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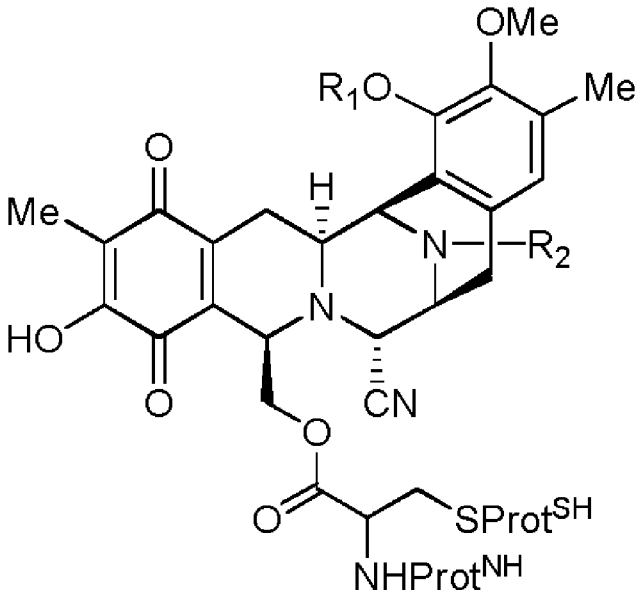
[Continued on next page]

(54) Title: SYNTHETIC PROCESS FOR THE MANUFACTURE OF ECTEINASCIDIN COMPOUNDS

(57) Abstract: This invention relates to compounds of formula II: wherein R_1, R_2, $Prot^{SH}$, and $Prot^{NH}$ are as defined, to processes for the synthesis of ectainascidins of formula I from compounds of formula II, and to processes for the synthesis of compounds of formula II.



II

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SYNTHETIC PROCESS FOR THE MANUFACTURE OF ECTEINASCIDIN COMPOUNDS

The present invention relates to synthetic processes, and in particular it relates to synthetic processes for producing ecteinascidin compounds.

BACKGROUND OF THE INVENTION

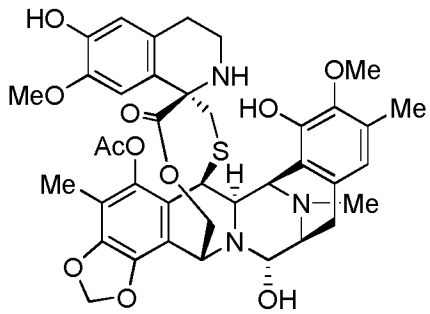
Ecteinascidins is a group of naturally occurring marine compounds and analogs thereof, which are well identified and structurally characterized, and are disclosed to have antibacterial and cytotoxic properties. See for example, European Patent 309.477; WO 03/66638; WO 03/08423; WO 01/77115; WO 03/014127; R. Sakai et al., 1992, *Proc. Natl. Acad. Sci. USA* 89, pages 11456-11460; R. Menchaca et al., 2003, *J. Org. Chem.* 68(23), pages 8859-8866; and I. Manzanares et al., 2001, *Curr. Med. Chem. Anti-Cancer Agents*, 1, pages 257-276; and references therein. Examples of ecteinascidins are provided by ET-743, ET-729, ET-745, ET-759A, ET-759B, ET-759C, ET-770, ET-815, ET-731, ET-745B, ET-722, ET-736, ET-738, ET-808, ET-752, ET-594, ET-552, ET-637, ET-652, ET-583, ET-597, ET-596, ET-639, ET-641, and derivatives thereof, such as acetylated forms, formylated forms, methylated forms, and oxide forms.

The structural characterizations of such ecteinascidins are not given again explicitly herein because from the detailed description provided in such references and citations any person of ordinary skill in this technology is capable of obtaining such information directly from the sources cited here and related sources.

At least one of the ecteinascidin compounds, ecteinascidin 743 (ET-743), has been extensively studied, and it will be referred to

specifically herein to illustrate features of this invention. ET-743 is being employed as an anticancer medicament, under the international nonproprietary name (INN) trabectedin, for the treatment of patients with advanced and metastatic soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive such agents, and for the treatment of relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin.

ET-743 has a complex tris(tetrahydroisoquinoline) structure of formula

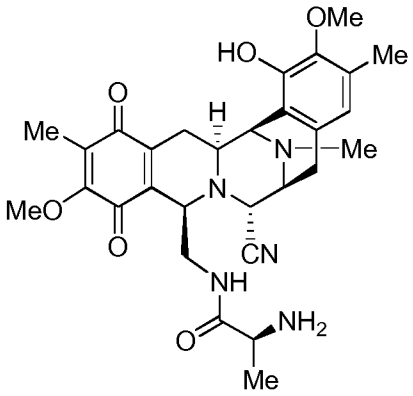


It was originally prepared by isolation from extracts of the marine tunicate *Ecteinascidia turbinata.* The yield was low, and alternative preparative processes had been sought.

The first synthetic process for producing ecteinascidin compounds was described in US Patent 5,721,362. This process employed sesamol as starting material and yielded ET-743 after a long and complicated sequence of 38 examples each describing one or more steps in the synthetic sequence.

An improvement in the preparation of one intermediate used in such process was disclosed in US Patent 6,815,544. Even with this improvement, the total synthesis was not suitable for manufacturing ET-743 at an industrial scale.

A hemisynthetic process for producing ecteinascidin compounds was described in EP 1.185.536. This process employs cyanosafracin B as starting material to provide ET-743. Cyanosafracin B is a pentacyclic antibiotic obtained by fermentation from the bacteria *Pseudomonas fluorescens*.

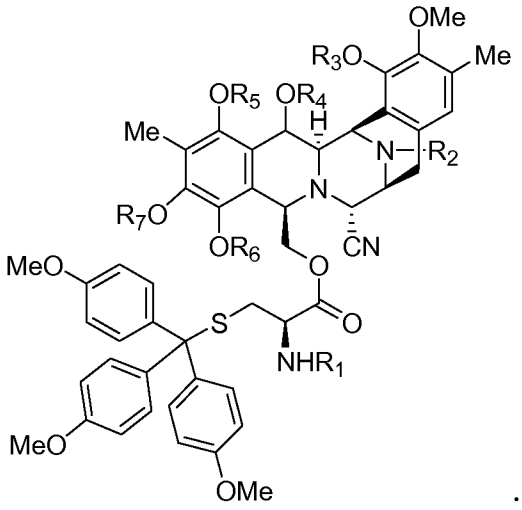


Cyanosafracin B

An improvement in such hemisynthetic process was disclosed in EP 1.287.004.

To date four additional synthetic process (2 total and 2 formal synthesis) have been disclosed in patent applications JP 2003221395, WO 2007/045686, and WO 2007/087220 and in *J. Org. Chem.* 2008, 73, pages 9594-9600.

WO 2007/045686 also relates to the synthesis of Ecteinascidins-583 and 597 using intermediate compounds of formula:



Total synthesis strategies for the synthesis of the pentacyclic core of ET-743 are overviewed in Figure I.

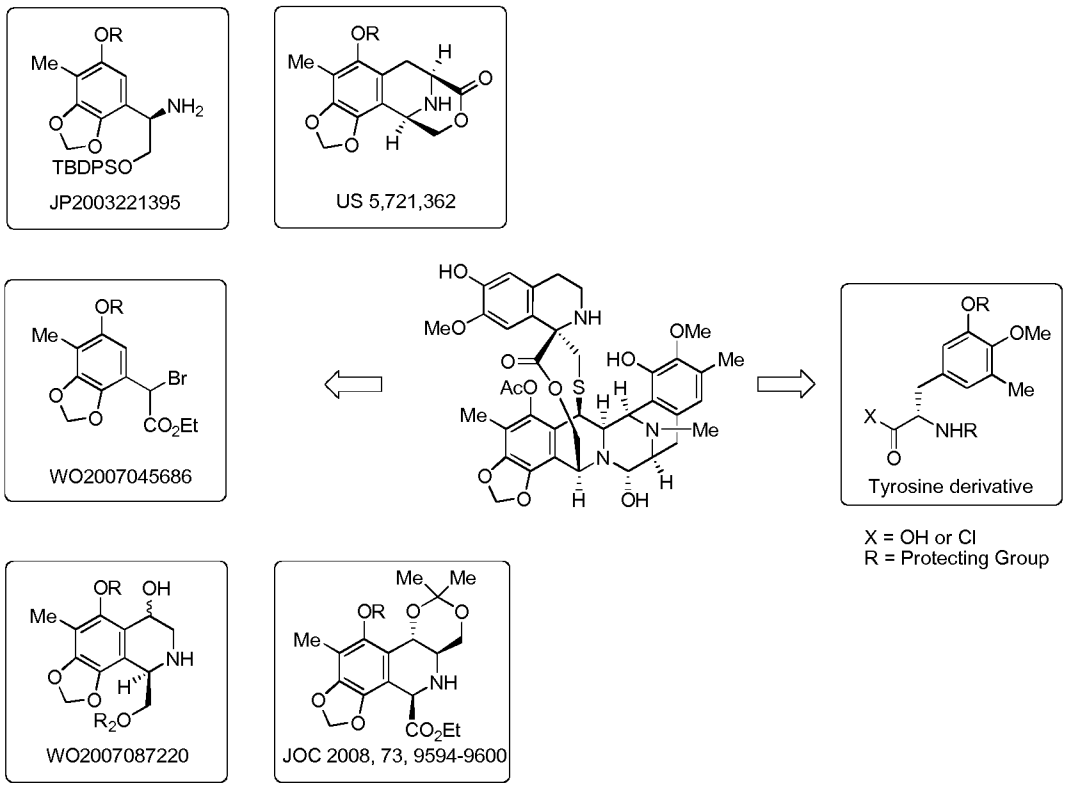


Figure I

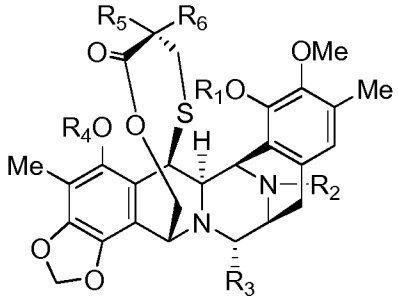
OBJECT OF THE INVENTION

The need remains for alternative hemisynthetic routes to the ecteinascidin compounds and related compounds. Such synthetic routes may provide more economic paths to the known antitumour agents as well as permitting the preparation of new active compounds.

SUMMARY OF THE INVENTION

This invention relates to a process for the synthesis of ecteinascidins. It also relates to intermediates for such process, to processes for their manufacture, and to their use in the synthesis of ecteinascidins.

In a first aspect, the invention relates to a process step for the manufacture of an ecteinascidin of formula **I**:



I

wherein

R_1 and R_4 are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for OH;

R_2 is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or

unsubstituted C_2-C_{12} alkynyl, C(=O)R^a, C(=O)OR^b, C(=O)N$R^c$$R^d$, and a protecting group for amino;

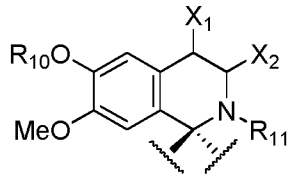
R_3 is CN or OH;

R_5 and R_6 together to the carbon to which they are attached form a group:

(a) C(=O);

(b) CH(OR_7) or CH(N$R_8$$R_9$) wherein R_7 is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH; and R_8 and R_9 are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

(c) a group of formula:



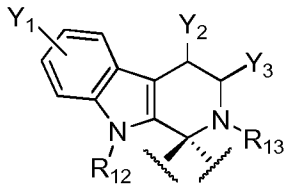
wherein

X_1 and X_2 are independently selected from hydrogen and substituted or unsubstituted C_1-C_{12} alkyl;

R_{10} is selected from hydrogen, C(=O)R^a, C(=O)OR^b, C(=O)N$R^c$$R^d$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl and a protecting group for OH;

R_{11} is selected from hydrogen, C(=O)R^a, C(=O)OR^b, C(=O)N$R^c$$R^d$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl and a protecting group for amino; or

(d) a group of formula:



wherein

Y_1 is selected from hydrogen, OR^b, $OC(=O)R^a$, $OC(=O)OR^b$, $OC(=O)NR^cR^d$, SR^e, SOR^a, SO_2R^a, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, NO_2, NR^cR^d, $N(R^c)C(=O)R^a$, $N(R^c)$-OR^b, $C(R^a)=NOR^b$, $N(R^c)C(=O)OR^b$, $N(R^c)C(=O)NR^cR^d$, CN, halogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

Y_2 and Y_3 are independently selected from hydrogen and substituted or unsubstituted C_1-C_{12} alkyl;

R_{12} and R_{13} are independently selected from hydrogen, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl; and

each R^a is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

each R^b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH;

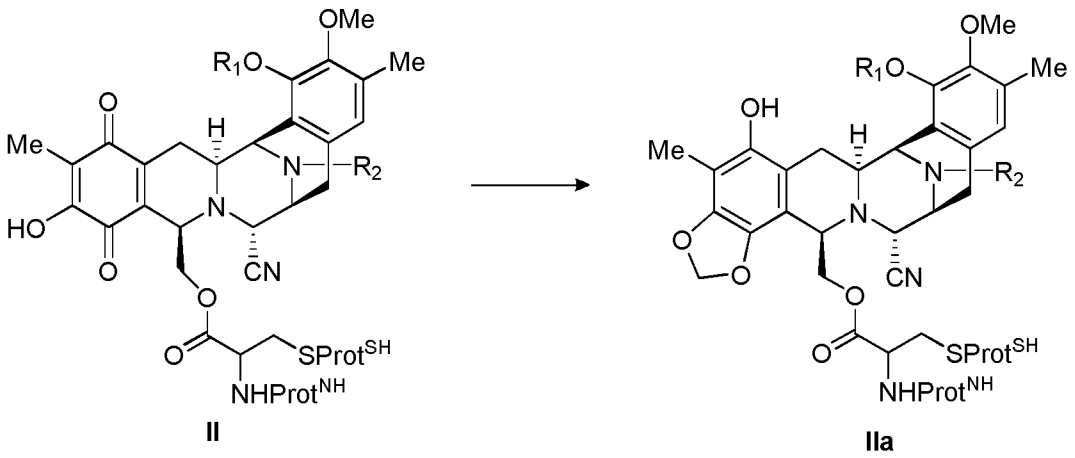
each R^c and R^d is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl,

substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

each R^e is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for SH;

or a pharmaceutical acceptable salt thereof,

wherein the process comprises the step of reducing a quinone of formula **II** followed by alkylation of the resulting hydroquinone with a suitable electrophilic reagent to give a compound of formula **IIa** in accordance with Scheme **I**:



Scheme **I**

wherein

R_1 is a protecting group for OH;

R_2 is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for amino;

R^a is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

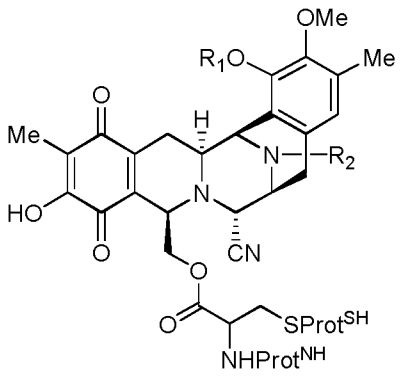
R^b is independently selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH;

R^c and R^d are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

$Prot^{NH}$ is a protecting group for amino; and

$Prot^{SH}$ is a protecting group for SH.

In another aspect, the present invention provides intermediates of formula **II**:



II

wherein

R_1 is a protecting group for OH;

R_2 is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or

unsubstituted C_2-C_{12} alkynyl, C(=O)R^a, C(=O)OR^b, C(=O)N$R^c R^d$, and a protecting group for amino;

R^a is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

R^b is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH;

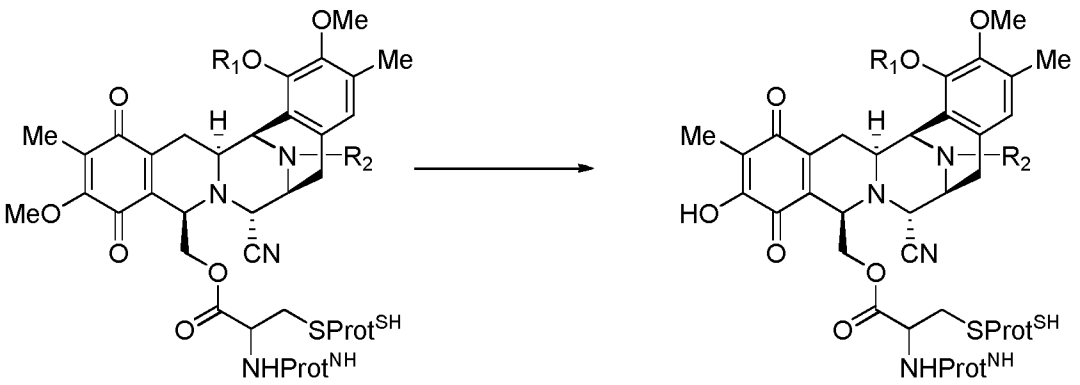
R^c and R^d are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

$Prot^{NH}$ is a protecting group for amino; and

$Prot^{SH}$ is a protecting group for SH.

In one particular aspect, the invention relates to the use of intermediates of formula **II** in the manufacture of compounds of formula **I**.

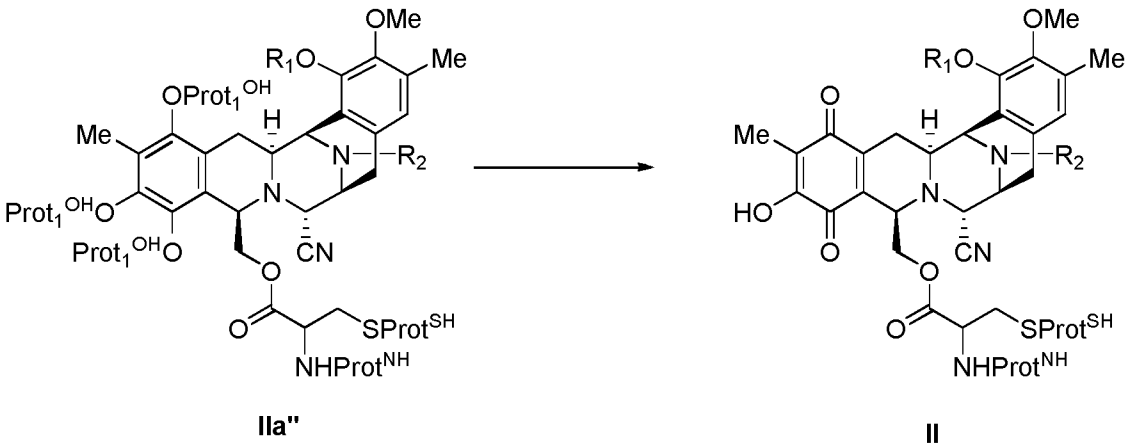
In a further aspect, the invention relates to a process for the synthesis of a compound of formula **II** comprising the demethylation of a methoxybenzoquinone of formula **IIa'** in accordance to Scheme **II**:



Scheme **II**

wherein R_1, R_2, $Prot^{NH}$, and $Prot^{SH}$ are as defined in formula **II**.

In another aspect, the invention relates to an alternative process for the synthesis of a compound of formula **II** comprising the deprotection and oxidation of a protected hydroquinone of formula **IIa"** in accordance to Scheme **III**:



Scheme **III**

wherein:

R_1 and $Prot_1^{OH}$ are protecting groups for OH, with the proviso that R_1 is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

R_2, $Prot^{NH}$, and $Prot^{SH}$ are as defined in formula **II**.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to processes for the manufacture of compounds of general formula **I** and **II** as defined above.

In the compounds defined by Markush formulae in this specification, the groups can be selected in accordance with the following guidance:

Alkyl groups may be branched or unbranched, and preferably have from 1 to about 12 carbon atoms. One more preferred class of alkyl groups has from 1 to about 6 carbon atoms. Even more preferred are alkyl groups having 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, tert-butyl, sec-butyl and isobutyl are particularly preferred alkyl groups in the compounds of the present invention.

Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more unsaturated linkages and from 2 to about 12 carbon atoms. One more preferred class of alkenyl and alkynyl groups has from 2 to about 6 carbon atoms. Even more preferred are alkenyl and alkynyl groups having 2, 3 or 4 carbon atoms.

Suitable aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Preferably aryl groups contain from 6 to about 14 carbon ring atoms. Specially preferred aryl groups include substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted

phenanthryl and substituted or unsubstituted anthryl. The most preferred aryl group is substituted or unsubstituted phenyl.

Suitable heterocyclic groups include heteroaromatic and heteroalicyclic groups containing from 1 to 3 separated or fused rings and from 5 to about 18 ring atoms. Preferably heteroaromatic and heteroalicyclic groups contain from 5 to about 10 ring atoms, more preferably 5, 6 or 7 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinolizinyl.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR',

SOR', SO_2R', NO_2, NHR', NR'R', =N-R', NHCOR', $N(COR')_2$, $NHSO_2R'$, NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCONR'R', CONHR', CONR'R', protected OH, protected amino, protected SH, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO_2, NH_2, SH, CN, halogen, COH, COalkyl, CO_2H, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

Suitable electrophilic reagents are compounds that react with a 1,2-dihydroxyaryl compound to give a [1,3]-dioxolo fused aryl compound. Examples of suitable electrophilic reagents include, but not are limited to, LG_1-CH_2-LG_2 and LG_1-CO-LG_2 where LG_1 and LG_2 are leaving groups which can be the same or different.

The term "pharmaceutically acceptable salts" refers to any pharmaceutically acceptable salt which, upon administration to the patient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of

pharmaceutically acceptable salts. The preparation of salts can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of both. Generally, nonaqueous media like ether, ethyl acetate, ethanol, 2-propanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and *p*-toluenesulfonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, *N*,*N*-dialkylenethanolamine, triethanolamine and basic aminoacids salts.

Suitable protecting groups are well known for the skilled person in the art. A general review of protecting groups in organic chemistry is provided by Wuts, P.G.M. and Greene T.W. in Protecting groups in Organic Synthesis, 4th Ed. Wiley-Interscience, and by Kocienski P.J. in Protecting Groups, 3rd Ed. Georg Thieme Verlag. These references provide sections on protecting groups for OH, amino, and SH groups. All these references are incorporated by reference in their entirety.

