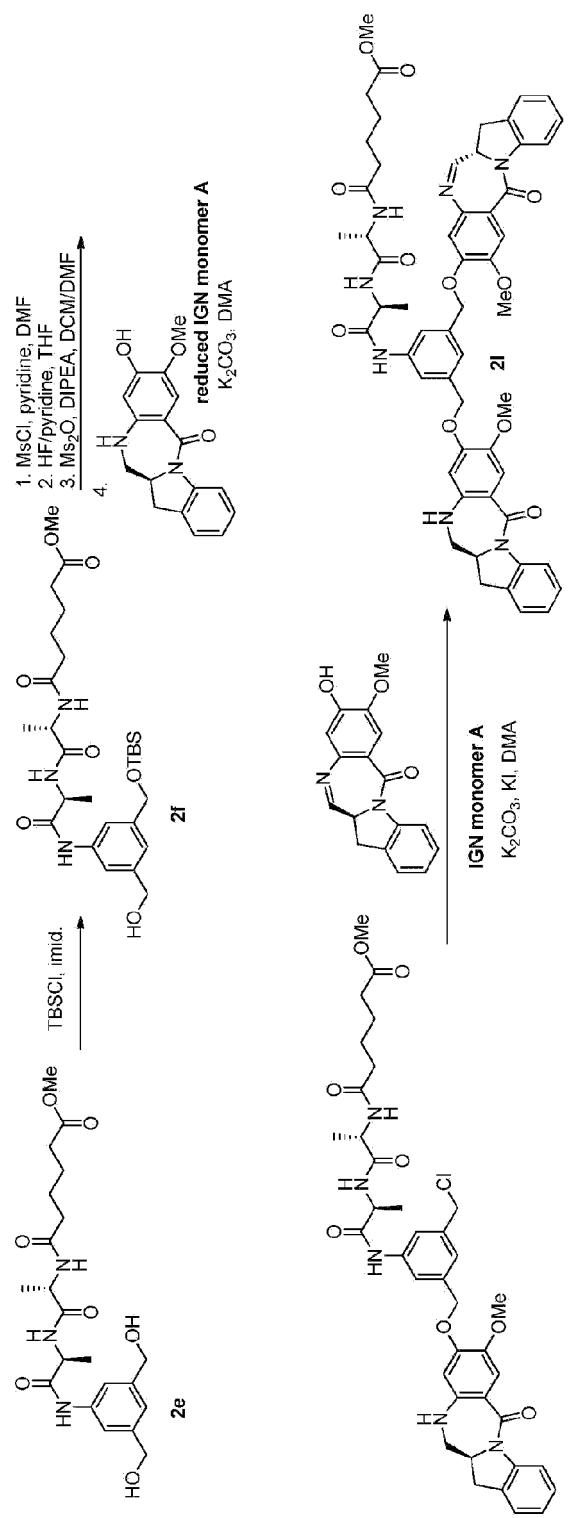


FIG. 10

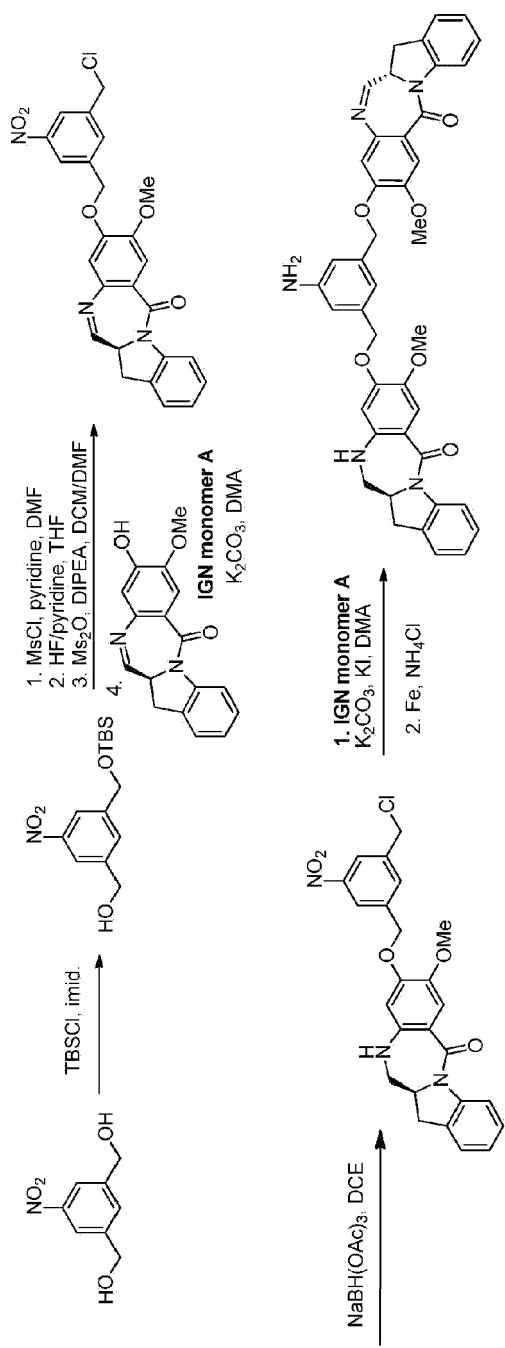


FIG. 11