Within the scope of the present invention an OH protecting group

is defined to be the *O*-bonded moiety resulting from the protection of the OH group through the formation of a suitable protected OH group. Examples of such protected OH groups include ethers, silyl ethers, esters, sulfonates, sulfenates and sulfinates, carbonates, and carbamates. In the case of ethers the protecting group for the OH can be selected from methyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)-methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, [(3,4-dimethoxybenzyl)oxy]methyl, *p*-nitrobenzyloxymethyl, *o*-nitrobenzyl-oxymethyl, [(*R*)-1-(2-nitrophenyl)ethoxy]methyl, (4-methoxy-phenoxy)-methyl, guaiacolmethyl, [(*p*-phenylphenyl)oxy]methyl, *t*-butoxy-methyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxy-methyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *O*-bis(2-acetoxy-ethoxy)methyl, tetrahydropyranyl, fluorous tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxy-tetrahydrothiopyranyl *S,S*-dioxide, 1-[(2-chloro-4-methyl)-phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperi-din-4-yl, 1-(4-chlorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3*a*,4,5,6,7,7*a*-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-hydroxyethyl, 2-bromoethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1,1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 1-(2-cyanoethoxy)ethyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-phenylselenyl)ethyl, *t*-butyl, cyclohexyl, 1-methyl-1'-cyclopropylmethyl, allyl, prenyl, cinnamyl, 2-phenallyl, propargyl, *p*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-

nitrobenzyl, *p*-nitrobenzyl, pentadienylnitrobenzyl, pentadienyl-nitropiperonyl, halobenzyl, 2,6-dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluorous benzyl, 4-fluorousalkoxybenzyl, trimethylsilylxylyl, *p*-phenylbenzyl, 2-phenyl-2-propyl, *p*-acylaminobenzyl, *p*-azidobenzyl, 4-azido-3-chlorobenzyl, 2-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, *p*-(methylsulfinyl)benzyl, *p*-siletanylbenzyl, 4-acetoxybenzyl, 4-(2-trimethylsilyl)ethoxymethoxy-benzyl, 2-naphthylmethyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxide, 2-quinolinylmethyl, 6-methoxy-2-(4-methylphenyl-4-quinoline-methyl, 1-pyrenylmethyl, diphenylmethyl, 4-methoxydiphenylmethyl, 4-phenyl-diphenylmethyl, *p,p*'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, tris(4-*t*-butylphenyl)methyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyl-diphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)-methyl, 4-(4'-bromophenacyloxy)phenyldiphenyl-methyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4"-tris(benzoyloxyphenyl)methyl, 4,4'-dimethoxy-3"-[*N*-(imidazolyl-methyl)]trityl, 4,4'-dimethoxy-3"-[*N*-(imidazolylethyl)carbamoyl]trityl, bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[*a,c,g,i*]fluorenyl-methyl)-4,4"-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-phenylthioxanthyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and 4,5-bis(ethoxycarbonyl)-[1,3]-dioxolan-2-yl, benzisothiazolyl *S,S*-dioxide. In the case of silyl ethers the protecting group for the OH can be selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenyl-methoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)-ethoxy]disiloxane-1-yl, and fluorous silyl. In the case of esters the protecting group for the OH together with the oxygen atom of the

unprotected OH to which it is attached form an ester that can be selected from formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trichloroacetamidate, trifluoroacetate, methoxyacetate, triphenyl-methoxy-acetate, phenoxyacetate, *p*-chlorophenoxyacetate, phenylacetate, diphenylacetate, 3-phenylpropionate, bisfluorous chain type propanoyl, 4-pentenoate, 4-oxopentanoate, 4,4-(ethylenedithio)-pentanoate, 5[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]levulinate, pivaloate, 1-adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate, 4-bromobenzoate, 2,5-difluorobenzoate, *p*-nitrobenzoate, picolinate, nicotinate, 2-(azidomethyl)benzoate, 4-azido-butyrate, (2-azidomethyl)phenylacetate, 2-{[(tritylthio)oxy]methyl}benzoate, 2-{[(4-methoxytritylthio)oxy]methyl}-benzoate, 2-{[methyl(tritylthio)amino]-methyl}benzoate, 2-{{[(4-methoxy-trityl)thio]methylamino}-methyl}benzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxymethyl)benzoate, 6-(levulinyloxy-methyl)-3-methoxy-2-nitrobenzoate, 6-(levulinyloxymethyl)-3-methoxy-4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsilyloxybutyrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzene-sulfonate, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxy-methyl)benzoate, 2-(chloroacetoxymethyl)benzoate, 2-[(2-chloroacetoxy)-ethyl]benzoate, 2-[2-(benzyloxy)ethyl]benzoate, 2-[2-(4-methoxybenzyl-oxy)ethyl]benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethyl-propyl)-phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate, *o*-(methoxycarbonyl)benzoate, α-naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, and 2-chlorobenzoate. In the case of sulfonates, sulfenates and sulfinates the protecting group for the OH together with the oxygen atom of the unprotected OH to which it is attached form a sulfonate, sulfenate or sulfinate that can be selected

from sulfate, allylsulfonate, methanesulfonate, benzylsulfonate, tosylate, 2-[(4-nitrophenyl)ethyl]-sulfonate, 2-trifluoromethylbenzenesulfonate, 4-monomethoxytrityl-sulfenate, alkyl 2,4-dinitrophenylsulfenate, 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate, and dimethylphosphinothiolyl. In the case of carbonates the protecting group for the OH together with the oxygen atom of the unprotected OH to which it is attached form a carbonate that can be selected from methyl carbonate, methoxymethyl carbonate, 9-fluorenylmethyl carbonate, ethyl carbonate, bromoethyl carbonate, 2-(methylthiomethoxy)ethyl carbonate, 2,2,2-trichloroethyl carbonate, 1,1-dimethyl-2,2,2-trichloroethyl carbonate, 2-(trimethylsilyl)ethyl carbonate, 2-[dimethyl(2-naphthylmethyl)silyl]ethyl carbonate, 2-(phenylsulfonyl) ethyl carbonate, 2-(triphenylphosphonio)ethyl carbonate, *cis*-[4-[[(methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-yl]oxy carbonate, isobutyl carbonate, *t*-butyl carbonate, vinyl carbonate, allyl carbonate, cinnamyl carbonate, propargyl carbonate, *p*-chlorophenyl carbonate, *p*-nitrophenyl carbonate, 4-ethoxy-1-naphthyl carbonate, 6-bromo-7-hydroxycoumarin-4-ylmethyl carbonate, benzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, anthraquinon-2-ylmethyl carbonate, 2-dansylethyl carbonate, 2-(4-nitrophenyl)ethyl carbonate, 2-(2,4-dinitrophenyl)ethyl carbonate, 2-(2-nitrophenyl)propyl carbonate, alkyl 2-(3,4-methylenedioxy-6-nitrophenyl)propyl carbonate, 2-cyano-1-phenylethyl carbonate, 2-(2-pyridyl)amino-1-phenylethyl carbonate, 2-[*N*-methyl-*N*-(2-pyridyl)]amino-1-phenylethyl carbonate, phenacyl carbonate, 3',5'-dimethoxybenzoin carbonate, methyl dithiocarbonate, and *S*-benzyl thiocarbonate. And in the case of carbamates the protecting group for the OH together with the oxygen atom of the unprotected OH to which it is attached form a carbamate that can be selected from dimethylthiocarbamate, *N*-phenylcarbamate, *N*-methyl-*N*-(*o*-nitrophenyl)-carbamate.

Within the scope of the present invention an amino protecting group is defined to be the *N*-bonded moiety resulting from the protection of the amino group through the formation of a suitable protected amino group. Examples of protected amino groups include carbamates, ureas, amides, heterocyclic systems, *N*-alkyl amines, *N*-alkenyl amines, *N*-alkynyl amines, *N*-aryl amines, imines, enamines, N-metal derivatives, N-N derivatives, N-P derivatives, N-Si derivatives, and N-S derivatives. In the case of carbamates the protecting group for the amino group together with the amino group to which it is attached form a carbamate that can be selected from methylcarbamate, ethylcarbamate, 9-fluorenylmethyl-carbamate, 2,6-di-*t*-butyl-9-fluorenylmethylcarbamate, 2,7-bis(trimethylsilyl)fluorenylmethylcarbamate, 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethylcarbamate, 17-tetrabenzo[*a,c,g,i*]fluorenylmethylcarbamate, 2-chloro-3-indenylmethylcarbamate, benz[*f*]inden-3-ylmethylcarbamate, 1,1-dioxobenzo[*b*]-thiophene-2-ylmethylcarbamate, 2-methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbamate, 2,7-di-*t*-butyl-[9,(10,10-dioxo-10,10,10,10-tetraydrothioxanthyl)]methylcarbamate, 2,2,2-trichloroethylcarbamate, 2-trimethylsilylethylcarbamate, (2-phenyl-2-trimethylsilyl)ethylcarbamate, 2-phenylethylcarbamate, 2-chloroethylcarbamate, 1,1-dimethyl-2-haloethylcarbamate, 1,1-dimethyl-2,2-dibromoethylcarbamate, 1,1-dimethyl-2,2,2-trichloroethylcarbamate, 2-(2'-pyridyl)ethylcarbamate, 2-(4'-pyridyl)ethylcarbamate, 2,2-bis(4'-nitrophenyl)ethylcarbamate, 2-[(2-nitrophenyl)dithio]-1-phenylethylcarbamate, 2-(*N,N*-dicyclohexyl-carboxamido)ethylcarbamate, *t*-butylcarbamate, $C_8F_{19}CH_2CH_2C(CH_3)_2$-carbamate, 1-adamantylcarbamate, 2-adamantyl carbamate, 1-(1-adamantyl)-1-methylethylcarbamate, 1-methyl-1-(4-byphenylyl)ethyl-arbamate, 1-(3,5-di-*t*-butylphenyl)-1-methyl-ethylcarbamate, triisopropyliloxylcarbamate, vinylcarbamate, allylcarbamate, prenylcarbamate, 1-isopropylallylcarbamate, cinnamylcarbamate, 4-nitrocinnamyl-carbamate, 3-(3'-pyridyl)prop-2-enylcarbamate, hexadienyloxycar-

bamate, propargyloxycarbamate, but-2-ynylbisoxycarbamate, 8-quinolyl-arbamate, *N*-hydroxypiperidinyl-carbamate, alkyldithiocarbamate, benzylcarbamate, 3,5-di-*t*-butylbenzylcarbamate, *p*-methoxybenzylcarbamate, *p*-nitrobenzylcarbamate, *p*-bromobenzylcarbamate, *p*-chlorobenzyl-carbamate, 2,4-dichlorobenzylcarbamate, 4-methylsulfinylbenzyl-carbamate, 4-trifluoromethylbenzylcarbamate, $C_8F_{17}CH_2CH_2$-carbamate, $(C_8F_{17}CH_2CH_2)_3Si$-carbamate, 2-naphthylmethylcarbamate, 9-anthryl-methylcarbamate, diphenylmethylcarbamate, 4-phenylacetoxybenzyl-carbamate, 4-azidobenzylcarbamate, 4-azidomethoxybenzylcarbamate, *m*-chloro-*p*-acyloxybenzylcarbamate, *p*-(dihydroxyboryl)benzylcarbamate, 5-benzisoxazolylmethylcarbamate, 2-(trifluoromethyl)-6-chromonylmethyl-carbamate, 2-methylthioethylcarbamate, 2-methylsulfonylethylcarbamate, 2-(*p*-toluenesulfonyl)-ethylcarbamate, 2-(4-nitrophenylsulfonyl)ethoxy-carbamate, 2-(2,4-dinitrophenylsulfonyl)ethoxycarbamate, 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbamate, [2-(1,3-dithianyl)]methyl-carbamate, 2-phosphonioethylcarbamate, 2-[phenyl(methyl)sulfonio]ethyl-carbamate, 1-methyl-1-(triphenylphosphonio)ethylcarbamate, 1,1-dimethyl-2-cyanoethylcarbamate, 2-dansylethylcarbamate, 2-(4-nitrophenyl)ethylcarbamate, 4-methylthiophenylcarbamate, 2,4-dimethylthiophenylcarbamate, *m*-nitrophenylcarbamate, 3,5-dimethoxy-benzylcarbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethylcarbamate, *a*-methylnitropiperonylcarbamate, *o*-nitrobenzylcarbamate, 3,4-dimethoxy-6-nitrobenzylcarbamate, phenyl(*o*-nitrophenyl)methylcarbamate, 2-nitrophenylethylcarbamate, 6-nitroveratrylcarbamate, 4-methoxyphenacyl-carbamate, 3',5'-dimethoxybenzoincarbamate, 9-xanthenylmethyl-carbamate, *N*-methyl-*N*-(*o*-nitrophenyl)carbamate, *N*-(2-acetoxyethyl)-aminecarbamate, *t*-amylcarbamate, 1-methylcyclobutylcarbamate, 1-methylcyclohexylcarbamate, 1-methyl-1-cyclopropylmethylcarbamate, cyclobutylcarbamate, cyclopentylcarbamate, cyclohexylcarbamate, isobutylcarbamate, isobornylcarbamate, cyclopropylmethylcarbamate, *p*-decyloxybenzylcarbamate, diisopropyl-

methylcarbamate, 2,2-dimethoxy-carbonylvinylcarbamate, *o*-(*N,N*-dimethylcarboxamido)benzylcarbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propylcarbamate, butynyl-carbamate, 1,1-dimethylpropynylcarbamate, 2-iodoethylcarbamate, 1-methyl-1-(4'-pyridyl)ethylcarbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl-carbamate, *p*-(*p'*-methoxyphenylazo)benzylcarbamate, *p*-(phenylazo)benzyl-carbamate, 2,4,6-trimethylbenzylcarbamate, isonicotinylcarbamate, 4-(trimethyl-ammonium)benzylcarbamate, *p*-cyanobenzylcarbamate, di(2-pyridyl)methylcarbamate, 2-furanylmethylcarbamate, phenylcarbamate, 2,4,6-tri-*t*-butylphenylcarbamate, 1-methyl-1-phenylethylcarbamate, and *S*-benzyl thiocarbamate. In the case of ureas the protecting groups for the amino group can be selected from phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothio-carbonyl, 4-hydroxyphenylaminocarbonyl, 3-hydroxytryptaminocarbonyl, and *N'*-phenyl-aminothiocarbonyl. In the case of amides the protecting group for the amino group together with the amino group to which it is attached form an amide that can be selected from formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenyl-acetamide, 3-phenylpropanamide, pent-4-enamide, picolinamide, 3-pyridyl-carboxamide, *N*-benzoylphenylalanyl, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, 2,2-dimethyl-2-(*o*-nitrophenyl)acetamide, *o*-nitrophenoxyacetamide, 3-(*o*-nitrophenyl)-propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *o*-nitrobenzamide, 3-(4-*t*-butyl-2,6-dinitrophenyl)-2,2-dimethylpropanamide, *o*-benzoyloxymethyl)-benzamide, 2-(acetoxymethyl)-benzamide, 2-[(*t*-butyldiphenylsiloxy)-methyl]benzamide, 3-(3',6'-dioxo-2',4',5'-trimethylcyclohexa-1',4'-diene)-3,3-dimethylpropionamide, *o*-hydroxy-*trans*-cinnamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, acetoacetamide, 3-(*p*-hydroxyphenyl)propanamide, (*N'*-dithiobenzyloxycarbonylamino)-acetamide, and *N*-acetylmethionine amide. In the case of heterocyclic systems the protecting group for the amino group together with the

amino group to which it is attached form a heterocyclic system that can be selected from 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dichlorophthalimide, *N*-tetrachlorophthalimide, *N*-4-nitrophthalimide, *N*-thiodiglycoloyl, *N*-dithiasuccinimide, *N*-2,3-diphenylmaleimide, *N*-2,3-dimethylmaleimide, *N*-2,5-dimethylpyrrole, *N*-2,5-bis(triisopropylsiloxy)pyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, *N*-1,1,3,3-tetramethyl-1,3-disilaisoindoline, *N*-diphenylsilyldiethylene, *N*-5-substituted-1,3-dimethyl-1,3,5-triazacyclohexan-2-one, *N*-5-substituted -1,3-benzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, and 1,3,5-dioxazine. In the case of *N*-alkyl, *N*-alkenyl, *N*-alkynyl or *N*-aryl amines the protecting group for the amino group can be selected from *N*-methyl, *N*-*t*-butyl, *N*-allyl, *N*-prenyl, *N*-cinnamyl, *N*-phenylallyl, *N*-propargyl, *N*-methoxymethyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-cyanomethyl, *N*-2-azanorbornenes, *N*-benzyl, *N*-4-methoxybenzyl, *N*-2,4-dimethoxybenzyl, *N*-2-hydroxybenzyl, *N*-ferrocenylmethyl, *N*-2,4-dinitrophenyl, *o*-methoxyphenyl, *p*-methoxyphenyl, *N*-9-phenylfluorenyl, *N*-fluorenyl, *N*-2-picolylamine N'-Oxide, *N*-7-methoxycoumar-4-ylmethyl, *N*-diphenylmethyl, *N*-bis(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methylphenyl)diphenylmethyl, and *N*-(4-methoxyphenyl)diphenylmethyl. In the case of imines the protecting group for the amino group can be selected from *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[2-pyridyl)mesityl]-methylene, *N*-(*N*',*N*'-dimethylaminomethylene), *N*-(*N*',*N*'-dibenzylamino-methylene), *N*-(*N*'-*t*-butylaminomethylene), *N*,*N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene, and *N*-*t*-butylidene. In the case of enamines the protecting group for the amino group can be selected from *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl), *N*-2,7-dichloro-9-fluorenylmethylene, *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl, *N*-(1,3-dimethyl-2,4,6-(1*H*,3*H*,5*H*)-trioxopyrimidine-5-ylidene)methyl, *N*-

4,4,4-trifluoro-3-oxo-1-butenyl, and *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl). In the case of N-metal derivatives the protecting group for the amino group can be selected from N-borane, *N*-diphenylborinic acid, *N*-diethylborinic acid, *N*-9-borabicyclononane, *N*-difluoroborinic acid, and 3,5-bis(trifluoromethyl)phenylboronic acid; and also including *N*-[phenyl(pentacarbonylchromium)]carbenyl, *N*-[phenyl(pentacarbonyltungsten)]carbenyl, *N*-[methyl(pentacarbonylchromium)]carbenyl, *N*-[methyl(pentacarbonyltungsten)]-carbenyl, *N*-copper chelate, *N*-zinc chelate, and a 18-crown-6-derivative. In the case of N-N derivatives the protecting group for the amino group can be selected from *N*-nitro, *N*-nitroso, *N*-oxide, azide, triazene, and *N*-trimethylsilylmethyl-*N*-benzylhydrazine. In the case of N-P derivatives the protecting group for the amino group together with the amino group to which it is attached form a N-P derivative that can be selected from diphenylphosphinamide, dimethylthiophosphinamide, diphenylthiophosphinamide, dialkyl phosphoramidate, dibenzyl phosphoramidate, diphenyl phosphoramidate, and iminotriphenylphosphorane. In the case of N-Si derivatives the protecting group for the NH_2 can be selected from t-butyldiphenylsilyl and triphenylsilyl. In the case of N-S derivatives the protecting group for the amino group together with the amino group to which it is attached form a N-S derivative that can be selected from N-sulfenyl or N-sulfonyl derivatives. The N-sulfenyl derivatives can be selected from benzenesulfenamide, 2-nitrobenzenesulfenamide, 2,4-dinitrobenzenesulfenamide, pentachloro-benzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenyl-methylsulfenamide, 1-(2,2,2)-trifluoro-1,1-diphenyl)ethylsulfenamide, and *N*-3-nitro-2-pyridinesulfenamide. The N-sulfonyl derivatives can be selected from methanesulfonamide, trifluoromethanesulfonamide, *t*-butylsulfonamide, benzylsulfonamide, 2-(trimethylsilyl)ethanesulfonamide, *p*-toluene-sulfonamide, benzenesulfonamide, *o*-anisylsulfonamide, 2-nitrobenzene-sulfonamide, 4-nitrobenzenesulfonamide, 2,4-dinitrobenzene-sulfonamide, 2-naphthalenesulfonamide, 4-(4',8'-dimethoxynaphthyl-

methyl)benzenesulfonamide, 2-(4-methylphenyl)-6-methoxy-4-methyl-sulfonamide, 9-anthracenesulfonamide, pyridine-2-sulfonamide, benzo-thiazole-2-sulfonamide, phenacylsulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide, 2,4,6-trimethoxybenzene-sulfonamide, 2,6-dimethyl-4-methoxybenzenesulfonamide, pentamethyl-benzene-sulfonamide, 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide, 4-methoxybenzenesulfonamide, 2,4,6-trimethylbenzenesulfonamide, 2,6-dimethoxy-4-methylbenzenesulfonamide, 3-methoxy-4-*t*-butylbenzene-sulfonamide, and 2,2,5,7,8-pentamethylchroman-6-sulfonamide.

Within the scope of the present invention an SH protecting group is defined to be the *S*-bonded moiety resulting from the protection of the SH group through the formation of a suitable protected SH group. Examples of such protected SH groups include thioethers, disulfides, silyl thioethers, thioesters, thiocarbonates, and thiocarbamates. In the case of thioethers the protecting group for the SH can be selected from *S*-alkyl, *S*-benzyl, *S*-*p*-methoxybenzyl, *S*-*o*-hydroxybenzyl, *S*-*p*-hydroxybenzyl, S-*o*-acetoxybenzyl, S-*p*-acetoxybenzyl, *S*-*p*-nitrobenzyl, *S*-*o*-nitrobenzyl, *S*-2,4,6-trimethylbenzyl, *S*-2,4,6,-trimethoxybenzyl, *S*-4-picolyl, *S*-2-picolyl-N-oxide, *S*-2-quinolinylmethyl, *S*-9-anthrylmethyl, *S*-9-fluorenylmethyl, *S*-xanthenyl, *S*-ferrocenylmethyl, *S*-diphenylmethyl, *S*-bis(4-methoxyphenyl)methyl, *S*-5-dibenzosuberyl, *S*-triphenylmethyl, 4-methoxytrityl, *S*-diphenyl-4-pyridylmethyl, *S*-phenyl, *S*-2,4-dinitrophenyl, *S*-2-quinolyl, *S*-*t*-butyl, *S*-1-adamantyl, *S*-methoxymethyl monothioacetal, *S*-isobutoxymethyl monothioacetal, *S*-benzyloxymethyl, *S*-1-ethoxyethyl, *S*-2-tetrahydropyranyl monothioacetal, *S*-benzylthiomethyl dithioacetal, S-phenylthiomethyl dithioacetal, thiazolidine derivative, *S*-acetamidomethyl aminothioacetal (Acm), *S*-trimethylacetamidomethyl aminothioacetal, *S*-benzamidomethyl aminothioacetal, *S*-allyloxycarbonylaminomethyl, *S*-*N*-[2,3,5,6-tetrafluoro-4-(*N*'-piperidino)-phenyl-*N*-allyloxycarbonylamino-methyl, *S*-phthalimidomethyl, *S*-phenylacetamidomethyl, *S*-(2-nitro-1-phenyl)ethyl,

S-2-(2,4-dinitrophenyl)ethyl, *S*-2-(4'-pyridyl)ethyl, *S*-2-cyanoethyl, *S*-2-(trimethylsilyl)ethyl, *S*-2,2-bis(carboethoxy)ethyl, *S*-(1-*m*-nitrophenyl-2-benzoyl)ethyl, *S*-2-phenylsulfonylethyl, *S*-1-(4-methylphenylsulfonyl)-2-methylprop-2-yl, and *S*-*p*-hydroxyphenacyl. In the case of disulfides the protecting group for the SH can be selected from *S*-*S*-Et, *S*-*S*-*t*Bu [*S*-(*tert*-butylsulfanyl)cysteine, *S*-*S*-*t*butyl) and S-Npys (*S*-3-nitro-2-pyridinesulfenyl). In the case of silyl thioethers the protecting group for the SH can be selected from the list of groups that was listed above for the protection of OH with silyl ethers. In the case of thioesters the protecting group for the SH can be selected from *S*-acetyl, *S*-benzoyl, *S*-2-methoxyisobutyryl, *S*-trifluoroacetyl, and the protecting group for the SH together with the SH group to which it is attached form a thioester that can be selected from *S*-*N*-[[*p*-biphenylyl)-isopropoxy]carbonyl]-*N*-methyl-γ-aminothiobutyrate, and *S*-*N*-(*t*-butoxycarbonyl)-*N*-methyl-γ-aminothiobutyrate. In the case of thiocarbonate protecting group for the SH can be selected from *S*-2,2,2-trichloroethoxycarbonyl, *S*-*t*-butoxycarbonyl, *S*-benzyloxycarbonyl, *S*-*p*-methoxybenzyloxycarbonyl, and *S*-fluorenylmethylcarbonyl. In the case of thiocarbamate the protecting group for the SH together with the SH group to which it is attached form a thiocarbamate that can be selected from *S*-(*N*-ethylcarbamate) and *S*-(*N*-Methoxymethylcarbamate).

The mention of these groups should not be interpreted as a limitation of the scope of the invention, since they have been mentioned as a mere illustration of protecting groups for OH, amino and SH groups, but further groups having said function may be known by the skill person in the art, and they are to be understood to be also encompassed by the present invention.

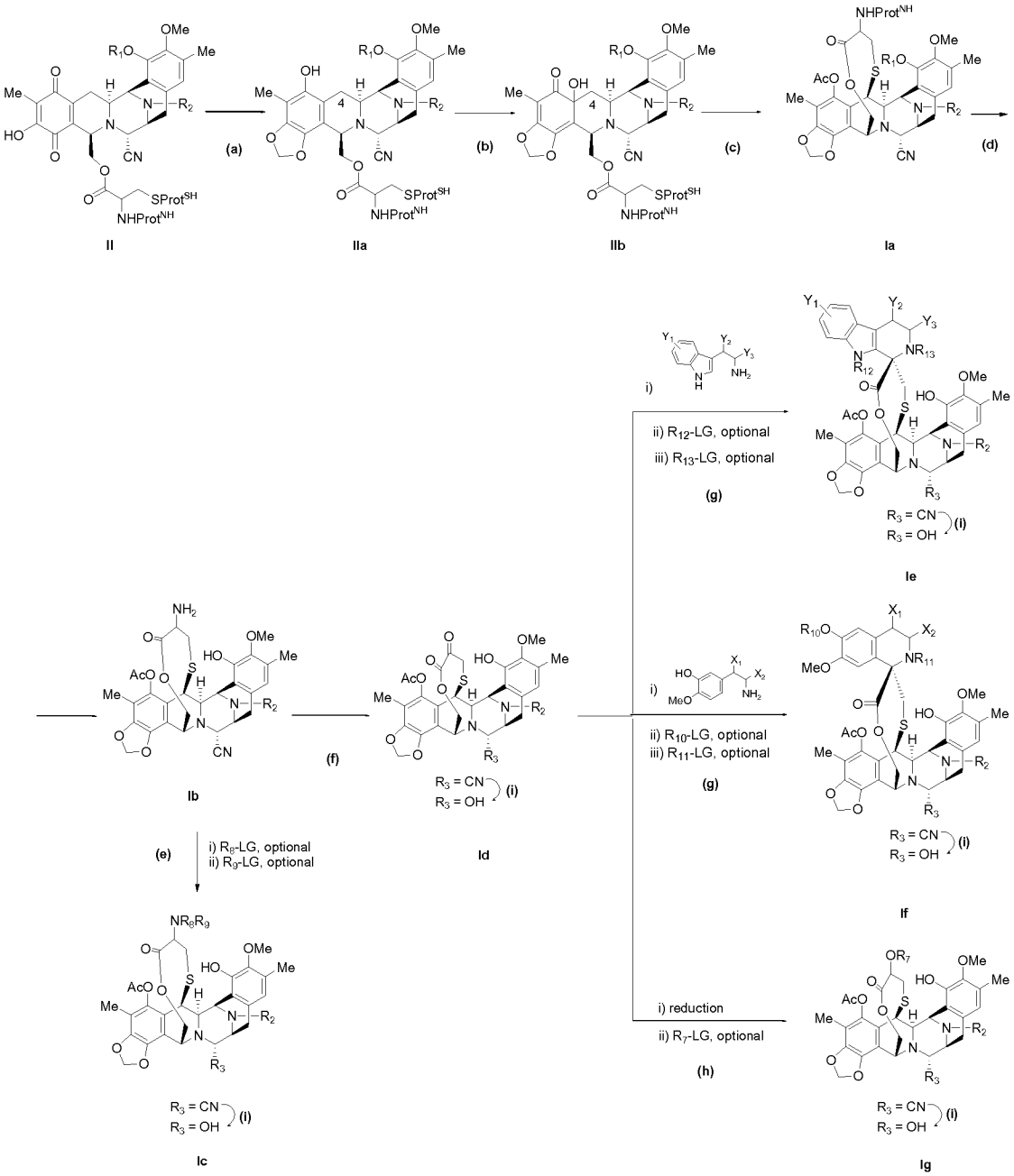
Suitable coupling agents are well known for the skilled person in the art. Examples of coupling agents are *N*,*N*'-dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDC) and its

salts, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC methiodide), *N*,*N*'-diisopropylcarbodiimide, 1-tert-butyl-3-ethyl carbodiimide, *N*-cyclohexyl-*N*'-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (CMC), *N*,*N*'-di-tert-butylcarbodiimide, 1,3-Di-p-tolylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), 1,1'-carbonyl-di-(1,2,4-triazole) (CDT), oxalic acid diimidazolide, 2-chloro-1,3-dimethylimidazolidinium chloride (DMC), 2-chloro-1,3-dimethylimidazolidinium tetrafluoroborate (CIB), 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP), 2-fluoro-1,3-dimethylimidazolidinium hexafluorophosphate (DFIH), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP), bromotris(dimethylamino)phosphonium hexafluorophosphate (BRoP), chlorotripyrrolidinophosphonium hexafluorophosphate (PyClOP), bromotripyrrolidinophosphonium hexafluorophosphate, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-bis(tetramethylene)uronium hexafluorophosphate (HBPyU), *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-bis(pentamethylene)uronium hexafluorophosphate (HBPipU), (benzotriazol-1-yloxy)dipiperidinocarbenium tetrafluoroborate (TBPipU), *O*-(6-chlorobenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HCTU), *O*-(6-chlorobenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium (TCTU), *O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TDBTU), *O*-(2-oxo-1(2H)pyridyl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TPTU), *O*-[(ethoxycarbonyl)cyanomethylenamino]-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HOTU), *O*-[(ethoxycarbonyl)cyanomethylenamino]-*N*,*N*,*N*',*N*'-tetramethyluronium

tetrafluoroborate (TOTU), *N*,*N*,*N*',*N*'-tetramethyl-*O*-(*N*-succinimidyl)uronium hexafluorophosphate (HSTU), *N*,*N*,*N*',*N*'-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU), dipyrrolidino(*N*-succinimidyloxy)carbenium (HSPyU), propylphosphonic anhydride (T3P) and *S*-(1-oxido-2-pyridyl)-*N*,*N*,*N*',*N*'-tetramethylthiouronium tetrafluoroborate (TOTT).

In the present description and definitions, when there are several groups R^a, R^b, R^c, R^d or R^e present in the compounds of the invention, and unless it is stated explicitly so, it should be understood that they can be each independently different within the given definition, i.e. R^a does not represent necessarily the same group simultaneously in a given compound of the invention.

The compounds of formula **I** can be obtained synthetically from intermediates of formula **II** following the sequence of key reactions indicated in Scheme **IV**:



Scheme **IV**

wherein

R_1, R_2, $Prot^{NH}$, and $Prot^{SH}$ in the compounds of formula **II**, **IIa**, **IIb**, **Ia**, and **Ib** are as defined above in intermediates of formula **II**;

R_2, R_3, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, X_1, X_2, Y_1, Y_2, and Y_3 in the compounds of formula **Ic**, **Id**, **Ie**, **If**, and **Ig** are as defined above in ecteinascidins of formula **I**;

LG is a leaving group; and

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} in the compounds of formula R_7-LG, R_8-LG, R_9-LG, R_{10}-LG, R_{11}-LG, R_{12}-LG, and R_{13}-LG, respectively, are as defined above in ecteinascidins of formula **I** with the proviso that they are not hydrogen.

Examples of leaving groups include, but are not limited to, iodine, bromine, chlorine, tosylate, mesylate, nosylate, betylate, alkyl fluorosulfonate, triflate, and nonaflate.

In general, the conversion of the intermediates of formula **II** to an ecteinascidin compound of formula **I** may involve one or more of the following key transformations as needed:

(a) Reduction of the quinone group in the compound of formula **II** followed by alkylation of the resulting hydroquinone with a suitable electrophilic reagent to give a compound of formula **IIa**.

(b) Oxidation of the compound of formula **IIa** to give a compound of formula **IIb**.

(c) Formation of the bridged ring system to provide a compound of formula **Ia**.

(d) Deprotection of the phenol and amino groups to give a compound of formula **Ib**.

(e) Conversion of the compound of formula **Ib** to give a compound of formula **Ic**.

(f) Oxidation of the α-aminolactone of formula **Ib** to the corresponding α-ketolactone of formula **Id** by transamination.

(g) Stereospecifically forming of a spirotetrahydro-*1H*-pyrido[3,4-b]indole of formula **Ie** or a spirotetrahydroisoquinoline of formula **If** by a Pictet-Spengler reaction from the α-ketolactone of formula **Id**.

(h) Reduction of the α-ketolactone of formula **Id** to the corresponding α-hydroxylactone of formula **Ig**.

(i) Replacing the cyano in R_3 by a hydroxy group.

Step (a) is typically effected by reduction of the quinone system into a hydroquinone using a transition-metal catalysed hydrogenation or a reducting reagent such as $Na_2S_2O_4$, followed by trapping with a suitable electrophile reagent, such as CH_2Br_2, $BrCH_2Cl$ or a similar divalent reagent, directly yielding the methylenedioxy ring system; or with a divalent reagent, such as thiocarbonyldiimidazole, which yields a substituted methylenedioxy ring system that can be converted to the desired ring.

Step (b) is typically effected by reaction with a suitable oxidant, for example with hydrogen peroxide, an organic peroxide, a perbenzoic acid, a periodate, lead tetraacetate, lead oxide, selenium dioxide, hypervalent iodine oxidants such as 2-iodoxybenzoic acid (IBX), or with an organic seleninic anhydride such as $(PhSeO)_2O$. More preferred oxidants are organic seleninic anhydrides and hypervalent iodine oxidants. Organic seleninic anhydrides are even more preferred. The most preferred oxidant is $(PhSeO)_2O$.

Step (c) is typically effected by forming an exendo quinone methide at the 4-position of ring B, allowing the methide to react with the sulphur atom of the cysteine residue and capturing the resulting phenoxide with an acetylating reagent such as acetic anhydride, a mixed acetyl anhydride, or acetyl chloride to give a compound of formula **Ia**. Suitable

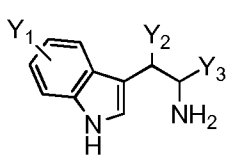
the methide is formed by reaction of the compound of formula **IIb** with the in situ-generated Swern reagent, followed by treatment with a base. Suitable the cyclization is carried out by removing the protecting group for SH under conditions that allow the formation of a thiolate ion, followed by nucleophile addition of sulphur to the quinone methide to generate the 10-membered lactone bridge, and the resulting phenoxide is captured to give the acetate of formula **Ia**.

Step (d) is preferably effected by deprotection of the phenol and amino groups in a single step rather than as two separate steps. More preferably, the one-pot deprotection is carried out under acidic conditions.

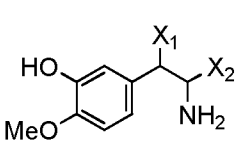
Step (e) is carried out when R_8 and/or R_9 are not hydrogen and is typically effected by reaction with a compound of formula R_8LG or R_9LG and, when both R_8 and R_9 are not hydrogen, followed by a second reaction with a compound of formula R_9LG or R_8LG, respectively.

Step (f) is typically effected by an oxidative conversion of the amino group into the corresponding oxo group by reaction with a suitable carbonyl reagent such as a hindered 1,2-benzoquinone or a pyridine- or pyridinium carboxaldehyde. More preferred carbonyl reagents are the methiodide of pyridine-4-carboxaldehyde and the methylbencene-sulfonate of pyridine-4-carboxaldehyde.

Step (g) is typically effected by Pictet-Spengler reaction with a β-arylethylamine of formula:



or



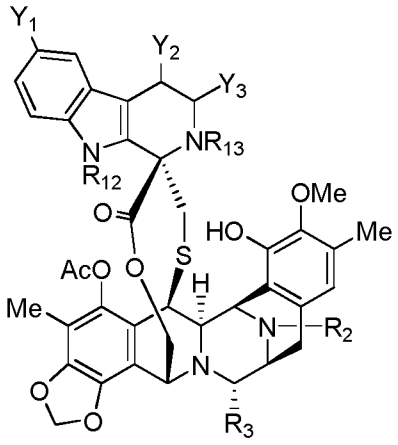
wherein Y_1, Y_2, Y_3, X_1, and X_2 are as defined above in ecteinascidins of formula **I.**

Step (h) is typically effected by reaction with a suitable reducting reagent. Examples of suitable reducting reagents are alkoxy aluminum hydrides and boron hydrides, for example borohydrides and cyanoborohydrides. More preferred reducting reagents are borohydrides and cyanoborohydrides. The most preferred reducting reagent is $NaCNBH_3$ in the presence of acetic acid.

Step (i) is typically carried out by reaction with a nitrile-coordinating transition metal salt. More preferred salts are salts of Ag(I) or Cu(I). The most preferred salts are $AgNO_3$ and CuCl.

Further transformations may be required to obtain certain compounds of formula **I** and for this purpose the procedures described in WO 01/87895, WO 03/014127, WO 03/66638, WO 03/08423 and WO 01/77115, which are incorporated herein in full by reference, can be followed.

Preferred processes for the synthesis of compounds of formula **Ie** are those that provide compounds of formula **Ie'**:



Ie'

where R_2, R_3, R_{12}, R_{13}, Y_1, Y_2, and Y_3 are as defined above in ecteinascidins of formula **I.**

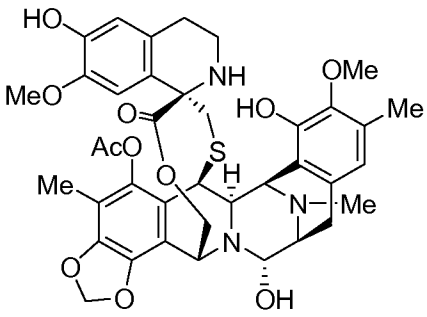
Particularly preferred processes for the synthesis of compounds of formula **I** are those that provide compounds of formula **Ic**, **Id**, **Ie, Ie', If**, or **Ig** wherein R_2 is methyl, R_3 is hydroxy, X_1, X_2, Y_2, Y_3, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are hydrogen, and Y_1 is selected from hydrogen and methoxy.

Particularly preferred processes for the synthesis of compounds of formula **I** are those that employ ether protected OH groups. More preferably ether protected OH groups are methoxyethoxymethyl ether and methoxymethyl ether. The most preferred ether protected OH group is methoxyethoxymethyl ether.

Particularly preferred processes for the synthesis of compounds of formula **I** are those that employ carbamate protected amino groups. More preferably carbamate protected amino groups are selected from allylcarbamate, 2,2,2-trichloroethylcarbamate, benzylcarbamate, 9-fluorenylmethyl-carbamate, and *t*-butylcarbamate. The most preferred carbamate protected amino group is *t*-butylcarbamate.

Particularly preferred processes are those that employ thioether protected SH groups. More preferably thioether protected SH groups are substituted or unsubstituted S-9-fluorenylmethyl thioethers. The most preferred thioether protected SH group is S-9-fluorenylmethyl (Fm) thioether.

More preferred processes for the synthesis of compounds of formula **I** are those that give compounds of formula:



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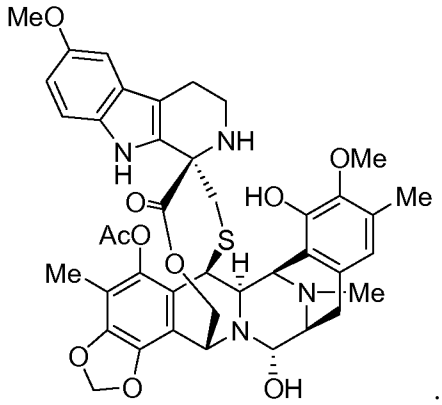
or



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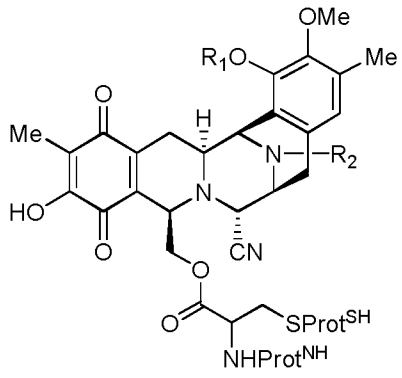
In addition, with this invention we provide novel intermediate compounds of formula **II**:



II

wherein R_1, R_2, $Prot^{SH}$ and $Prot^{NH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

In compounds of formula **II**, particularly preferred R_1 is a protecting group for OH that together with the O atom to which it is attached form an ether. More preferably R_1 is methoxyethoxymethyl or methoxymethyl. The most preferred R_1 is methoxyethoxymethyl.

Particularly preferred R_2 is a substituted or unsubstituted C_1-C_6 alkyl, a substituted or unsubstituted C_2-C_6 alkenyl or C(=O)OR^b, where R^b is selected from substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted C_2-C_6 alkenyl. Particularly preferred R_2 is

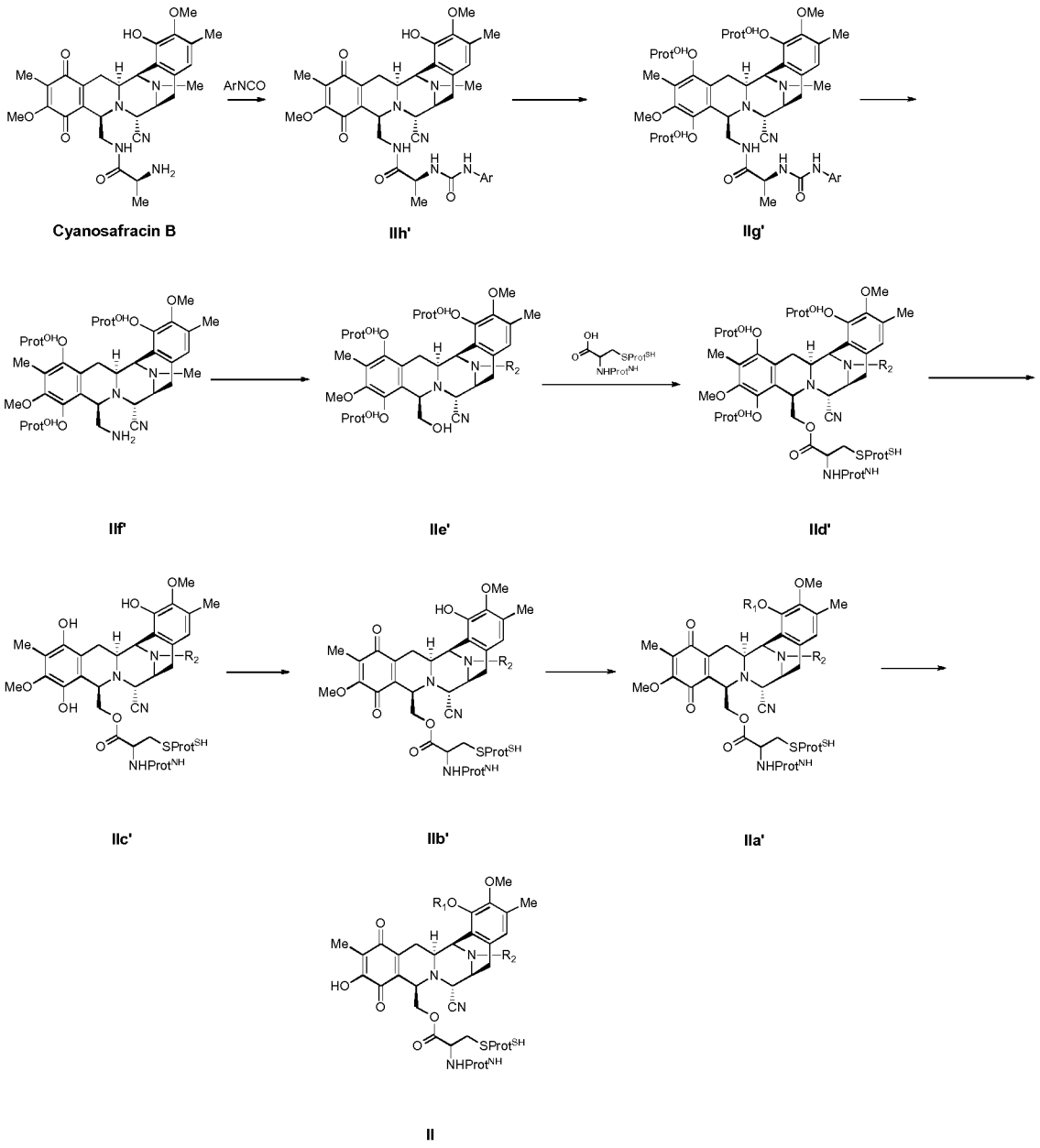
an unsubstituted C_1-C_6 alkyl or an unsubstituted C_2-C_6 alkenyl. More preferably R_2 is methyl or allyl. The most preferred R_2 is methyl.

Particularly preferred $Prot^{NH}$ is a protecting group for amino that together with the N atom to which is attached form a carbamate. More preferably $Prot^{NH}$ is selected from allyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and *t*-butyloxycarbonyl. The most preferred $Prot^{NH}$ is *t*-butyloxycarbonyl.

Particularly preferred $Prot^{SH}$ is a protecting group for SH that together with the S group to which is attached form a thioether. More preferably $Prot^{SH}$ is a substituted or unsubstituted S-9-fluorenylmethyl. The most preferred $Prot^{SH}$ is S-9-fluorenylmethyl (Fm).

Suitable starting materials for the synthesis of the intermediates of formula **II** include compounds related to the natural bis(tetrahydroisoquinoline) alkaloids. Such starting materials may be prepared either from the different classes of saframycin and safracin antibiotics available from different culture broths as detailed in WO 00/69862 or by other synthetic or biochemical processes such as those disclosed in US 5,721,362, US 6,815,544, JP 2003221395, WO 2007/045686, WO 2007/087220 and J. Org. Chem. 2008, 73, 9594-9600, which are all incorporated herein in full by reference.

In one embodiment, compounds of formula **II** are obtained from cyanosafracin B following the sequence of reactions indicated in Scheme **V**:



Scheme **V**

wherein:

$Prot^{OH}$ is a protecting group for OH;

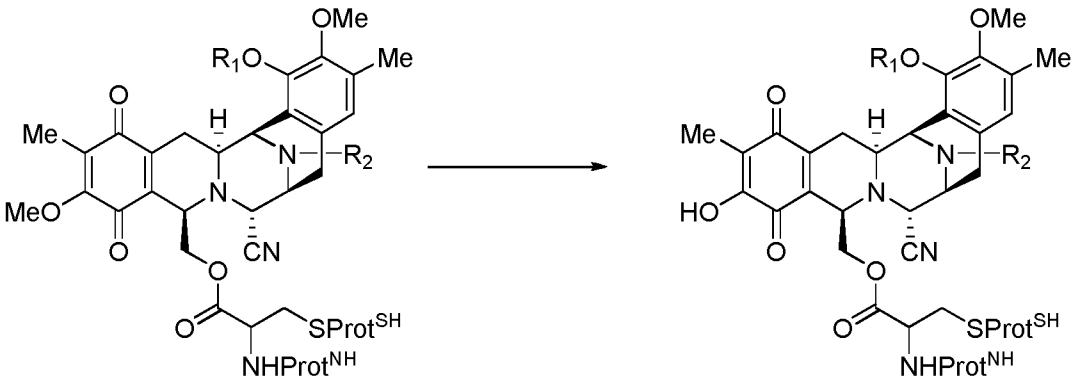
Ar is a substituted or unsubstituted aryl group;

$Prot^{NH}$ is a protecting group for amino;

$Prot^{SH}$ is a protecting group for SH; and

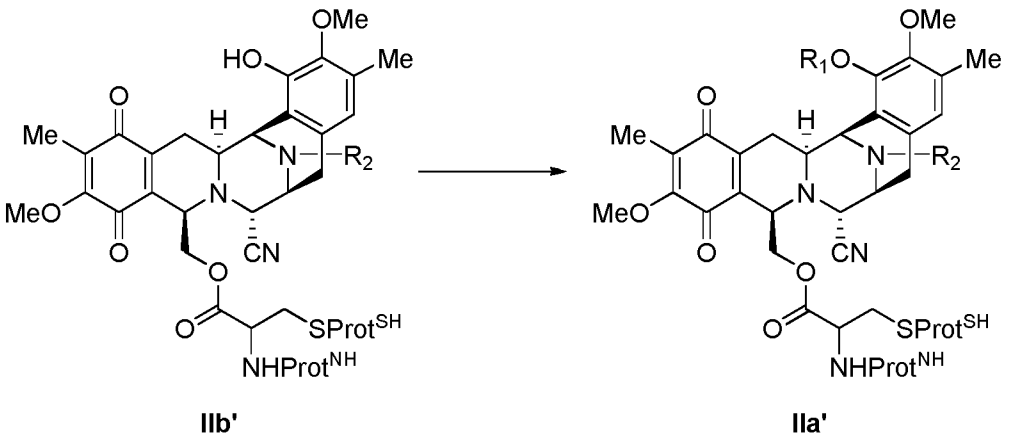
R_1 and R_2 are as defined above in formula **II**.