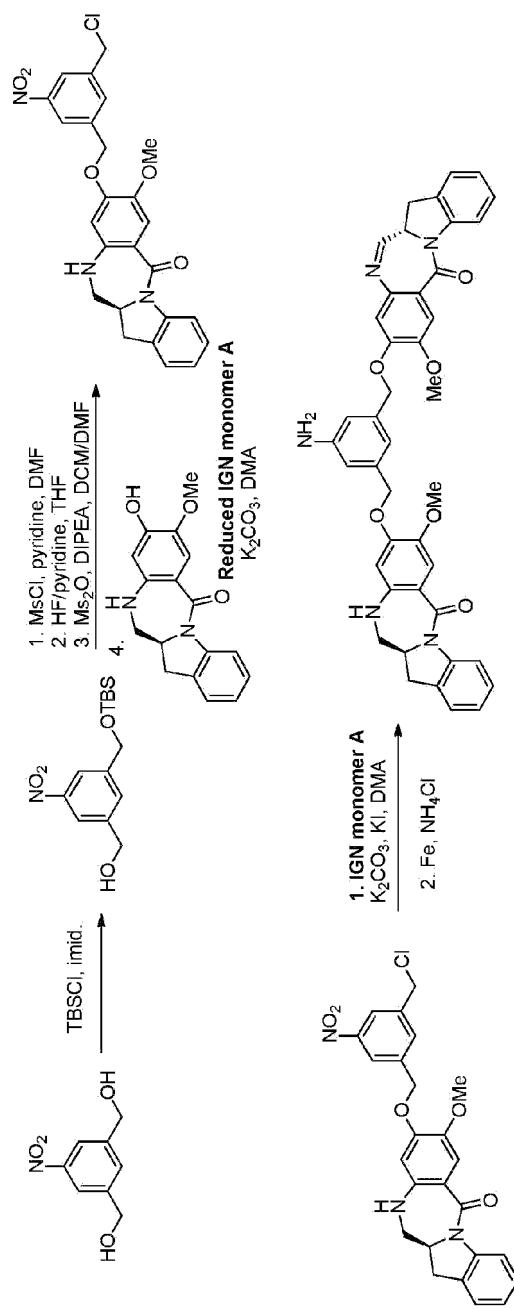


FIG. 12

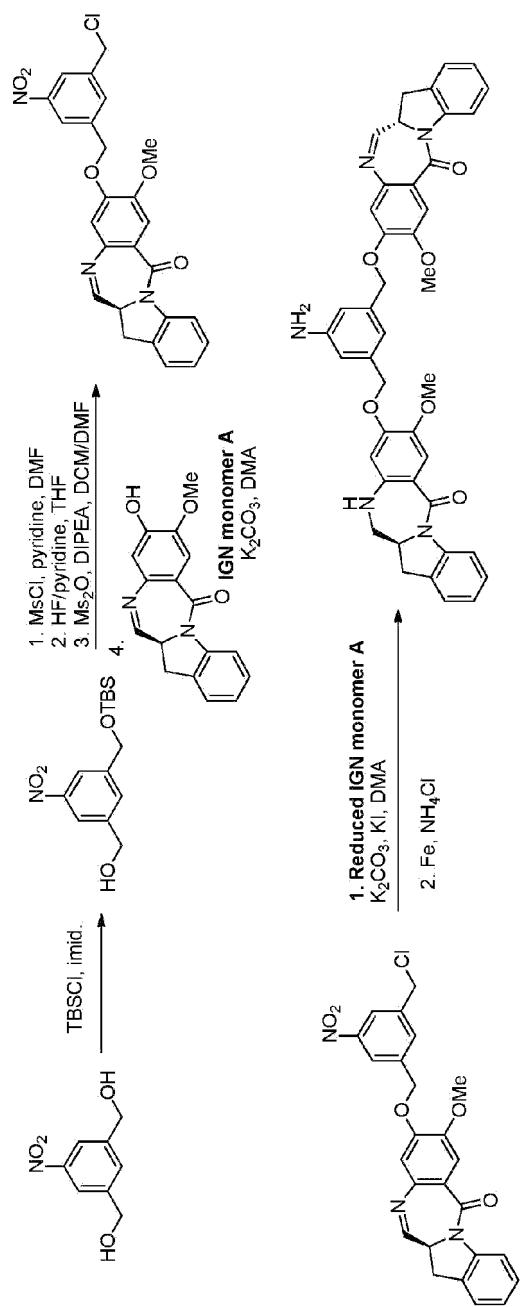


FIG. 13