Accordingly, in this embodiment, the process for the synthesis of a compound of formula **II** comprises the step of demethylating a methoxyquinone of formula **IIa'**:



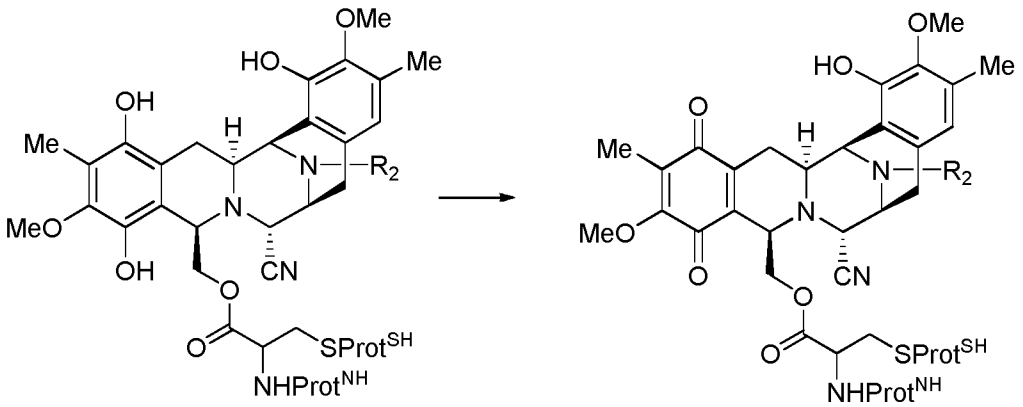
wherein R_1, R_2, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

Moreover, this process can further comprise the step of preparing the compound of formula **IIa'** by protecting a phenol of formula **IIb'**:



wherein R_1, R_2, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

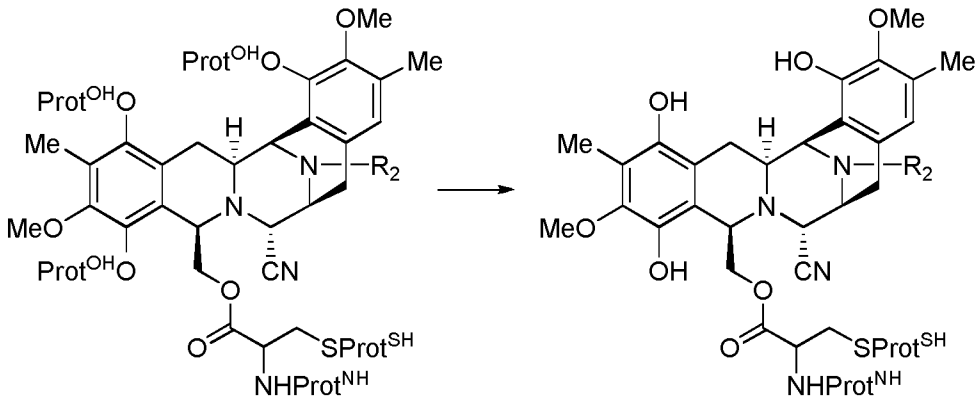
Moreover, this process can further comprise the step of preparing the compound of formula **IIb'** by oxidation of a hydroquinone of formula **IIc'**:



IIc' **IIb'**

wherein R_2, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

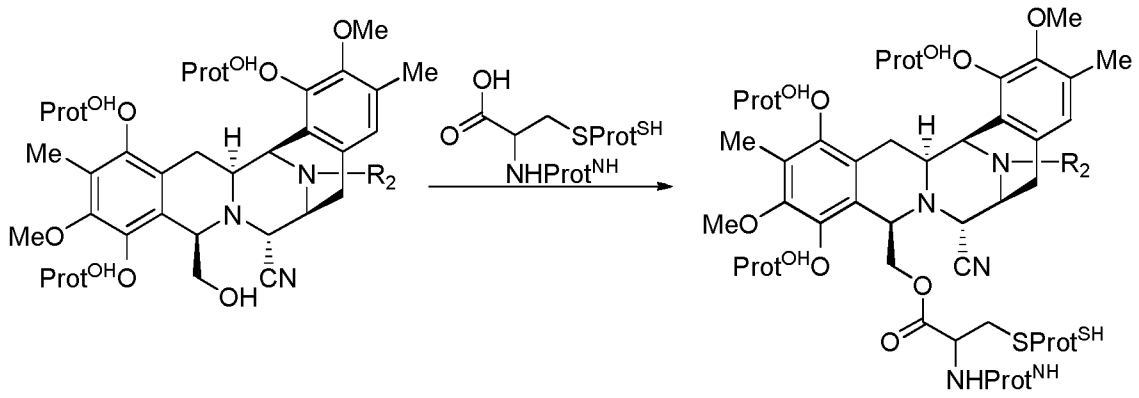
Moreover, this process can further comprise the step of preparing a compound of formula **IIc'** by deprotection of a compound of formula **IId'**:



IId' **IIc'**

wherein R_2, $Prot^{OH}$, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

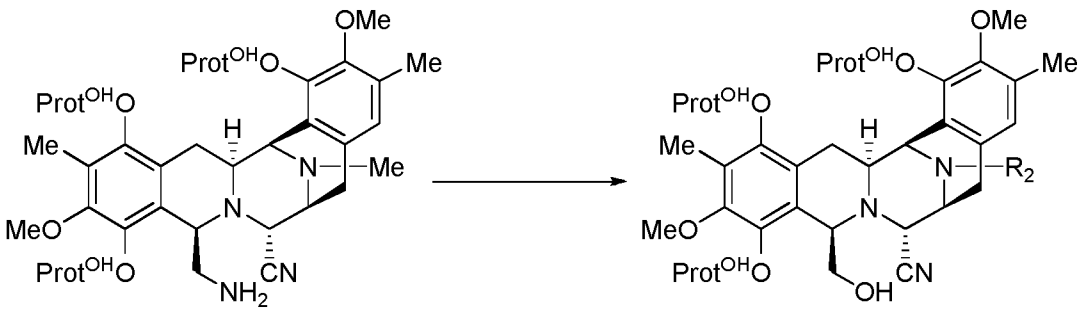
Moreover, this process can further comprise the step of preparing the compound of formula **IId'** by coupling the primary hydroxyl group in a compound of formula **IIe'** with a protected cysteine derivative:



IIe' **IId'**

wherein R_2, $Prot^{OH}$, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

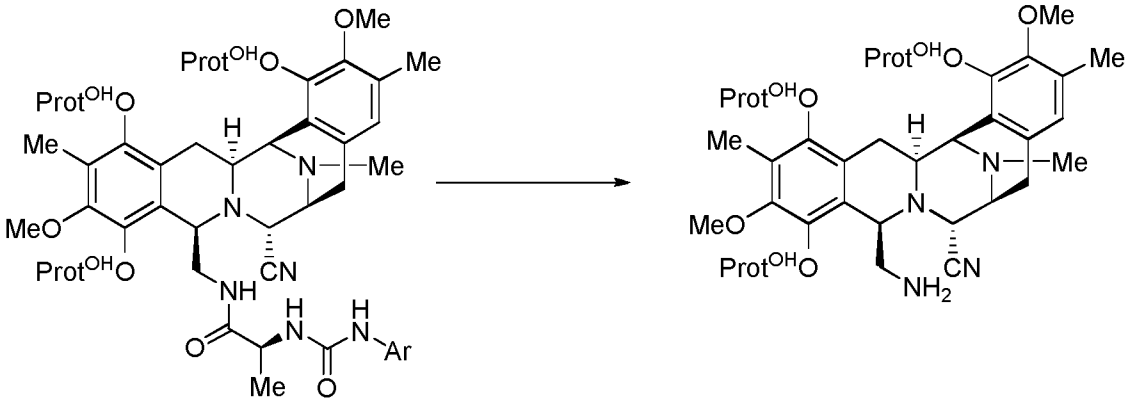
Moreover, this process can further comprise the step of preparing the compound of formula **IIe'** by converting a primary amine of formula **IIf'** to a primary alcohol with a suitable oxidizing reagent and, optionally, when R_2 in the compound of formula **IIe'** is not methyl, followed by protecting the primary alcohol with a silyl protecting group for OH, demethylating the NMe group, reacting the resulting secundary amine with a compound of formula R_2-LG wherein LG is a leaving group and R_2 is as defined in formula **II** except methyl and hydrogen, and deprotecting the silyl-protected primary alcohol:



IIf' **IIe'**

wherein R_2 is as defined above in the previous disclosure of intermediates of formula **II** and $Prot^{OH}$ is a protecting group for OH.

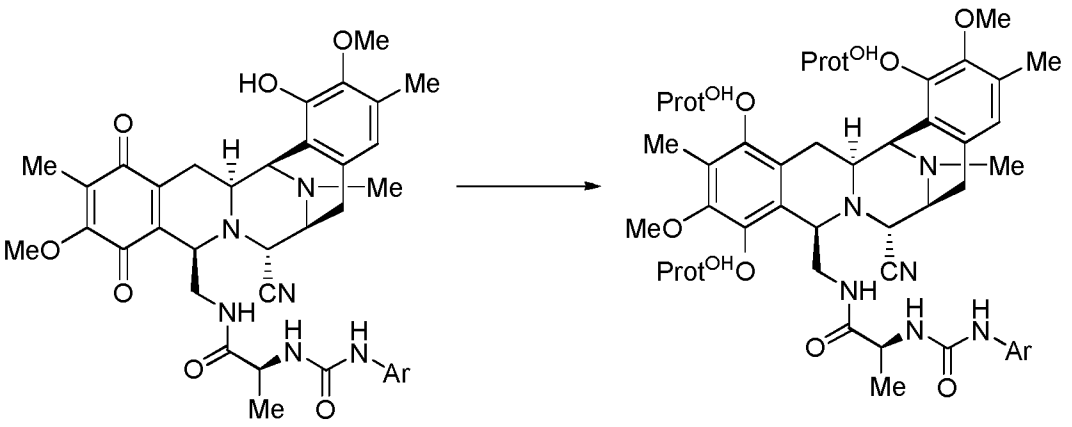
Moreover, this process can further comprise the step of preparing the compound of formula **IIf'** by amidolysis of a compound of formula **IIg'**:



IIg' **IIf'**

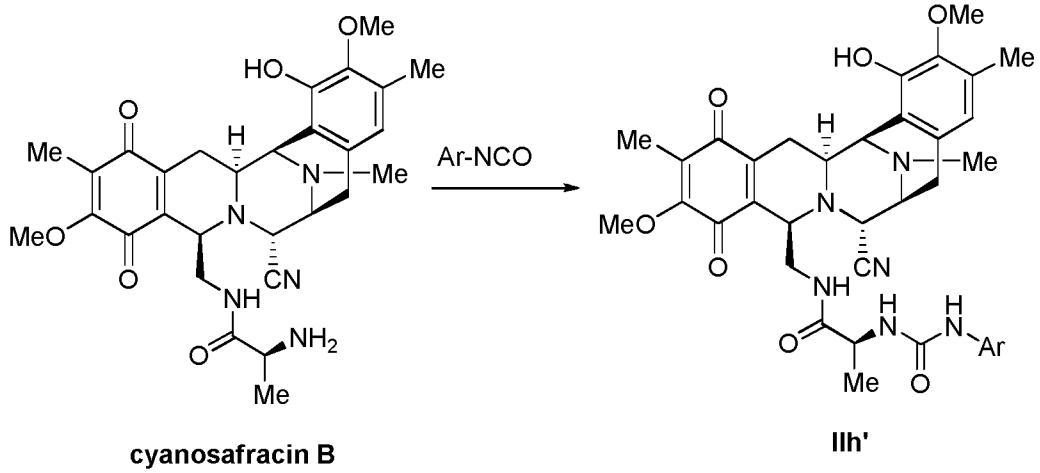
wherein $Prot^{OH}$ is a protecting group for OH and Ar is a substituted or unsubstituted aryl group.

Moreover, this process can further comprise the step of preparing a compound of formula **IIg'** by reduction of the quinone of formula **IIh'** followed by protection of the hydroxy groups:



wherein $Prot^{OH}$ is a protecting group for OH and Ar is a substituted or unsubstituted aryl group.

Moreover, this process can further comprise the step of preparing a compound of formula **IIh'** by reaction of cyanosafracin B with a substituted or unsubstituted arylisocyanate:



wherein Ar is a substituted or unsubstituted aryl group.

The conversion of the methoxyquinone of formula **IIa'** to give the compound of formula **II** is typically carried out by reaction with a suitable reagent for the deprotection of methoxy groups. Preferred

reagent for such reaction is LiI in presence of a base such as an optionally substituted quinoline or collidine. More preferred base is a collidine. The most preferred base is 2,4,6-collidine.

The protection of the phenol of formula **IIb'** to give a compound of formula **IIa'** is typically carried out by reaction with a suitable reagent for the protection of phenol groups. Preferred reagents for such reaction are alkoxymethyl chlorides, alkoxymethylbromides and alkoxyalkoxymethyl chlorides. Alkoxyalkoxymethyl chlorides are particularly preferred reagents. The most preferred reagent is methoxyethoxymethyl chloride (MEMCl).

The oxidation of the hydroquinone of formula **IIc'** to give a compound of formula **IIb'** is carried out by reaction with a suitable oxidizing reagent. Particularly preferred oxidants are oxygen and Pd - oxygen. The most preferred oxidant is Pd/C - oxygen.

Deprotection of the phenol groups in a compound of formula **IId'** to give a hydroquinone of formula **IIc'** is carried out under conditions very well known by an expert in the art taking into account the structure of $Prot^{OH}$. Particularly preferred conditions are those employed for the deprotection of allyl protected phenol groups. Most preferred is a palladium catalyzed deprotection in presence of a reducing reagent such as a trialkyltin hydride.

The preparation of a compound of formula **IId'** from a compound of formula **IIe'** is typically carried out by reaction with an amino- and sulphur-protected cysteine amino acid wherein the amino acid is activated by a coupling agent such as a carbodiimide, a phosphonium salt, an uronium salt, a guanidinium salt, an imidazolium derived reagent, or a triazolium derived reagent. Particularly preferred coupling agents are carbodiimides. Most preferred coupling agents are 1-ethyl-3-

(3-dimethylaminopropyl)-carbodiimide (EDC) and its chlorohydrate (EDC·HCl).

The conversion of the primary amine of formula **IIf'** to the primary alcohol of formula **IIe'** is typically carried out by reaction with a suitable oxidizing reagent such as an inorganic nitrite, nitrogen tetroxide or a nitroferricyanide. More preferred oxidizing reagents are inorganic nitrites. Sodium nitrite is the most preferred oxidizing reagent for this step.

The optional demethylation during the synthesis of a compound of formula **IIe'** typically involves a reaction with a suitable oxidant to provide the corresponding *N*-oxide. Particularly preferred oxidants for such reaction are peracids. The most preferred oxidant is *m*-chloroperbenzoic acid.

The conversion of the compound of formula **IIg'** to provide a primary amine of formula **IIf'** is carried out by reaction with a suitable amidolysis reagent. Particularly preferred is the use of chlorotrimethylsilane / methanol or iodotrimethylsilane as amidolysis reagents.

The reduction of the quinone group in the compound of formula **IIh'** is typically carried out using a transition metal catalysed hydrogenation or a reducting reagent such as $Na_2S_2O_4$. A transition metal catalysed hydrogenation is particularly preferred. The most preferred transition metal catalyst is Pd / C. The protection of the hydroxy groups of the intermediate compound to give a compound of formula **IIg'** is typically carried out by reaction with a suitable reagent for the protection of phenol groups. Preferred reagents for such reaction are allyl halides and allyloxycarbonyl halides. More preferred reagents for such reactions are allyl halides. The most preferred reagent is allyl

bromide.

The formation of the urea of formula **IIh'** from cyanosafracin B is typically carried out by reaction with an aryl isocyanate. The most preferred reagent is phenylisocyanate.

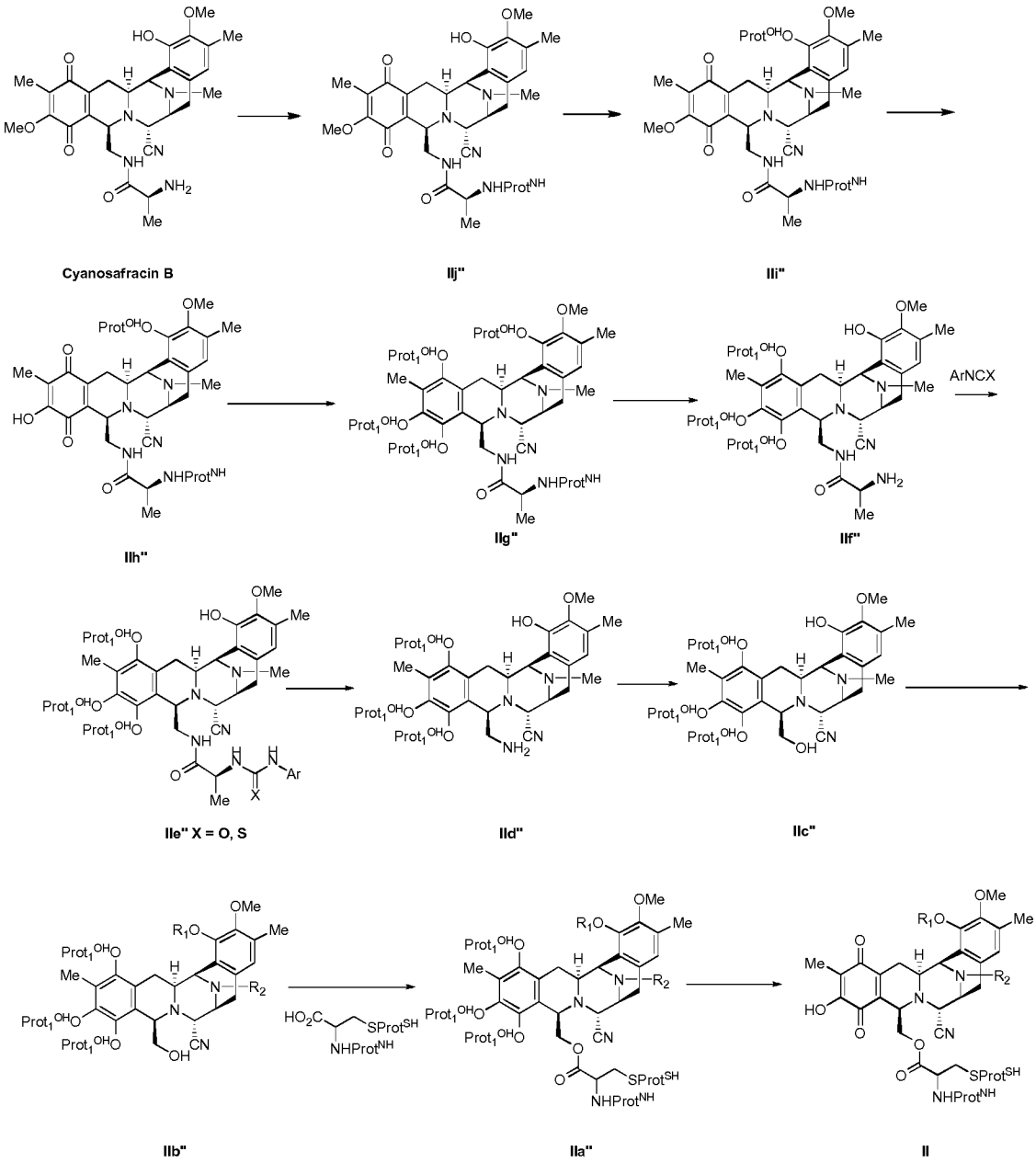
In this process, the use of ether protected OH groups is particularly preferred. More preferably the ether protected groups are selected from alkyl silyl ethers, allyl ether, methoxyethoxymethyl ether, and methoxymethyl ether. The most preferred ether protected OH groups are allyl and methoxyethoxymethyl ether.

In this process, particularly preferred Ar group is phenyl.

In this process, the use of carbamate protected NH groups is particularly preferred. More preferably carbamate protected amino groups are selected from allylcarbamate, 2,2,2-trichloroethylcarbamate, benzylcarbamate, 9-fluorenylmethyl-carbamate, and *t*-butylcarbamate. The most preferred carbamate protected amino group is *t*-butylcarbamate.

In this process, the use of thioether protected SH groups is particularly preferred. More preferably thioether protected SH groups are substituted or unsubstituted S-9-fluorenylmethyl thioethers. The most preferred thioether protected SH group is S-9-fluorenylmethyl (Fm) thioether.

In another embodiment, the compounds of formula **II** can also be obtained from cyanosafracin B following the sequence of reactions indicated in Scheme **VI**:



Scheme **VI**

wherein:

$Prot_1^{OH}$, $Prot^{OH}$ and R_1 are protecting groups for OH, with the proviso that $Prot^{OH}$ and R_1 are selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa.

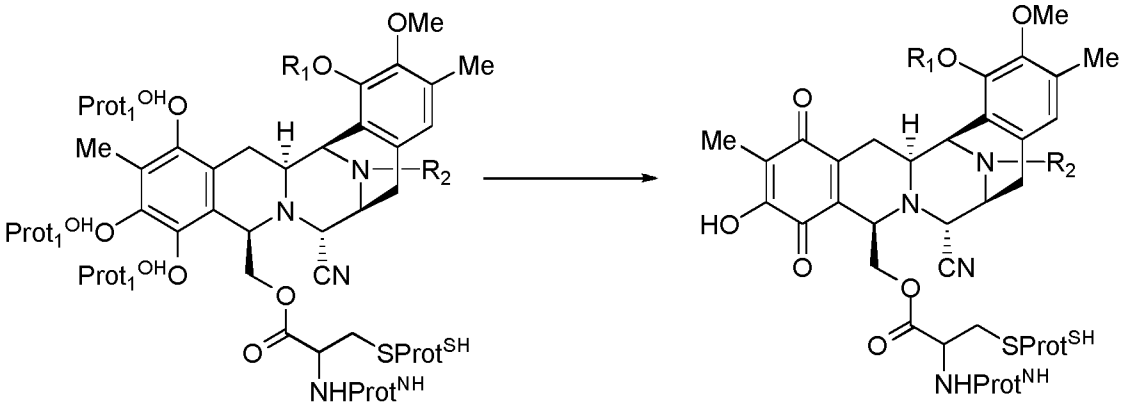
Ar is a substituted or unsubstituted aryl group;

$Prot^{NH}$ is a protecting group for amino;

$Prot^{SH}$ is a protecting group of SH;

and R_2 is as defined above in formula **II**.

Accordingly, in this embodiment, the process for the synthesis of a compound of formula **II** comprises the step of deprotecting the $Prot_1^{OH}O$- groups of a compound of formula **IIa"** and oxidating the resulting hydroquinone:



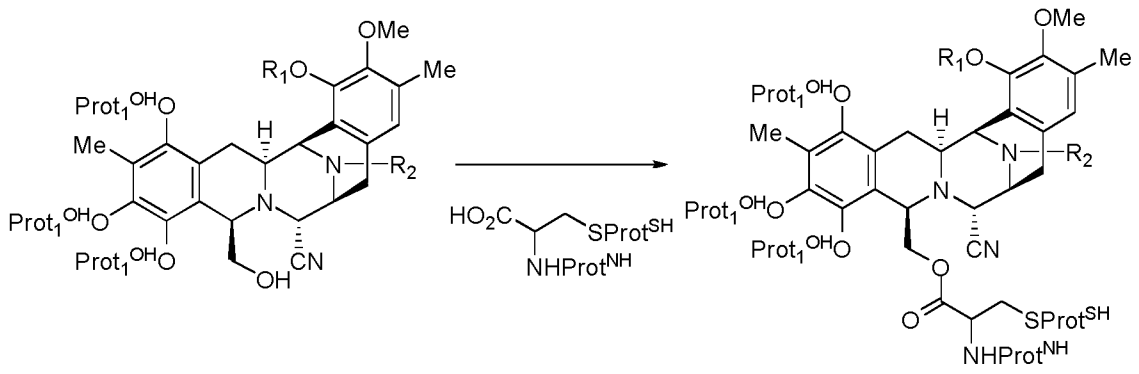
IIa" **II**

wherein

$Prot_1^{OH}$ and R_1 are protecting groups for OH, with the proviso that R_1 is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

R_2, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

Moreover, this process can further comprise the step of preparing the compound of formula **IIa"** by coupling the primary hydroxyl group in a compound of formula **IIb"** with a protected cysteine derivative:



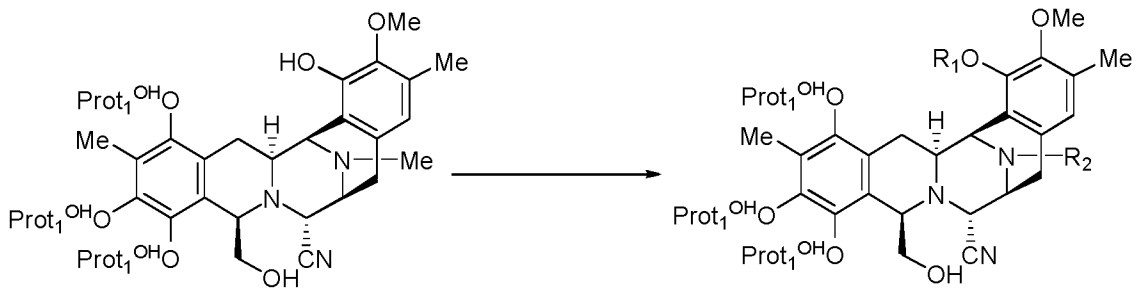
IIb" IIa"

wherein

$Prot_1^{OH}$ and R_1 are protecting groups for OH, with the proviso that R_1 is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

R_2, $Prot^{NH}$ and $Prot^{SH}$ are as defined above in the previous disclosure of intermediates of formula **II**.

Moreover, this process can further comprise the step of preparing the compound of formula **IIb"** by protecting of the phenol of formula **IIc"** and, optionally, when R_2 in the compound of formula **IIb"** is not methyl, followed by protecting the primary alcohol with a silyl protecting group for OH, demethylating the NMe group, reacting the resulting secundary amine with a compound of formula R_2-LG wherein LG is a leaving group and R_2 is as defined in formula **II** except methyl, and deprotecting the silyl-protected primary alcohol:



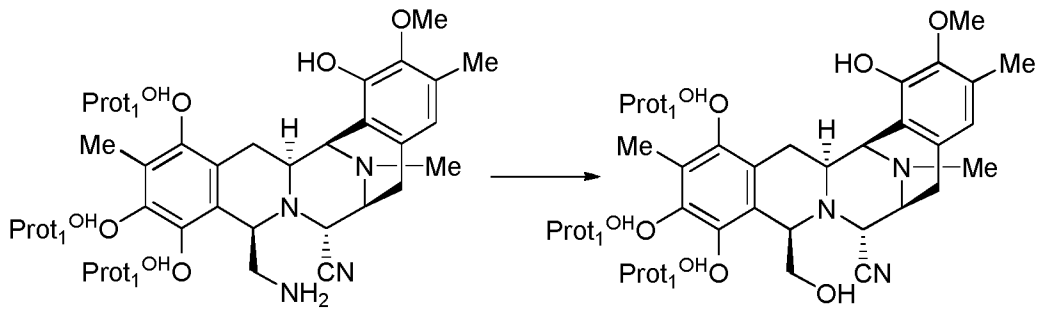
IIc" IIb"

wherein

$Prot_1^{OH}$ and R_1 are protecting groups for OH, with the proviso that R_1 is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

R_2 is as defined above in the previous disclosure of intermediates of formula **II**.

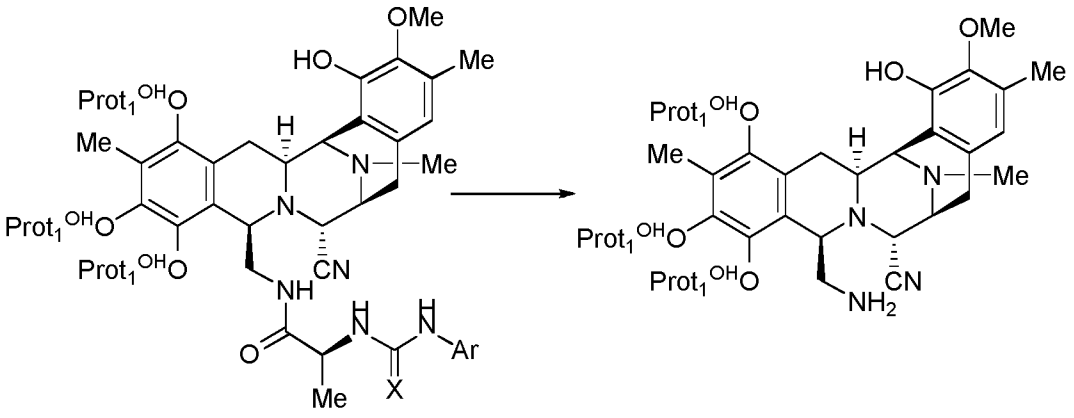
Moreover, this process can further comprise the step of preparing a compound of formula **IIc"** by converting the primary amine in a compound of formula **IId"** to a primary alcohol with a suitable oxidizing reagent:



IId" IIc"

wherein $Prot_1^{OH}$ is a protecting group for OH.

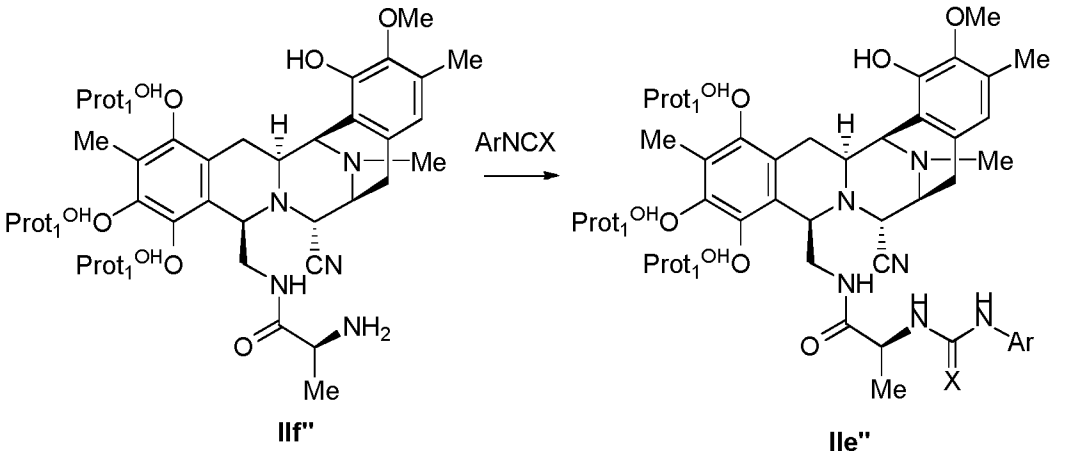
Moreover, this process can further comprise the step of preparing the compound of formula **IId"** by amidolysis of a compound of formula **IIe"** to give a primary amine:



IIe" **IId"**

wherein $Prot_1^{OH}$ is a protecting group for OH, Ar is a substituted or unsubstituted aryl group, and X is O or S.

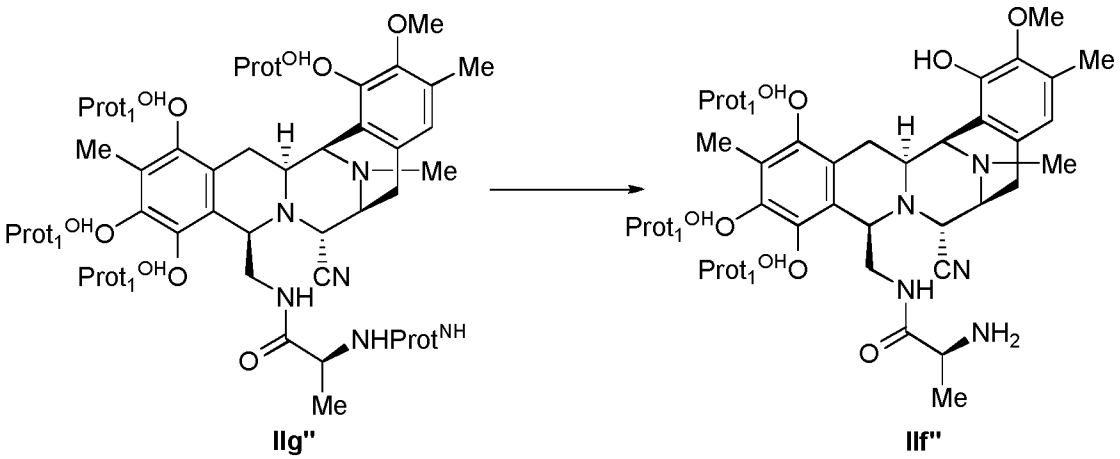
Moreover, this process can further comprise the step of preparing a compound of formula **IIe"** by reaction of a compound of formula **IIf"** with a substituted or unsubstituted arylisocyanate or arylisothiocyanate:



IIf" **IIe"**

wherein $Prot_1^{OH}$ is a protecting group for OH, Ar is a substituted or unsubstituted aryl group, and X is O or S.

Moreover, this process can further comprise the step of partial deprotecting a compound of formula **IIg"** to provide a compound of formula **IIf"**:

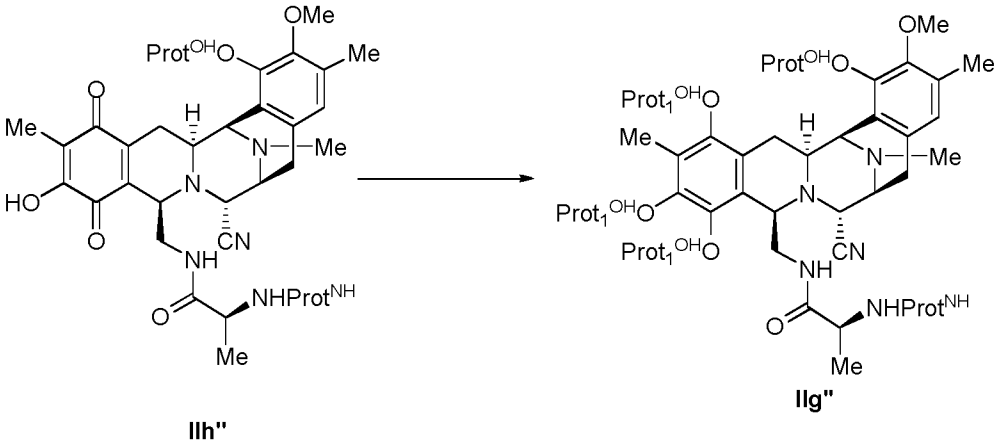


wherein

$Prot_1^{OH}$ and $Prot^{OH}$ are protecting groups for OH, with the proviso that $Prot^{OH}$ is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

$Prot^{NH}$ is a protecting group for amino.

Moreover, this process can further comprise the step of preparing a compound of formula **IIg"** by reduction of the hydroxyquinone of formula **IIh"** followed by protection of the hydroxy groups:

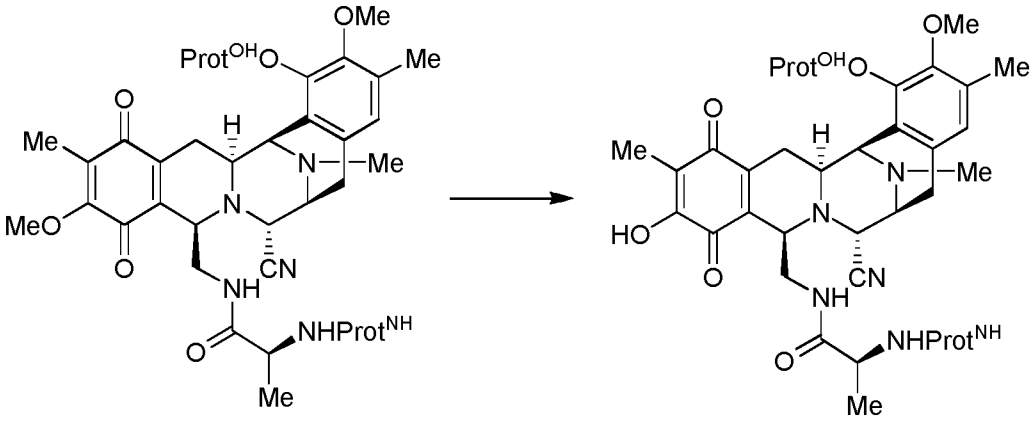


wherein

$Prot_1^{OH}$ and $Prot^{OH}$ are protecting groups for OH, with the proviso that $Prot^{OH}$ is selected to be removed selectively in the presence of $Prot_1^{OH}$ and vice versa; and

$Prot^{NH}$ is a protecting group for amino.

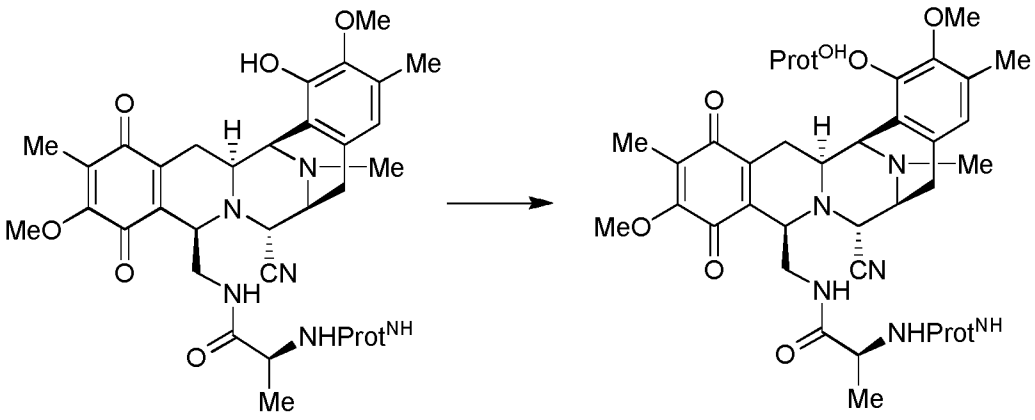
Moreover, this process can further comprise the step of hydrolysing or demethylating a methoxyquinone of formula **IIi"** to provide a compound of formula **IIh"**:



IIi" **IIh"**

wherein $Prot^{OH}$ is a protecting group for OH and $Prot^{NH}$ is a protecting group for amino.

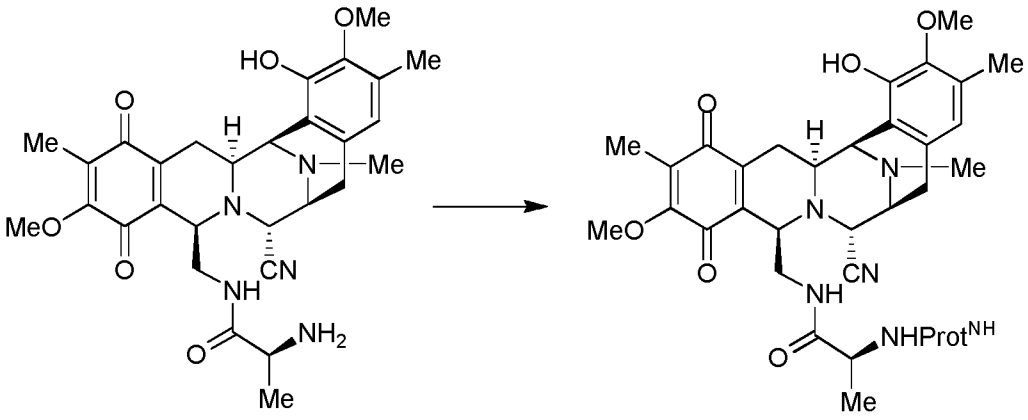
Moreover, this process can further comprise the step of protecting the phenol of formula **IIj"** to provide a compound of formula **IIi"**:



IIj" **IIi"**

wherein $Prot^{OH}$ is a protecting group for OH and $Prot^{NH}$ is a protecting group for amino.

Moreover, this process can further comprise the step of preparing a compound of formula **IIj"** by protecting the amino group of cyanosafracin B:



Cyanosafracin B **IIj"**

wherein $Prot^{NH}$ is a protecting group for amino.

The deprotection of the compound of formula **IIa"** is carried out following standard procedures very well known by a skilled person. The oxidation of the deprotected intermediate is carried out by reaction with a suitable oxidizing reagent. Particularly preferred oxidants are oxygen and Pd - oxygen. The most preferred oxidant is Pd/C - oxygen.

The preparation of a compound of formula **IIa"** from a compound of formula **IIb"** is typically carried out by reaction with an amino- and sulphur- protected cysteine amino acid wherein the amino acid is activated by a coupling agent such as a carbodiimide, a phosphonium salt, an uronium salt, a guanidinium salt, an imidazolium derived reagent, or a triazolium derived reagent. Particularly preferred coupling agents are carbodiimides. Most preferred coupling agents are 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and its chlorohydrate (EDC·HCl).

The protection of the phenol of formula **IIc"** to give a compound of formula **IIb"** is typically carried out by reaction with a suitable reagent for the protection of phenol groups. Preferred reagents for such reaction are alkoxymethyl chlorides, alkoxymethylbromides and alkoxyalkoxymethyl chlorides. Alkoxyalkoxymethyl chlorides are particularly preferred reagents. The most preferred reagent is methoxyethoxymethyl chloride (MEMCl). The optional demethylation during the synthesis of a compound of formula **IIb"** typically involves a reaction with a suitable oxidant to provide the corresponding *N*-oxide. Particularly preferred oxidants for such reaction are peracids. The most preferred oxidant is *m*-chloroperbenzoic acid.

The conversion of the primary amine of formula **IId"** to provide the primary alcohol of formula **IIc"** is typically carried out by reaction with a suitable oxidizing reagent such as an inorganic nitrite, nitrogen tetroxide or a nitroferricyanide. More preferred oxidizing reagents are inorganic nitrites. Sodium nitrite is the most preferred oxidizing reagent for this step.

The conversion of the compound of formula **IIe"** to a primary amine of formula **IId"** is typically carried out by reaction with a suitable amidolysis reagent. Particularly preferred is the use of chlorotrimethylsilane / methanol or iodotrimethylsilane as amidolysis reagents.

The formation of a urea or thiourea of formula **IIe"** from a compound of formula **IIf"** is typically carried out by reaction with an aryl isocyanate or with an arylisothiocyanate. Particularly preferred reagents for such reaction are arylisothiocyanates. The most preferred reagent is phenylisothiocyanate.

The partial deprotection of the compound of formula **IIg''** to provide a compound of formula **IIf''** is preferably carried out in a one-pot step using acidic conditions.

The reduction of the hydroxyquinone of formula **IIh''** is typically carried out using a transition metal catalysed hydrogenation or a reducting reagent such as $Na_2S_2O_4$. A transition metal catalysed hydrogenation is particularly preferred. The most preferred transition metal catalyst is Pd / C. The hydroxy groups in the intermediate hydroquinone are protected to provide a compound of formula **IIg''**. Protection of the hydroxy groups is typically carried out by reaction with a suitable reagent for the protection of phenol groups. Particularly preferred protecting groups for this step are allyl and allyloxycarbonyl groups. The most preferred protecting group is allyl.

The conversion of the methoxyquinone of formula **IIi''** to give the hydroxyquinone of formula **IIh''** is typically carried out by reaction with a suitable reagent for the deprotection of methoxy groups or by reaction with a hydroxide. Preferred reagents for such reaction are a hydroxide or LiI in presence of a base. More preferably the reaction is carried out with an alkaline hydroxide. The most preferred alkaline hydroxide is LiOH.

The protection of the phenol of formula **IIj''** to give a compound of formula **IIi''** is typically carried out by reaction with a suitable reagent for the protection of phenol groups. Preferred reagents for such reaction are alkoxymethyl chlorides, alkoxymethylbromides and alkoxyalkoxymethyl chlorides. Alkoxyalkoxymethyl chlorides are particularly preferred reagents. The most preferred reagent is methoxyethoxymethyl chloride (MEMCl).

The protection of Cyanosafracin B to give a compound of formula

IIj" is typically carried out by reaction with a suitable reagent for the protection of amino groups. Preferred reagents for such reaction are dicarbonates and alkoxycarbonylchlorides. Dicarbonates are particularly preferred reagents. The most preferred reagent is di-tert-butyl dicarbonate (Boc_2O).

In this process, particularly preferred $Prot^{OH}$ groups are those that together with the O atom to which they are attached form an ether group. More preferably $Prot^{OH}$ groups are methoxyethoxymethyl and methoxymethyl. The most preferred $Prot^{OH}$ group is methoxyethoxymethyl. Particularly preferred $Prot_1{}^{OH}$ groups are those that together with the O atom to which they are attached form an ether or a carbonate groups. More preferably $Prot_1{}^{OH}$ groups are allyl and allyloxycarbonyl. The most preferred $Prot_1{}^{OH}$ group is allyl.

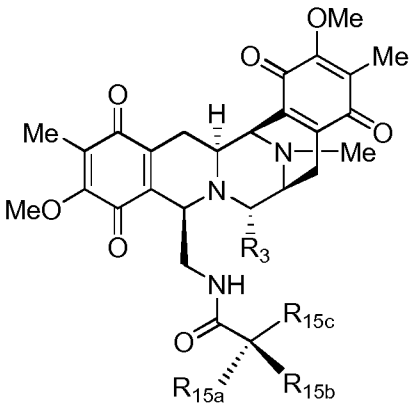
In this process, the most preferred Ar group is phenyl.

In this process, the use of carbamate protected NH groups is particularly preferred. More preferably carbamate protected amino groups are selected from allylcarbamate, 2,2,2-trichloroethylcarbamate, benzylcarbamate, 9-fluorenylmethyl-carbamate, and *t*-butylcarbamate. The most preferred carbamate protected amino group is *t*-butylcarbamate.

In this process, the use of thioether protected SH groups is particularly preferred. More preferably thioether protected SH groups are substituted or unsubstituted S-9-fluorenylmethyl thioethers. The most preferred thioether protected SH group is S-9-fluorenylmethyl (Fm) thioether.

Examples of suitable starting materials for the synthesis of compounds of formula **II** include:

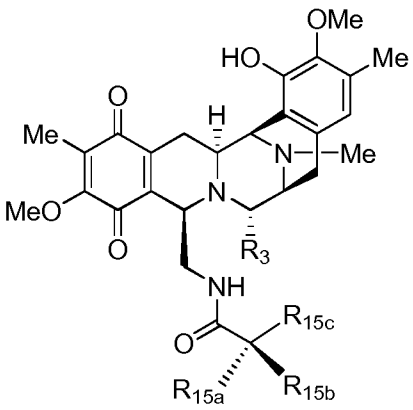
(a) Saframycin A, saframycin H, saframycin S, saframycin Y_3, saframycin Y_{d1}, saframycin A_{d1}, saframycin Y_{d2}, saframycin AH_2, saframycin AH_2Ac, saframycin AH_1, and saframycin AH_1Ac of formula:



Compound	R_3	R_{15a}	R_{15b}	R_{15c}
Saframycin A	CN	O		Me
Saframycin H	CN	OH	CH_2COMe	Me
Saframycin S	OH	O		Me
Saframycin Y_3	CN	NH_2	H	Me
Saframycin Y_{d1}	CN	NH_2	H	C_2H_5
Saframycin A_{d1}	CN	O		C_2H_5
Saframycin Y_{d2}	CN	NH_2	H	H
Saframycin AH_2	CN	H[a]	OH[a]	Me
Saframycin AH_2Ac	CN	H	OAc	Me
Saframycin AH_1,	CN	OH[a]	H[a]	Me
Saframycin AH_1Ac	CN	OAc	H	Me

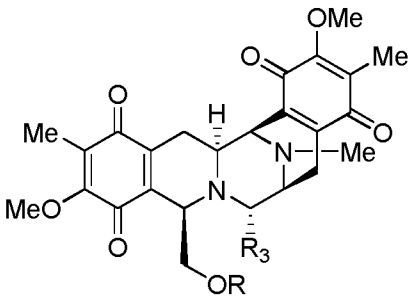
[a] Assignments are interchangeable.

(b) Safracin B and cyanosafracin B of formula:



Compound	**R_3**	**R_{15a}**	**R_{15b}**	**R_{15c}**
Safracin B	OH	NH_2	H	Me
Cyanosafracin B	CN	NH_2	H	Me

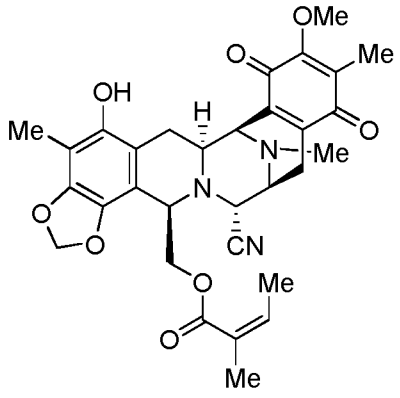
(c) Jorumycin, cyanojorumycin, renieramycin E, jorunnamycin A, and jorunnamycin C of formula:



Compound	R_3	R
Jorumycin	OH	COMe
Cyanojorumycin	CN	COMe
Renieramycin E	OH	$CO\text{-}C(CH_3)=CH\text{-}CH_3$
Jorunnamycin A	CN	H
Jorunnamycin C	CN	$COCH_2CH_3$

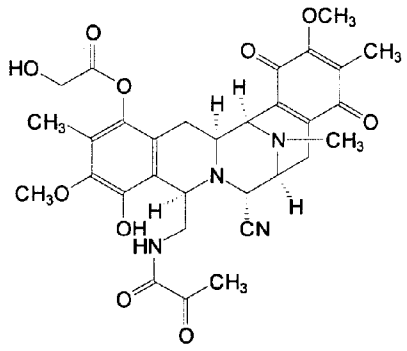
that are disclosed in Charupant, K. et. al. Bioorganic Medicinal Chemistry, 2009, 17, 4548-4558.

d) Renieramycin T (described in Daikuhara, N. et. al. Tetrahedron Letters, 2009, 50, 4276-4278)



and

e) Saframycin R



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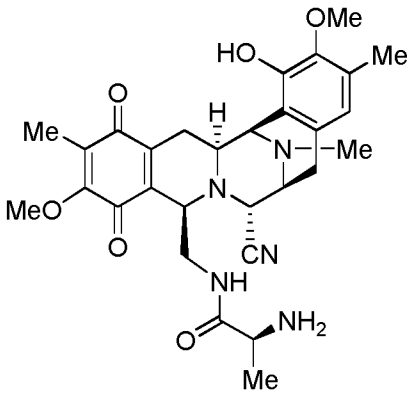
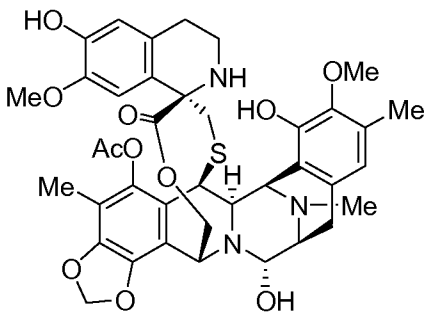
The most preferred starting material for the synthesis of compounds of formula **II** is cyanosafracin B of formula:



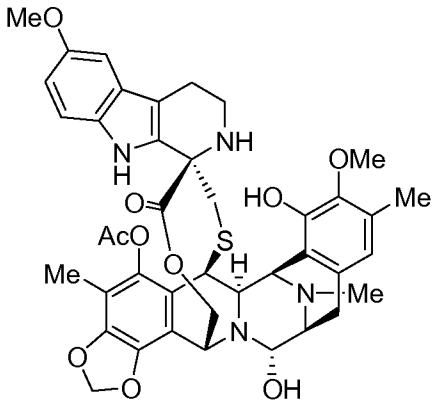
Cyanosafracin B

This invention also relates to the use of intermediates of formula **II** in the manufacture of compounds of formula **I**, and in particular in the manufacture of:



ET-743

or



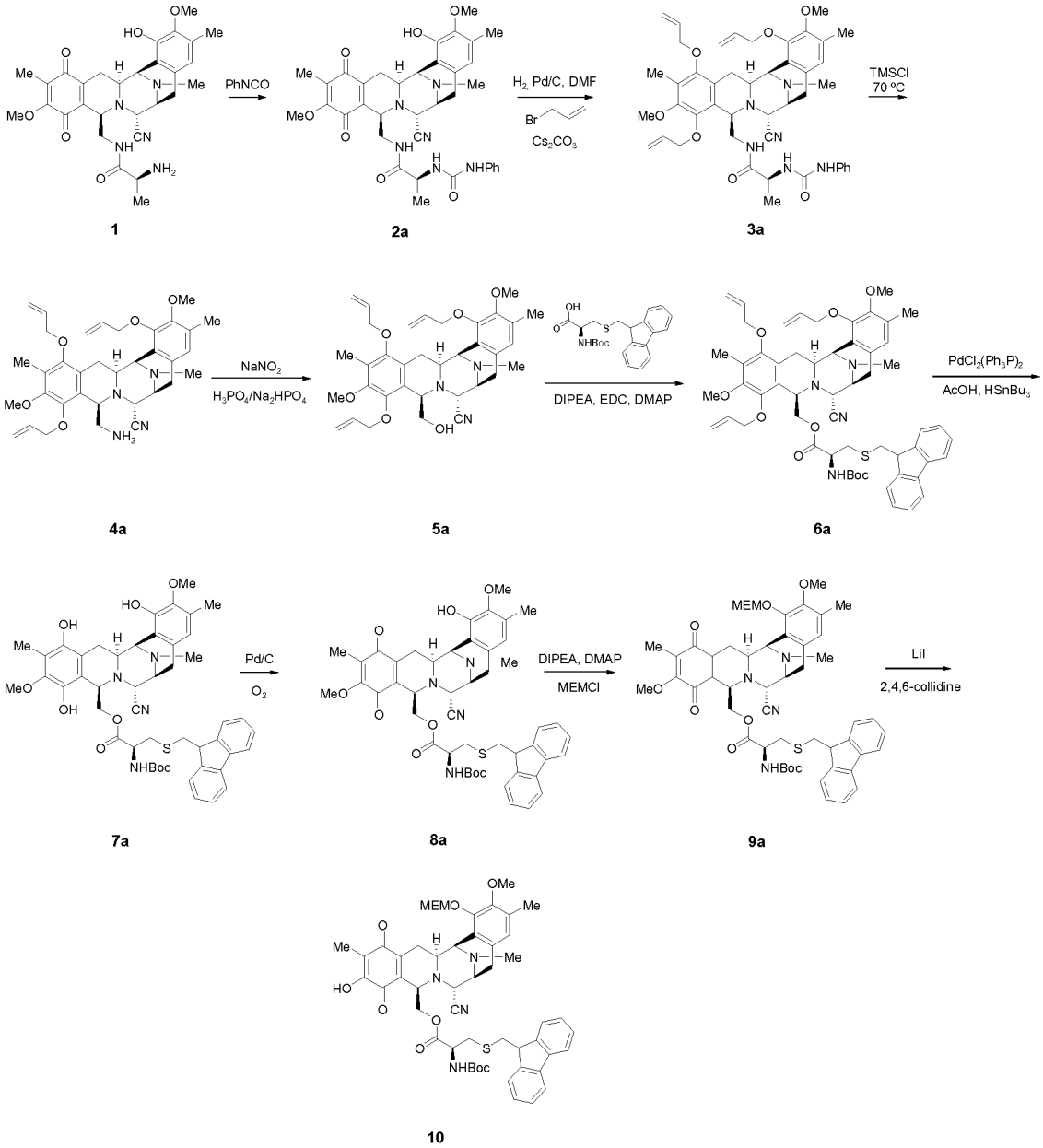
In additional preferred embodiments, the preferences described above for the different groups and substituents are combined. The present invention is also directed to such combinations of preferred groups and substitutions in the formulae above.

EXAMPLES

EXAMPLE 1: SYNTHESIS OF INTERMEDIATE **10**

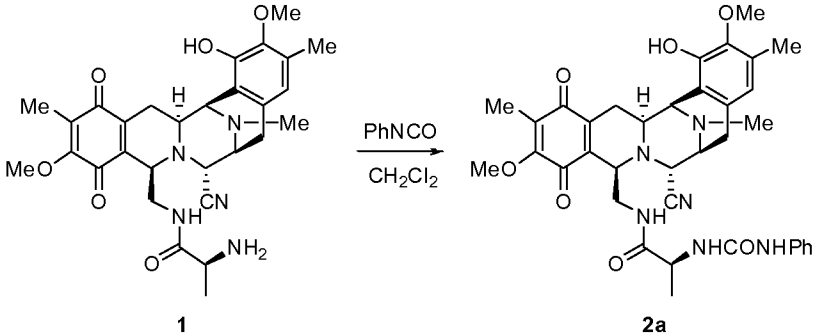
Route A

Scheme **VII** provides an example of the synthesis of intermediate **10** (a compound of formula **II**).



Scheme **VII**

Synthesis of intermediate **2a**



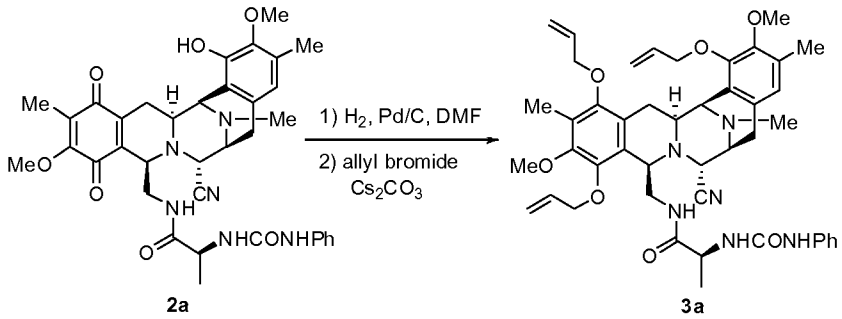
A mixture of cyanosafracin B (**1**) (3.06 g, 5.6 mmol) and phenyl isocyanate (0.6 mL, 5.6 mmol) in CH_2Cl_2 (29 mL, 5.2 mL/mmol) was stirred for 4 h at 23 °C. The reaction mixture was concentrated under vacuum and the crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 60:40 to 20:80) to give pure **2a** (3.7 g, 100% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.23-6.95 (m, 6H), 6.47 (s, 1H), 6.37 (s, 1H), 5.51 (d, 1H, J= 7.7 Hz), 5.40 (m, 1H), 4.18 (s, 1H), 4.02 (m, 1H), 3.86 (s, 3H), 3.76 (m, 1H), 3.71 (s, 3H), 3.35-3.02 (m, 6H), 2.48-2.41 (d, 1H, J= 18.0 Hz), 2.35 (s, 3H), 2.24 (s, 3H), 1.95-1.85 (m, 1H), 1.00 (d, 3H, J= 6.0 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 185.6, 181.1, 173.9, 155.6, 154.7, 147.4, 143.6, 142.4, 138.6, 135.0, 130.5, 129.5, 129.0, 128.6, 123.0, 120.2, 119.7, 117.5, 117.0, 60.8, 60.5, 59.0, 56.0, 55.7, 55.1, 54.8, 49.4, 41.7, 41.4, 25.5, 24.2, 18.6, 15.7, 8.6.

MS (ES): *m/z* 669.2 $[M+1]^+$.

Synthesis of intermediate **3a**



A suspension of **2a** (450 mg, 0.67 mmol) and Pd on carbon (90 mg, 10%) in anhydrous DMF (10 mL, 15 mL/mmol) was degasified under vacuum and stirred under an hydrogen atmosphere for 2 h at 23 °C. The reaction mixture was filtered through a 0.45 μm PTFE filter over anhydrous Cs_2CO_3 (1.3 g, 4.0 mmol), washed with DMF (5 mL), and allyl bromide (1.7 mL, 20 mmol) was added at 23 °C. The reaction

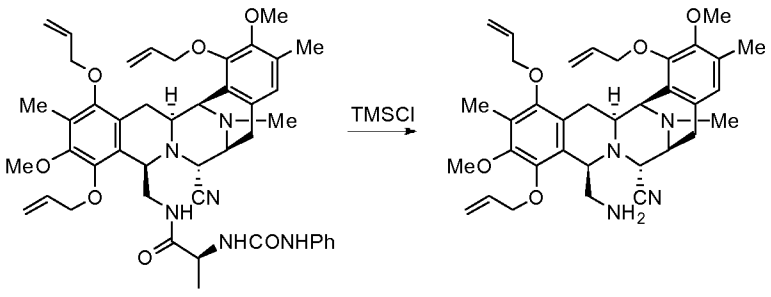
mixture was stirred for 4 h at 23 °C and filtered through Celite®. An aqueous saturated solution of NaCl was added to the filtered solution which was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with CH_2Cl_2:EtOAc (40:60) to afford pure **3a** (296 mg, 56% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.31-6.87 (m, 5H), 6.62 (s, 1H), 6.24 (d, 1H, J= 7.8 Hz), 6.13-6.00 (m, 3H), 5.86 (m, 1H), 5.43 (s, 1H), 5.37 (s, 2H), 5.31-5.19 (m, 4H), 4.73 (dd, 1H, J= 12.3 and 5.7 Hz), 4.50 (m, 1H), 4.27 (m, 2H), 4.11 (m, 3H), 3.92 (m, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.61 (s, 3H), 3.50 (m, 1H), 3.20 (m, 2H), 3.0 (dd, 2H, J= 18.0 and 8.4 Hz), 2.45 (d, 1H, J= 18.0 Hz), 2.28 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 1.86 (m, 1H), 1.03 (d, 3H, J=9 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 173.8, 154.5, 150.5, 150.4, 149.7, 149.1,144.2, 139.0, 134.1, 133.8, 130.9, 129.6, 128.6, 125.0, 124.9, 124.5, 123.7, 122.2, 119.1, 118.0, 117.8, 117.7, 117.6, 74.0, 73.8, 73.3, 60.2, 60.0, 56.7, 56.4, 55.1, 49.3, 43.6, 41.6, 26.3, 25.5, 19.2, 15.8, 9.6, 6 carbon signals overlap.

MS (ES): *m/z* 791.3 $[M+1]^+$.

Synthesis of intermediate **4a**



3a **4a**

A solution of **3a** (90 mg, 0.13 mmol) and TMSCl (0.2 mL, 1.6 mmol) in MeOH (2.45 mL, 18.8 mL/mmol) was stirred for 6 h at 70 °C. The reaction mixture was cooled to 23 °C and concentrated under vacuum. The crude obtained was diluted with EtOAc and acidified with

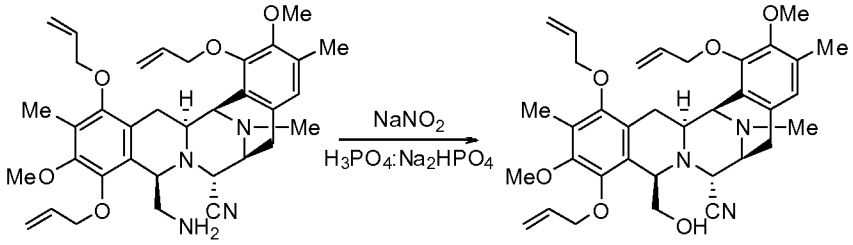
HCl 1M until acid pH. The aqueous layer was washed with EtOAc (3x), basified with K_2CO_3 until basic pH, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude **4a** (61 mg, 76% yield) which was used in the next step without further purification.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.69 (s, 1H), 6.13-6.04 (m, 3H), 5.44-5.20 (m, 3H), 4.71 (dd, 1H, J= 12.3 and 5.4 Hz), 4.59-4.41 (m, 2H), 4.33-4.01 (m, 8H), 3.76 (s, 6H), 3.34-3.05 (m, 4H), 2.72-2.50 (m, 3H), 2.34 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 1.76 (dd, 1H, J= 15.6 and 12.0 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.1, 149.9, 149.5, 149.0, 144.4, 134.2, 134.2, 133.8, 130.8, 129.9, 129.1, 128.2, 125.8, 125.2, 124.7, 124.2, 123.8, 118.0, 74.0, 73.7, 73.5, 60.7, 60.2, 59.9, 58.9, 57.2, 56.6, 55.4, 46.5, 41.7, 29.7, 26.5, 25.8, 15.8, 9.6.

MS (ES): *m/z* 601.3 $[M+1]^+$, 623.2 $[M+23]^+$.

Synthesis of intermediate **5a**



4a **5a**

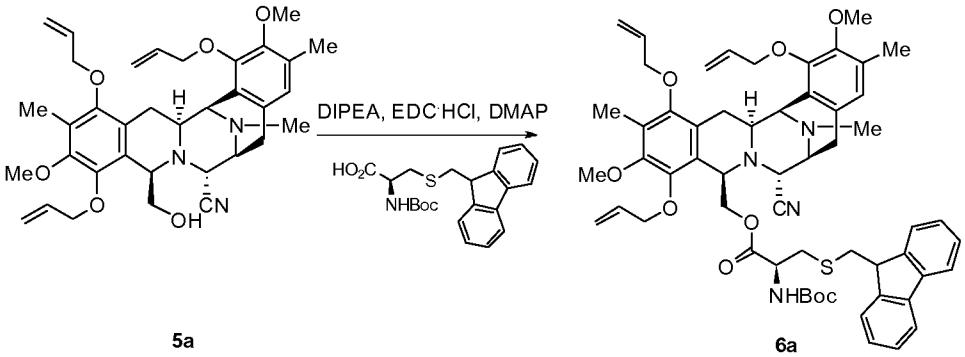
To a mixture of **4a** (6.89 g, 11.5 mmol) and H_3PO_4:Na_2HPO_4 aqueous solution (35 mL, 0.018 g H_3PO_4:0.186 g Na_2HPO_4 per mL of H_2O) in CH_2Cl_2 (69 mL, 6 mL/mmol), an aqueous solution of $NaNO_2$ (7.9 mL, 23.0 mmol, 20%) was portion wise added over 1 h at 23 °C. The reaction mixture was stirred overnight at 23 °C, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with CH_2Cl_2:EtOAc (40:60) to afford pure **5a** (4.62 g, 67% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.72 (s, 1H), 6.16-6.05 (m, 3H), 5.44-5.2 (m, 6H), 4.71 (dd, 1H, J= 12.3 and 5.4 Hz), 4.60-4.44 (m, 2H), 4.34-4.04 (m, 6H), 3.76 (s, 3H), 3.75 (s, 3H), 3.60-3.56 (m, 1H), 3.35 (d, 1H, J= 7.5 Hz), 3.28-3.22 (m, 3H), 3.13 (dd, 1H, J= 18.0 and 7.5 Hz), 2.52 (d, 1H, J= 18.0 Hz), 2.37 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 1.90 (dd, 1H, J= 8.5 and 4.0 Hz), 1.76 (dd, 1H, J= 16.0 and 12.5 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.1, 149.7, 149.6, 149.2, 144.5, 134.1, 133.8, 130.9, 129.5, 125.6, 124.8, 124.6, 124.2, 123.7, 117.8, 117.6, 117.5, 73.9, 73.7, 73.5, 65.7, 60.8, 60.1, 59.8, 58.6, 57.2, 56.7, 55.4, 41.7, 26.2, 25.8, 15.7, 9.5, two carbon signals overlap.

MS (ES): *m/z* 602.3 $[M+1]^+$, 624.2 $[M+23]^+$.

Synthesis of intermediate **6a**



5a 6a

To a solution of **5a** (4.65 g, 7.7 mmol) and Boc-L-Cys(Fm)-OH (6.1 g, 15.4 mmol) in CH_2Cl_2 (264 mL, 34 mL/mmol), DIPEA (2.67 mL, 15.4 mmol), EDC·HCl (4.41 g, 23.0 mmol) and DMAP (0.938 g, 7.7 mmol) were added at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C, diluted with CH_2Cl_2, and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 90:10 to 80:20) to afford pure **6a** (7.12 g, 94% yield).

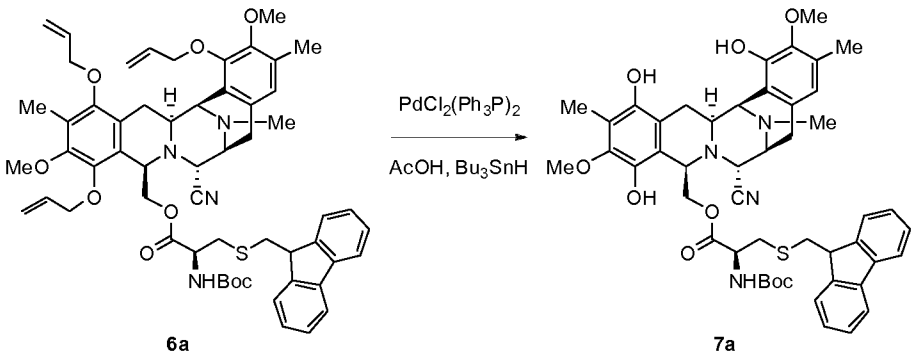
^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.75-7.28 (m, 8H), 6.60 (s, 1H), 6.13-5.99 (m, 3H), 5.42-5.16 (m, 7H), 4.73-4.67 (m, 1H), 4.56-4.51 (m, 1H), 4.43-

3.80 (m, 10H), 3.76 (s, 3H), 3.73 (s, 3H), 3.28-2.81 (m, 7H), 2.61-2.48 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H), 1.77-1.68 (m, 1H), 1.45 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 170.9, 155.2, 150.5, 150.0, 149.7, 148.9, 146.0, 144.9, 141.2, 134.5, 134.2, 133.9, 130.7, 130.6, 127.8, 127.2, 125.5, 125.0, 124.8, 124.4, 123.8, 120.1, 118.4, 118.2, 117.9, 117.7, 80.34, 74.3, 74.1, 73.6, 69.0, 61.6, 60.4, 60.2, 57.4, 57.2, 56.5, 55.7, 53.6, 47.0, 41.9, 37.3, 35.6, 29.9, 28.6, 26.6, 25.8, 15.9, 9.8.

MS (ES): *m/z* 983.3 $[M+1]^+$.

Synthesis of intermediate **7a**



6a **7a**

To a suspension of **6a** (7.12 g, 7.2 mmol) and $PdCl_2(Ph_3P)_2$ (814 mg, 1.16 mmol) in CH_2Cl_2 (132 mL, 18 mL/mmol), AcOH (4.14 mL, 72.4 mmol) and Bu_3SnH (11.68 mL, 43.4 mmol) were added at 23 °C. The reaction mixture was stirred for 1 h at 23 °C, loaded into a column flash chromatography over SiO_2 and eluted with Hexane:EtOAc (from 80:20 to 60:40) to afford pure **7a** (6.28 g, 100% yield).

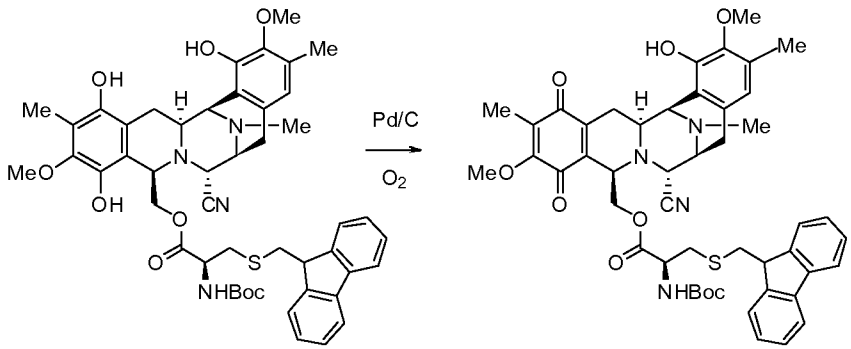
^{1}H-NMR (CD_3OD, 300 MHz): δ 7.76-7.56 (m, 4H), 7.37-7.23 (m, 4H), 6.44-6.34 (m, 1H), 4.28-4.01 (m, 6H), 3.85-3.80 (m, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.25 (m, 1H), 3.07-2.86 (m, 5H), 2.71-2.54 (m, 2H), 2.41-2.34 (m, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 2.08 (s, 3H), 1.84 (m, 1H), 1.41 (s, 9H).

^{13}C-NMR (CD_3OD, 75 MHz): δ 171.1, 147.6, 146.2, 144.3, 143.9, 143.6, 141.2, 139.9, 131.2, 129.3, 127.4, 126.9, 124.9, 124.8, 120.9, 120.2, 119.6, 118.3, 117.6, 79.6, 67.3, 61.1, 59.7, 57.8, 56.9, 56.6, 55.7, 53.8,

40.6, 36.5, 34.5, 27.5, 25.9, 25.5, 14.9, 8.6, twelve carbon signals overlap.

MS (ES): *m/z* 863.0 $[M+1]^+$.

Synthesis of intermediate **8a**



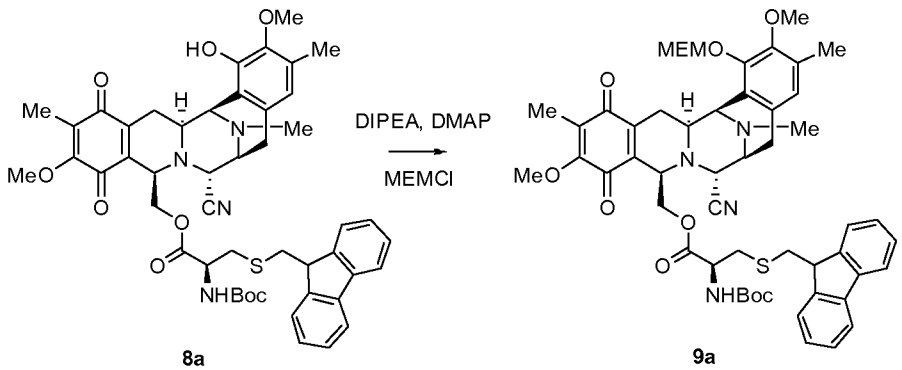
A suspension of **7a** (1.7 g, 2.0 mmol) and Pd on carbon (855 mg, 10%) in MeOH (50 mL, 25.5 mL/mmol) was stirred for 24 h under an air atmosphere at 23 °C. The reaction mixture was filtered through Celite®, washed with CH_2Cl_2, and concentrated. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 70:30 to 60:40) to afford pure **8a** (1.41 g, 82% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.74-7.58 (m, 4H), 7.4-7.25 (m, 4H), 6.37 (s, 1H), 5.81 (s, 1H), 4.90 (d, 1H, J= 8.4 Hz), 4.57 (m, 1H), 4.13-4.01 (m, 5H), 3.95 (s, 3H), 3.70 (s, 3H), 3.31 (d, 1H), J= 8.1 Hz), 3.15-2.88 (m, 5H), 2.53 (d, 1H, J= 18.6 Hz), 2.39 (m, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.85 (s, 3H), 1.69 (m, 1H), 1.38 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 185.6, 181.2, 170.4, 155.5, 154.8, 146.8, 145.8, 142.9, 142.8, 140.9, 140.8, 134.8, 131.1, 130.9, 129.1, 128.6, 127.5, 126.9, 124.9, 124.8, 120.7, 119.8, 117.4, 116.1, 79.8, 63.1, 61.0, 60.8, 59.1, 56.4, 55.8, 55.4, 55.1, 52.7, 46.9, 46.6, 41.7, 41.6, 36.9, 36.6, 34.7, 34.4, 29.6, 28.2, 24.7, 15.8, 8.7.

MS (ES): *m/z* 861.2 $[M+1]^+$.

Synthesis of intermediate **9a**



8a **9a**

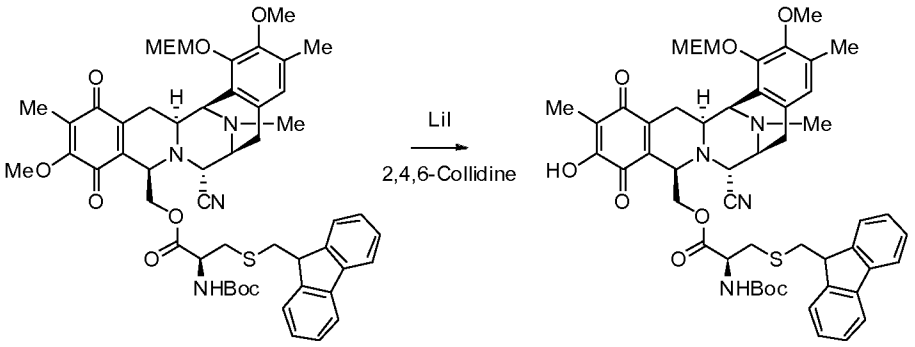
To a solution of **8a** (4.5 g, 5.2 mmol) in CH_3CN (166 mL, 32 mL/mmol), DIPEA (18.2 mL, 104 mmol), MEMCl (8.86 mL, 78 mmol) and catalytic DMAP were added at 23 °C. The reaction mixture was stirred for 5 h at 23 °C, diluted with CH_2Cl_2, and washed with HCl 1M and an aqueous saturated solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with CH_2Cl_2:EtOAc (from 90:10 to 70:30) to afford pure **9a** (2.51 g, 51% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.73-7.58 (m, 4H), 7.40-7.29 (m, 4H), 6.56 (s, 1H), 5.28-5.14 (m, 2H), 4.94 (m, 1H), 4.48 (m, 1H), 4.20 (bs, 1H), 4.09-3.94 (m, 5H), 3.94 (s, 3H), 3.80 (m, 1H), 3.68 (s, 3H), 3.58 (t, 2H, J= 4.8 Hz), 3.38 (s, 3H), 3.31 (m, 1H), 3.14-2.87 (m, 6H), 2.53 (d, 1H, J= 18.6 Hz), 2.40 (m, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 1.83 (s, 3H), 1.56 (m, 1H), 1.38 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 185.5, 181.1, 170.4, 155.5, 154.7, 148.7, 148.2, 145.7, 142.9, 140.9, 140.8, 134.7, 130.9, 130.3, 128.5, 127.5, 127.0, 124.8, 124.7, 123.1, 119.8, 117.4, 98.1, 79.9, 71.6, 69.3, 63.3, 61.0, 60.0, 59.2, 58.9, 56.3, 56.1, 55.2, 55.0, 52.8, 46.6, 41.4, 37.3, 36.6, 34.6, 28.2, 24.8, 24.6, 15.7, 8.6.

MS (ES): *m/z* 949.2 $[M+1]^+$.

Synthesis of intermediate **10**



9a 10

A solution of **9a** (194 mg, 0.2 mmol) in 2,4,6-collidine (4.3 mL, 21.5 mL/mmol) was degasified and LiI (401 mg, 3.0 mmol) was added at 23 °C. The reaction mixture was stirred for 24 h at 23 °C, diluted with CH_2Cl_2, and washed with HCl 1M. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 50:50 to 40:60) to afford pure **10** (115 mg, 57% yield).

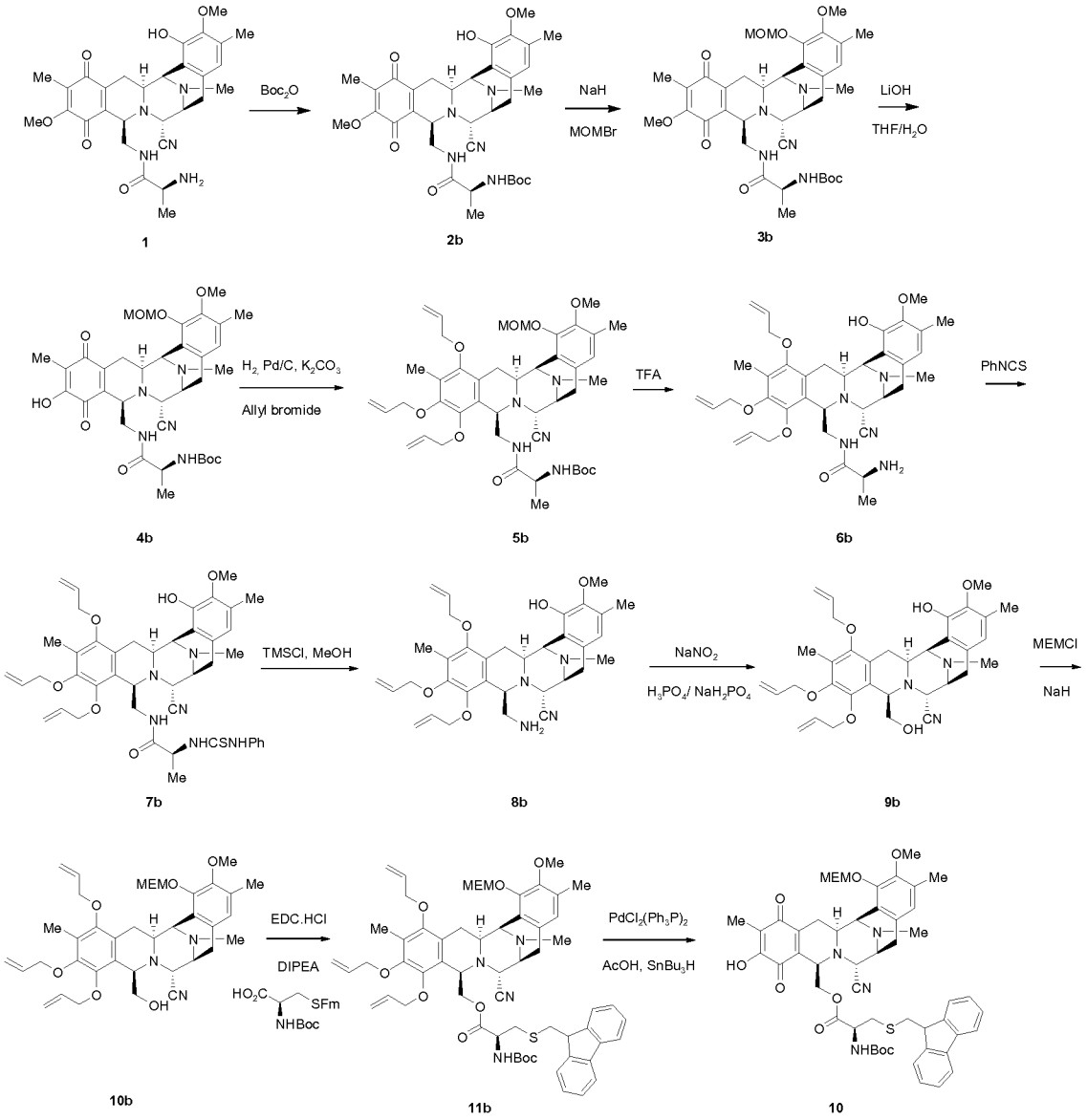
^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.74-7.57 (m, 4H), 7.40-7.28 (m, 4H), 6.58 (s, 1H), 5.29-5.14 (m, 2H), 5.00 (m, 1H), 4.43 (m, 1H), 4.21 (bs, 1H), 4.09-3.79 (m, 8H), 3.69 (s, 3H), 3.58 (t, 2H, J= 4.8 Hz), 3.39 (s, 3H), 3.32 (m, 1H), 3.14-2.88 (m, 5H), 2.53 (d, 1H, J= 18.6 Hz), 2.38 (m, 1H), 2.28 (s, 3H), 2.17 (s, 3H), 1.85 (s, 3H), 1.39 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 184.9, 181.1, 170.6, 154.7, 151.0, 148.8, 148.3, 145.7, 145.6, 140.9, 132.7, 131.1, 130.3, 127.6, 127.0, 124.8, 123.1, 119.9, 117.4, 117.1, 98.2, 80.2, 71.7, 69.3, 63.1, 60.0, 59.3, 59.0, 56.1, 55.8, 55.3, 55.1, 52.8, 46.7, 41.4, 36.7, 34.8, 29.7, 28.2, 25.2, 24.8, 15.8, 8.0.

MS (ES): *m/z* 935.3 $[M+1]^+$.

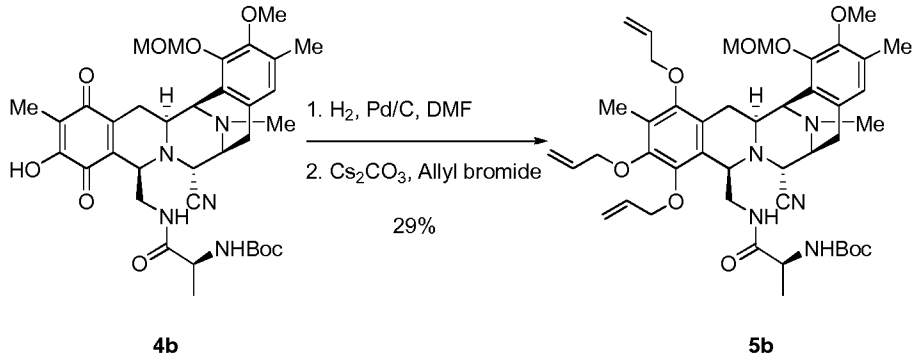
ROUTE B

Scheme **VIII** provides another example of the synthesis of intermediate **10**.



Scheme **VIII**

5 Synthesis of intermediate **5b**



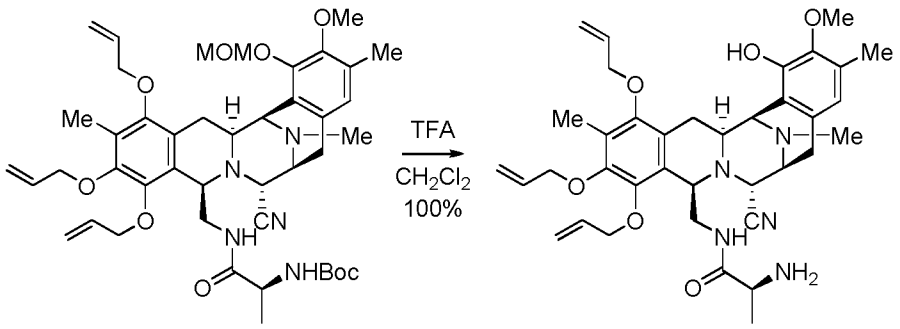
Compound **4b** was obtained as disclosed in WO 00/69862. A suspension of **4b** (1.14 g, 1.68 mmol) and 10% Palladium on Carbon (228 mg, 20% w/w) in anhydrous DMF (15 mL) was stirred for 2 h at 23 °C under a H_2 atmosphere. The reaction mixture was filtered through Celite® to a flask containing anhydrous Cs_2CO_3 (3.28 g, 10.1 mmol), washed with DMF (10 mL), and allyl bromide (2.9 mL, 33.6 mol) added at 23 °C. The reaction mixture was stirred for 3 h at 23 °C, was filtered through Celite®, and washed with CH_2Cl_2. The combined organic layers were washed with an aqueous saturated solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation. The resulting crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 70:30 to 50:50) to afford pure **5b** (384 mg, 29% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.05 (m, 3H), 5.51 (bs, 1H), 5.38-5.17 (m, 6H), 5.11 (s, 2H), 4.88, (bs, 1H), 4.62-463 (m, 3H), 4.30-4.01 (m, 6H), 3.73 (s, 3H), 3.56 (s, 3H), 3.52-3.16 (m, 6H), 3.04 (dd, *J* = 18.0 and 7.9 Hz, 1H), 2.56 (d, *J* = 18.0 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.14 (s, 3H), 1.82 (m, 1H), 1.30 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.8, 154.8, 150.1, 148.7, 148.5, 148.4, 144.5, 133.9, 133.8, 133.8, 130.9, 130.2, 125.1, 125.0, 124.8, 124.6, 124.0, 118.0, 117.9, 117.5, 117.2, 99.2, 79.3, 77.2, 73.7, 73.6, 73.4, 59.9, 59.7, 57.7, 57.7, 57.2, 56.7, 56.1, 55.1, 49.6, 43.0, 41.5, 28.1, 26.3, 25.4, 18.7, 15.7, 9.8.

MS (ES): *m/z* 802.4 $[M+1]^+$.

Synthesis of intermediate **6b**



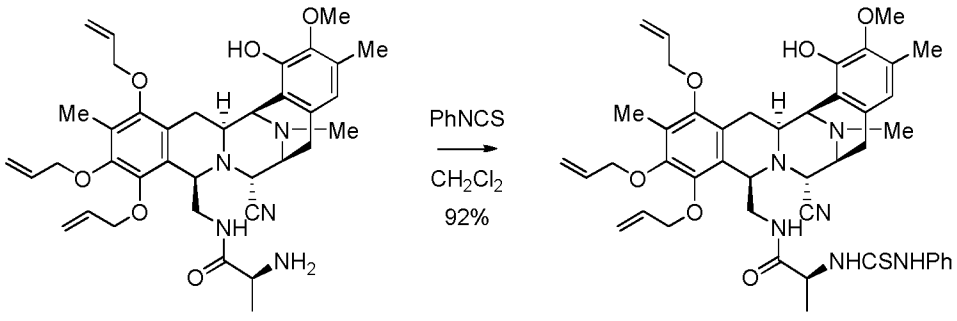
5b **6b**

To a solution of **5b** (370 mg, 0.46 mmol) in CH_2Cl_2 (7.6 mL), TFA (1.42 mL, 18.4 mmol) was added at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C and concentrated to dryness in vacuo by rotary evaporation. The crude obtained was dissolved with CH_2Cl_2, neutralized by addition of an aqueous saturated solution of K_2CO_3 until basic pH, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation to give crude **6b** (340 mg, 100% yield) which was used in the next step without further purification

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.55 (m, 1H), 6.49 (s, 1H), 6.15-5.99 (m, 3H), 5.37-5.11 (m, 7H), 4.60-4.03 (m, 9H), 3.76 (s, 3H), 3.46-3.17 (m, 5H), 3.04-2.87 (m, 3H), 2.60 (d, J = 18.3 Hz, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.96-1.88 (m, 1H).

MS (ES): m/z 658.3 $[M+1]^+$.

Synthesis of intermediate **7b**

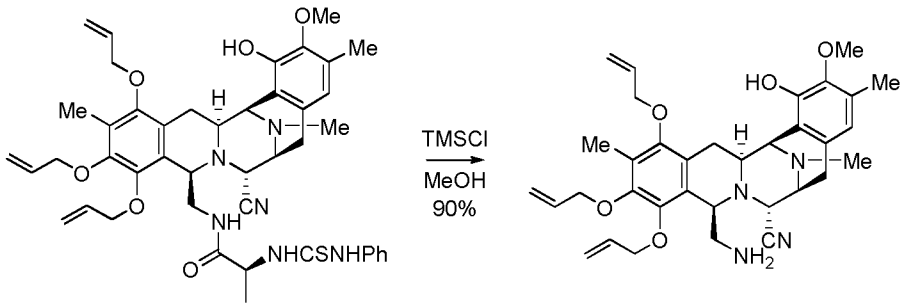


6b **7b**

A solution of **6b** (236 mg, 0.3 mmol) and phenyl isothiocyanate (0.21 mL, 1.8 mmol) in CH_2Cl_2 (65.7 mL) was stirred for 2 h at 23 °C. The reaction mixture was loaded into a column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 90:10 to 40:60) to afford pure **7b** (220 mg, 92% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.30 (s, 1H), 6.13-5.96 (m, 3H), 5.79 (s, 1H), 5.45-5.11 (m, 8H), 4.62-4.34 (m, 3H), 4.34-3.99 (m, 8H), 3.77 (s, 3H), 3.56 (m, 2H), 3.35-3.16 (m, 4H), 3.0 (dd, *J* = 18.0 and 7.9 Hz, 1H), 2.50 (d, *J* = 18.0 Hz, 1H), 2.28 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 1.84 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 1H).

Synthesis of intermediate **8b**



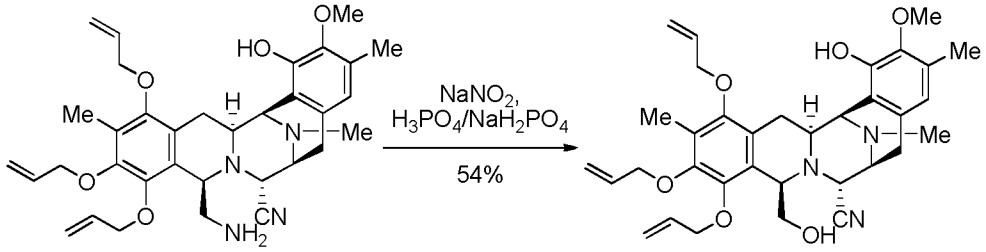
7b **8b**

To a solution of **7b** (295 mg, 0.32 mmol) in MeOH (2.5 mL), chlorotrimethylsilane (0.24 mL, 1.92 mmol) was added at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C and concentrated to dryness in vacuo by rotary evaporation. The crude obtained was dissolved with EtOAc, HCl 1M was added until acid pH, and extracted with EtOAc. The aqueous layer was basified with solid K_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation to obtain crude **8b** (196 mg, 90% yield) which was used in the next step without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 6.15-5.97 (m, 3H), 5.43-5.19 (m, 6H), 4.63-4.42 (m, 3H), 4.31-4.10 (m, 7H), 3.76 (s, 3H), 3.34-3.22 (m, 3H), 3.10 (dd, *J* = 18.2 and 7.6 Hz, 1H), 2.80 (m, 1H), 2.62 (d, *J* = 17.7 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 1.77 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 150.7, 149.0, 146.8, 144.6, 143.2, 134.2, 134.0, 130.8, 129.4, 125.3, 121.3, 118.6, 118.2, 117.8, 117.8, 117.0, 74.3, 73.7, 61.0, 60.7, 57.5, 56.8, 55.7, 46.3, 41.9, 29.9, 26.5, 25.8, 16.1, 10.3, four carbon signals overlap.

Synthesis of intermediate **9b**



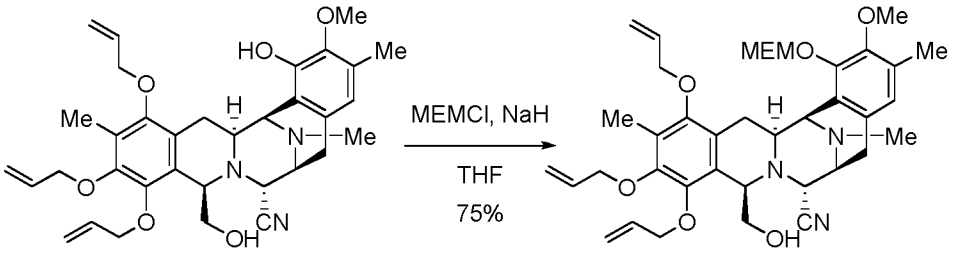
8b **9b**

To a mixture of **8b** (120 mg, 0.21 mmol) and H_3PO_4:Na_2HPO_4 solution (0.63 mL, 8.6 mL H_2O:0.151 g H_3PO_4:1.6 g Na_2HPO_4) in CH_2Cl_2 (1.3 mL), an aqueous solution of $NaNO_2$ (7.9 mL, 0.31 mmol, 20%) was slowly added over 1 h at 23 °C. The reaction mixture was stirred for 18 h at 23 °C, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 70:30 to 60:40) to afford pure **9b** (68 mg, 54% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.16-5.97 (m, 3H), 5.79 (s, 1H), 5.44-5.18 (m, 6H), 4.61-4.41 (m, 3H), 4.31-4.18 (m, 4H), 4.05 (m, 2H), 3.73 (s, 3H), 3.59 (m, 1H), 3.35-3.08 (m, 6H), 2.53 (d, *J* = 18.0 Hz, 1H), 2.36 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H), 1.84 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 150.1, 148.5, 146.6, 144.5, 143.0, 134.0, 133.9, 130.3, 129.0, 125.7, 125.0, 124.4, 120.7, 117.9, 117.5, 117.4, 117.3, 116.8, 77.2, 74.0, 73.6, 73.5, 65.9, 60.8, 60.7, 58.5, 57.1, 56.7, 55.4, 41.6, 26.0, 25.8, 15.7, 9.9.

Synthesis of intermediate **10b**



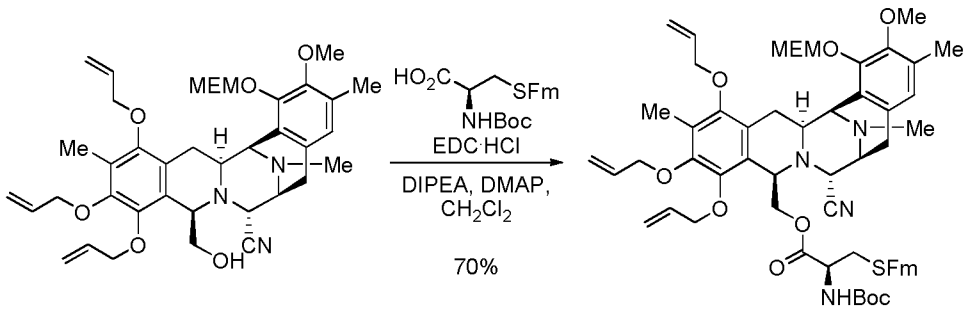
9b **10b**

To a solution of **9b** (20 mg, 0.033 mmol) in THF (0.2 mL), 1-chloromethoxy-2-methoxyethane (4.4 μL, 0.039 mmol) and NaH (1.5 mg, 0.038 mmol, 60% dispersion in mineral oil) were added at 0 °C. The reaction mixture was stirred for 1 h at 23 °C, catalytic amount of NaH was added and the stirring was maintained for an additional 1 h at 23 °C. Then the reaction mixture was diluted with an aqueous saturated solution of NaCl, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 70:30 to 60:40) to afford pure **10b** (16.5 mg, 75% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.16-5.97 (m, 3H), 5.47-5.16 (m, 8H), 4.61-4.41 (m, 3H), 4.30-4.19 (m, 4H), 4.05-3.81 (m, 4H), 3.68 (s, 3H), 3.59 (m, 4H), 3.39 (s, 3H), 3.34-3.10 (m, 5H), 2.50 (d, J = 18.0 Hz, 1H), 2.37 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H), 1.78 (m, 1H).

MS (ES): m/z 676.2 $[M+1]^+$.

Synthesis of intermediate **11b**



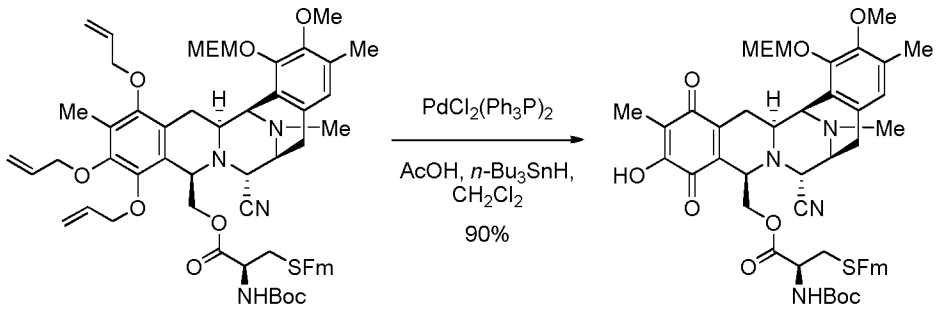
10b **11b**

To a solution of **10b** (75 mg, 0.11 mmol) and Boc-L-Cys(Fm)-OH (88 mg, 0.22 mmol) in CH_2Cl_2 (2.3 mL), DIPEA (38 μL, 0.22 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol) and DMAP (13 mg, 0.11 mmol) were added at 23 °C. The reaction mixture was stirred for 3 h at 23 °C, diluted with CH_2Cl_2, and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo by rotary evaporation. The crude was purified by column flash chromatography over SiO_2 eluted with Hexane:EtOAc (from 70:30 to 60:40) to afford pure **11b** (81 mg, 70% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76-7.61 (m, 4H), 7.38-7.26 (m, 4H), 6.60 (s, 1H), 6.12-5.96 (m, 3H), 5.44-5.13 (m, 8H), 4.53-3.82 (m, 13H), 3.70 (s, 3H), 3.57 (m, 2H), 3.38 (s, 3H), 3.25-2.83 (m, 8H), 2.63-2.48 (m, 2H), 2.30 (s, 3H), 2.17-2.14 (m, 6H), 1.72 (m, 1H), 1.44 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.6, 154.9, 150.2, 150.1, 148.5, 148.4, 148.2, 145.7, 144.8, 144.7, 140.9, 140.9, 134.0, 133.84, 133.76, 130.5, 127.6, 127.0, 125.3, 124.9, 124.8, 124.1, 123.7, 119.9, 118.2, 118.0, 117.5, 117.4, 117.3, 98.2, 80.1, 77.2, 73.9, 73.4, 71.7, 69.3, 61.4, 59.7, 59.0, 57.2, 56.9, 56.3, 55.4, 53.4, 46.9, 46.8, 41.5, 37.0, 35.4, 29.7, 28.3, 26.2, 25.5, 23.6, 15.7, 9.9.

Synthesis of intermediate **10** from intermediate **11b**.



11b **10**

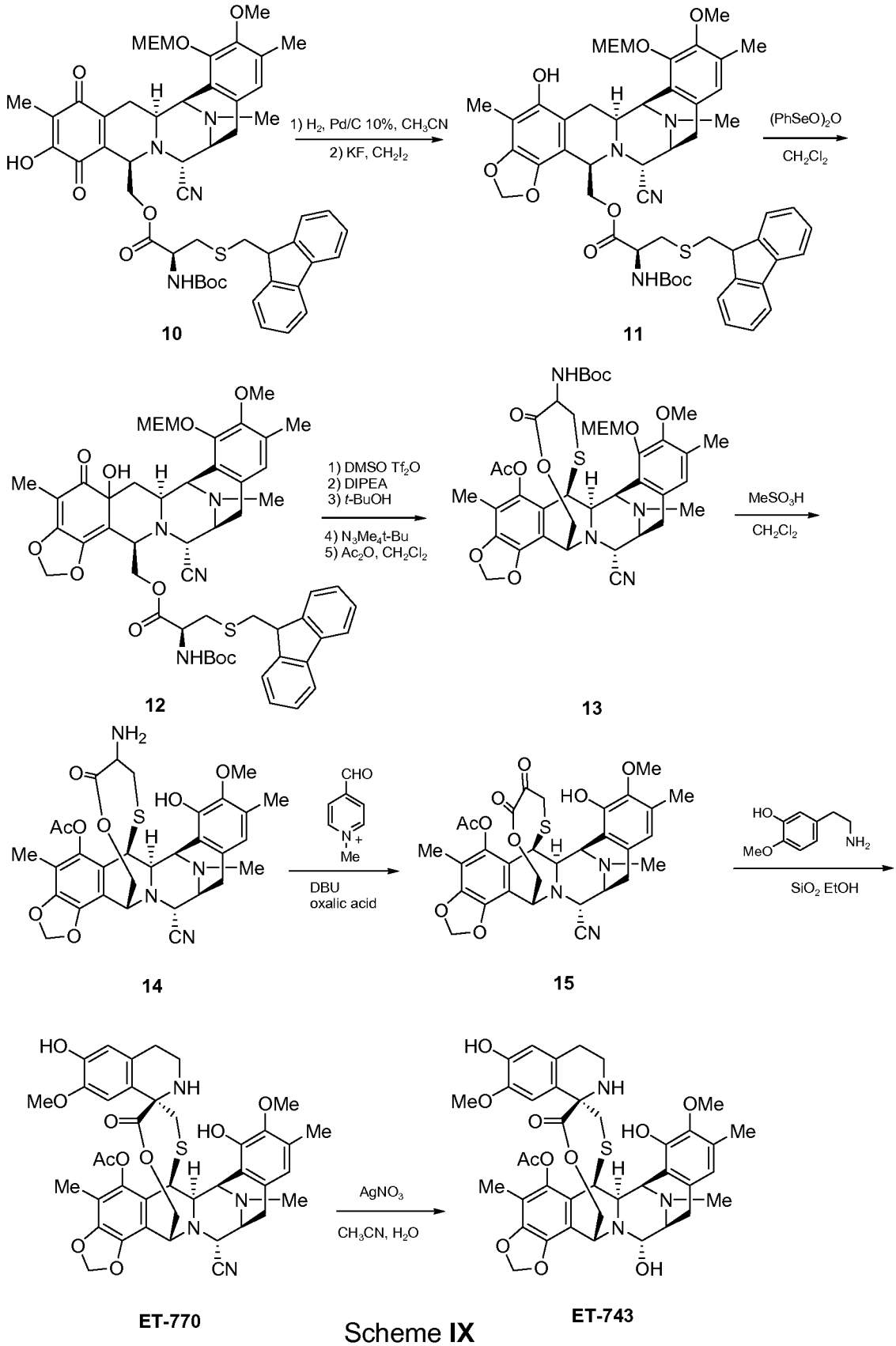
To a suspension of **11b** (13 mg, 0.013 mmol) and $PdCl_2(Ph_3P)_2$ (1.5 mg, 0.0021 mmol) in CH_2Cl_2 (0.3 mL), AcOH (7 μL, 0.13 mmol) and *n*-Bu_3SnH (21 μL, 0.078 mmol) were added at 23 °C. The reaction mixture was stirred for 45 minutes at 23 °C and loaded into a column flash chromatography over SiO_2 eluted with different mixtures of Hexane:EtOAc (90:10, 70:30, 40:60) to afford pure **10** (10.4 mg, 90% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.74-7.57 (m, 4H), 7.40-7.28 (m, 4H), 6.58 (s, 1H), 5.29-5.14 (m, 2H), 5.00 (m, 1H), 4.43 (m, 1H), 4.21 (bs, 1H), 4.09-3.79 (m, 8H), 3.69 (s, 3H), 3.58 (t, 2H, J= 4.8 Hz), 3.39 (s, 3H), 3.32 (m, 1H), 3.14-2.88 (m, 5H), 2.53 (d, 1H, J= 18.6 Hz), 2.38 (m, 1H), 2.28 (s, 3H), 2.17 (s, 3H), 1.85 (s, 3H), 1.39 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 184.9, 181.1, 170.6, 154.7, 151.0, 148.8, 148.3, 145.7, 145.6, 140.9, 132.7, 131.1, 130.3, 127.6, 127.0, 124.8, 123.1, 119.9, 117.4, 117.1, 98.2, 80.2, 71.7, 69.3, 63.1, 60.0, 59.3, 59.0, 56.1, 55.8, 55.3, 55.1, 52.8, 46.7, 41.4, 36.7, 34.8, 29.7, 28.2, 25.2, 24.8, 15.8, 8.0.

MS (ES): *m/z* 935.3 $[M+1]^+$.

EXAMPLE 2: SYNTHESIS OF ET-743

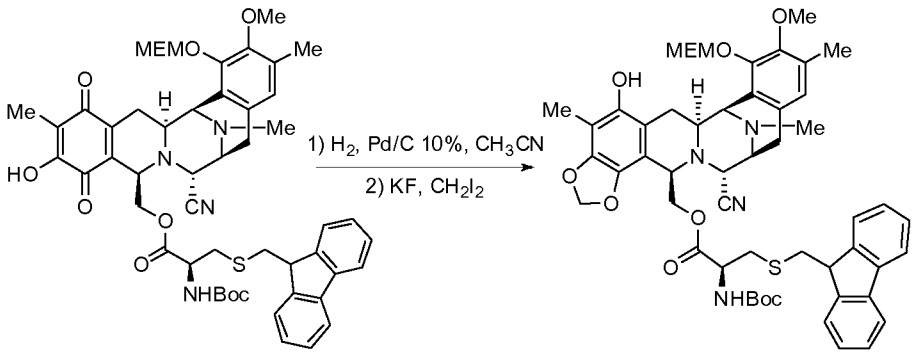


Scheme **IX**

Scheme **IX** above provides an example of the synthesis of ET-743 from

intermediate **10**.

Synthesis of intermediate **11**

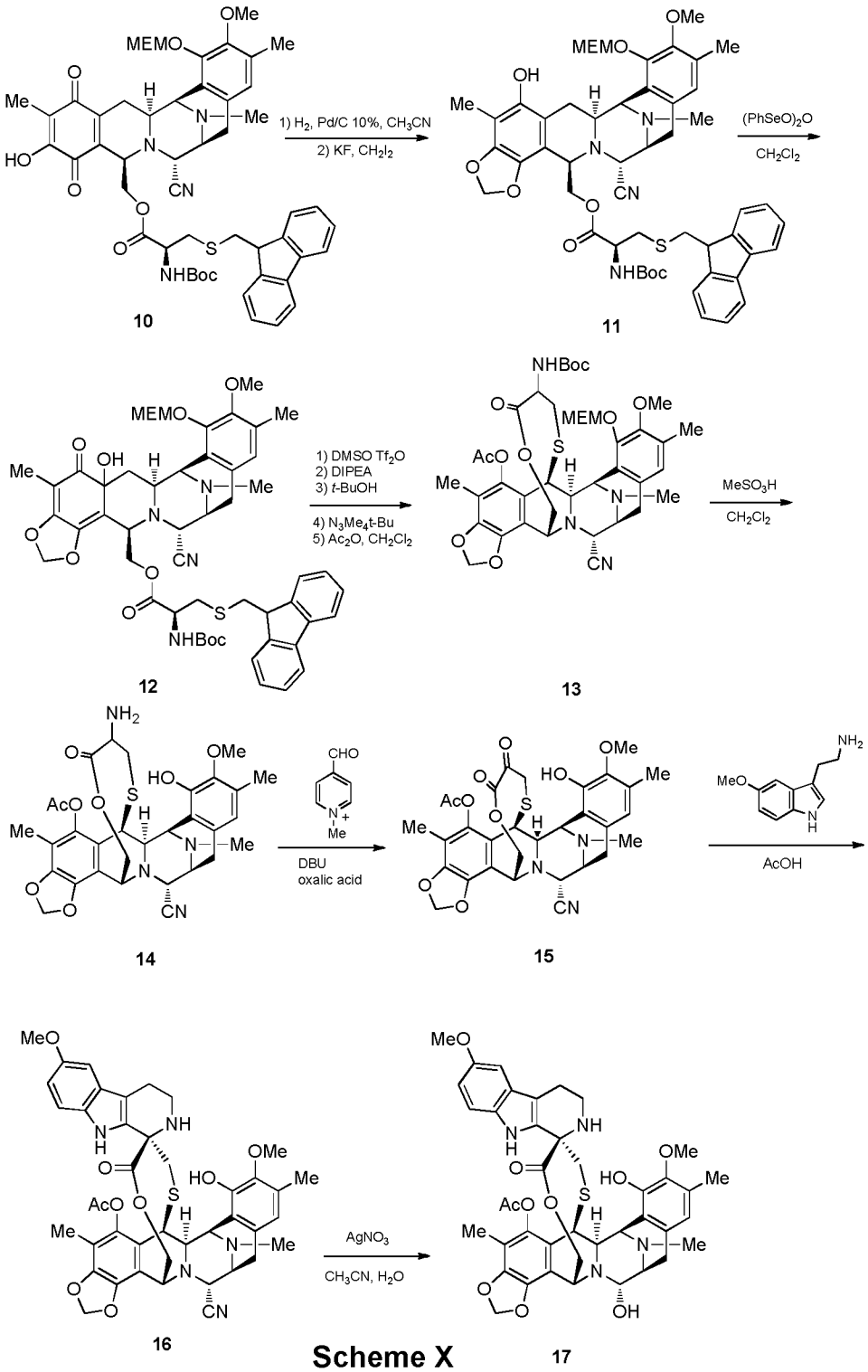


10 **11**

A suspension of **10** (56 mg, 0.06 mmol) and Pd on carbon (17 mg, 10%) in anhydrous CH_3CN (3.0 mL, 51 mL/mmol) was stirred under a hydrogen atmosphere for 2.5 h at 23 °C. The reaction mixture was filtered through a 0.45 μm PTFE filter over KF (34 mg, 0.6 mmol), washed with CH_3CN (2 mL), and diiodomethane (0.19 mL, 2.4 mmol) was added at 23 °C. The reaction mixture was heated for 20 h at 70 °C, diluted with CH_2Cl_2, and washed with an aqueous saturated solution of NaCl. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by column flash chromatography over SiO_2 eluted with CH_2Cl_2:EtOAc (from 90:10 to 80:20) to afford pure **11** (20 mg, 36% yield) which exhibited spectroscopic and spectrometric characteristics identical to those reported for this compound in WO 01/87895.

Compounds **12**, **13**, **14**, **15**, **ET-770** and **ET-743** are obtainable following the procedures described in WO 00/69862, WO 01/87895 and WO 03/008423.

EXAMPLE 3: SYNTHESIS OF COMPOUND **17.**



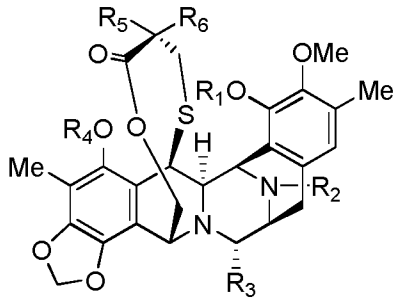
Scheme X

Scheme **X** above provides an example of the synthesis of compound **17** from intermediate **10**.

Compounds **16** and **17** are obtainable from intermediate **15** using the same procedures than those previously described in WO03/014127.

CLAIMS

1. A process for the synthesis of a compound of formula **I**



I

wherein:

R_1 and R_4 are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for OH;

R_2 is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for amino;

R_3 is CN or OH;

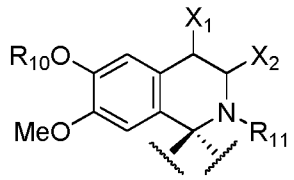
R_5 and R_6 together to the carbon to which they are attached form a group:

(a) C(=O);

(b) $CH(OR_7)$ or $CH(NR_8R_9)$ wherein R_7 is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH; and R_8 and R_9 are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl,

substituted or unsubstituted heterocyclic group, and a protecting group for amino;

(c) a group of formula:

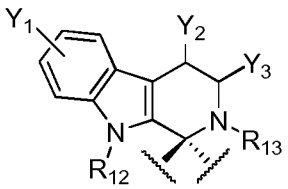


wherein

X_1 and X_2 are independently selected from hydrogen and substituted or unsubstituted C_1-C_{12} alkyl;

R_{10} and R_{11} are independently selected from hydrogen, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl; or

(d) a group of formula:



wherein

Y_1 is selected from hydrogen, OR^b, $OC(=O)R^a$, $OC(=O)OR^b$, $OC(=O)NR^cR^d$, SR^e, SOR^a, SO_2R^a, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, NO_2, NR^cR^d, $N(R^c)C(=O)R^a$, $N(R^c)$-OR^b, $C(R^a)=NOR^b$, $N(R^c)C(=O)OR^b$, $N(R^c)C(=O)NR^cR^d$, CN, halogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

Y_2 and Y_3 are independently selected from hydrogen and substituted or unsubstituted C_1-C_{12} alkyl;

R_{12} and R_{13} are independently selected from hydrogen, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, and substituted or unsubstituted C_2-C_{12} alkynyl; and

each R^a is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

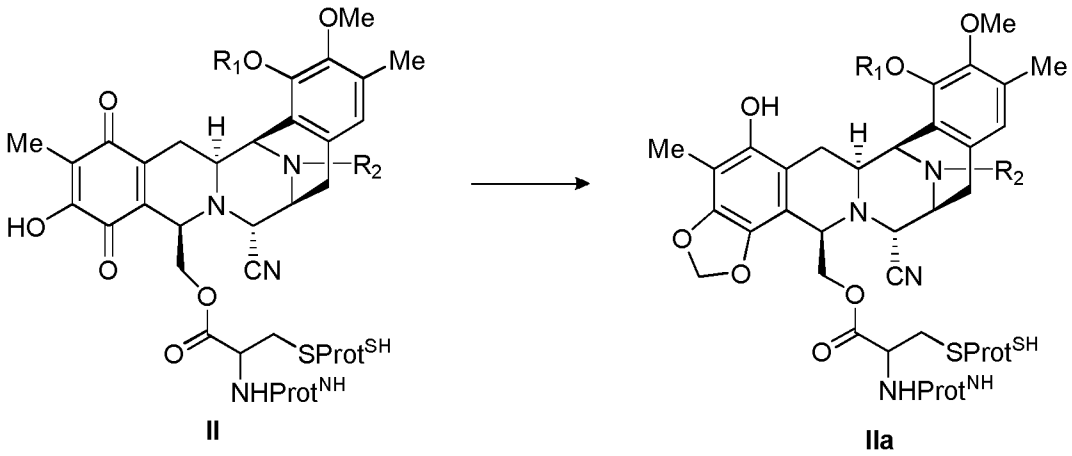
each R^b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH;

each R^c and R^d is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

each R^e is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for SH;

or a pharmaceutical acceptable salt thereof,

wherein the process comprises the step of reducing a quinone of formula **II** followed by alkylation of the resulting hydroquinone with a suitable electrophilic reagent to give a compound of formula **IIa**:



wherein

R_1 is a protecting group for OH;

R_2 is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for amino;

R^a is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

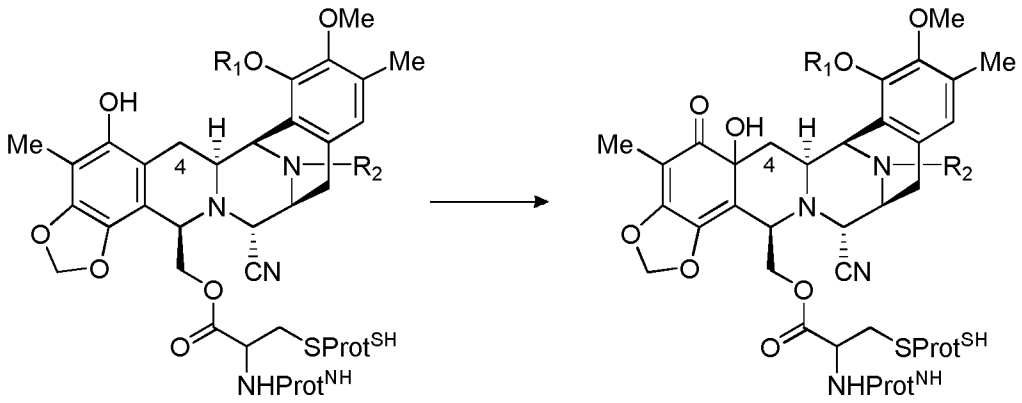
R^b is independently selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for OH;

R^c and R^d are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

$Prot^{NH}$ is a protecting group for amino; and

$Prot^{SH}$ is a protecting group for SH.

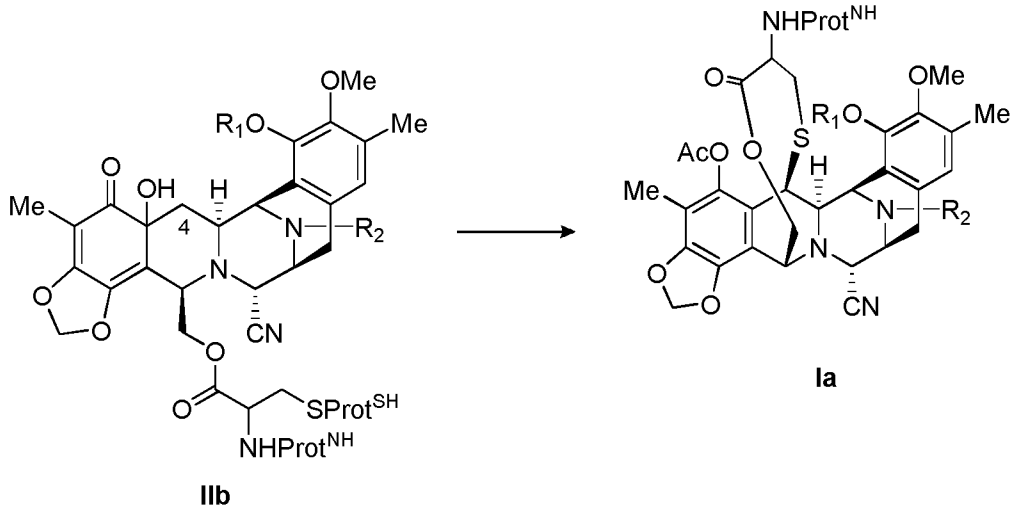
2. A process according to claim 1, which further comprises the step of oxidising the compound of formula **IIa** to give a compound of formula **IIb**:



IIa **IIb**

wherein R_1, R_2, $Prot^{SH}$, and $Prot^{NH}$ are as defined in formula **II** of claim 1.

3. A process according to any preceding claim, which further comprises the step of forming a bridged ring system to provide a compound of formula **Ia**:

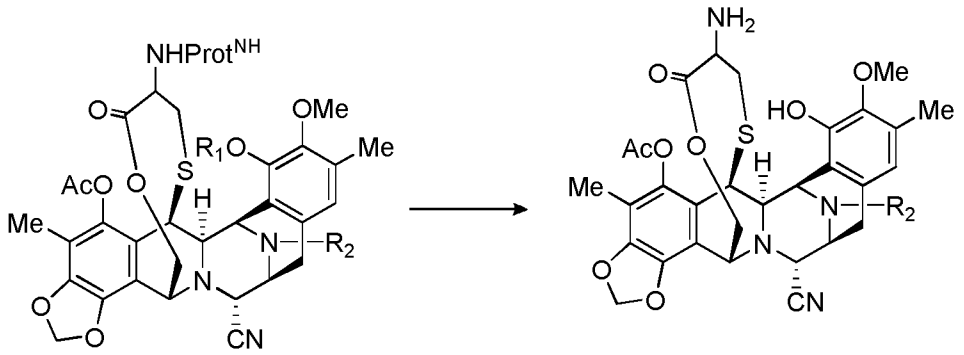


IIb **Ia**

wherein R_1, R_2, $Prot^{SH}$, and $Prot^{NH}$ are as defined in formula **II** of claim 1.

4. A process according to any preceding claim wherein $Prot^{SH}$ is an S-9-fluorenylmethyl (Fm) group.

5. A process according to any preceding claim, which further comprises the step of deprotecting a compound of formula **Ia** to give a compound of formula **Ib**:



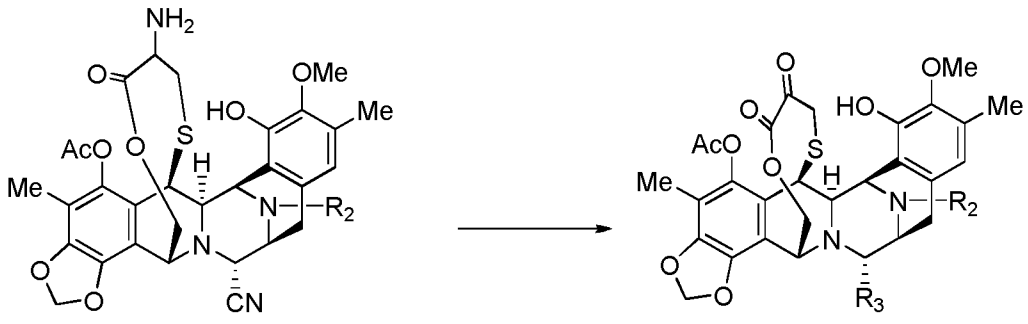
Ia **Ib**

wherein

R_1, R_2, and $Prot^{NH}$ are as defined in formula **II** of claim 1.

6. A process according to any preceding claim wherein R_1 is a methoxyethoxymethyl group and $Prot^{NH}$ is a *t*-butoxycarbonyl group.

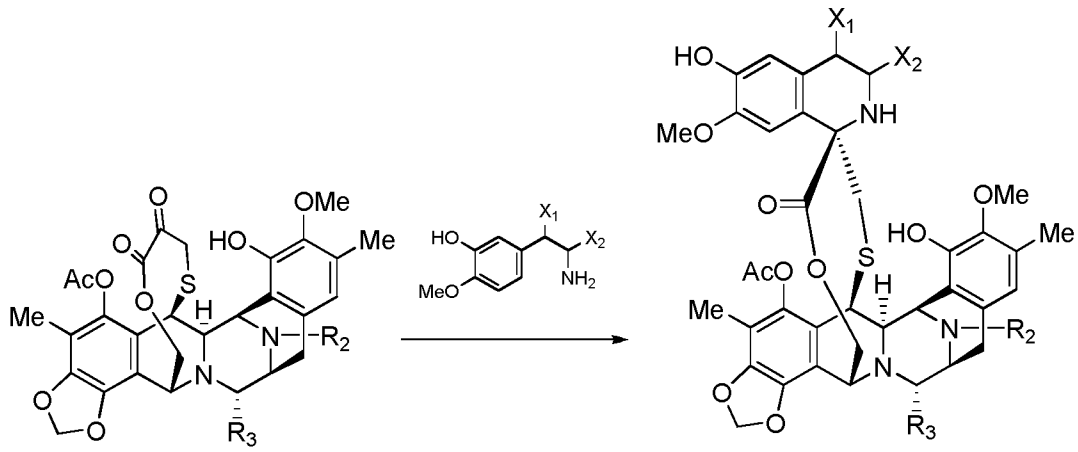
7. A process according to any preceding claim, which further comprises the step of oxidising the α-aminolactone of formula **Ib** to the corresponding α-ketolactone of formula **Id** by transamination:



Ib **Id**

wherein R_2 is as defined in formula **I** of claim 1 and R_3 is cyano.

8. A process according to any preceding claim, which further comprises the step of stereospecifically forming a spirotetrahydroisoquinoline compound of formula **If** from the α-ketolactone of formula **Id** by a Pictet-Spengler reaction:

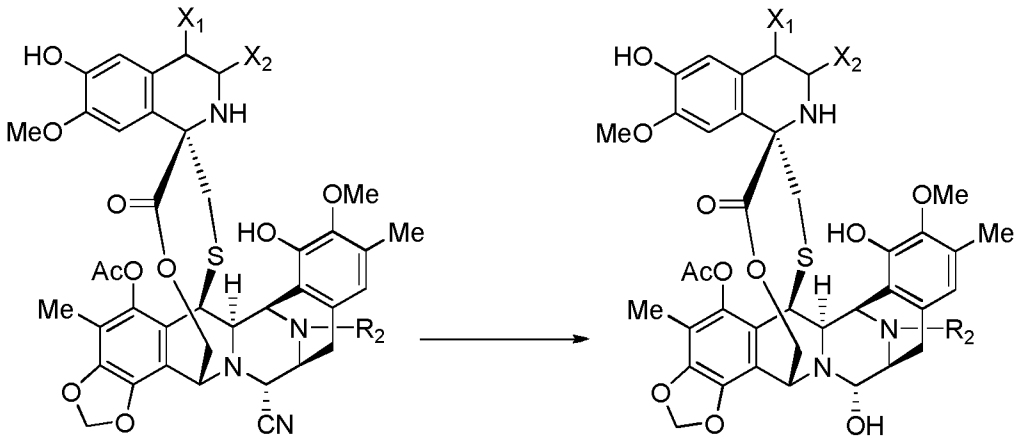


Id **If**

wherein

R_2, X_1, and X_2 are as defined in formula **I** of claim 1 and R_3 is cyano.

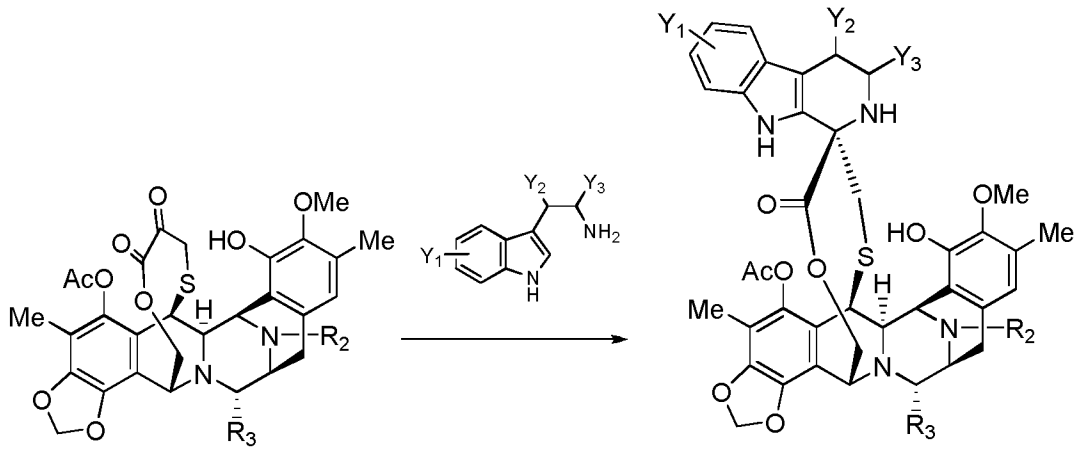
9. A process according to any preceding claim, which further comprises the step of replacement of the cyano group at R_3 in the compound of formula **If** by a hydroxy group:



wherein R_2, X_1, and X_2 are as defined in formula **I** of claim 1.

10. A process according to claim 8 or 9 wherein X_1 and X_2 are H.

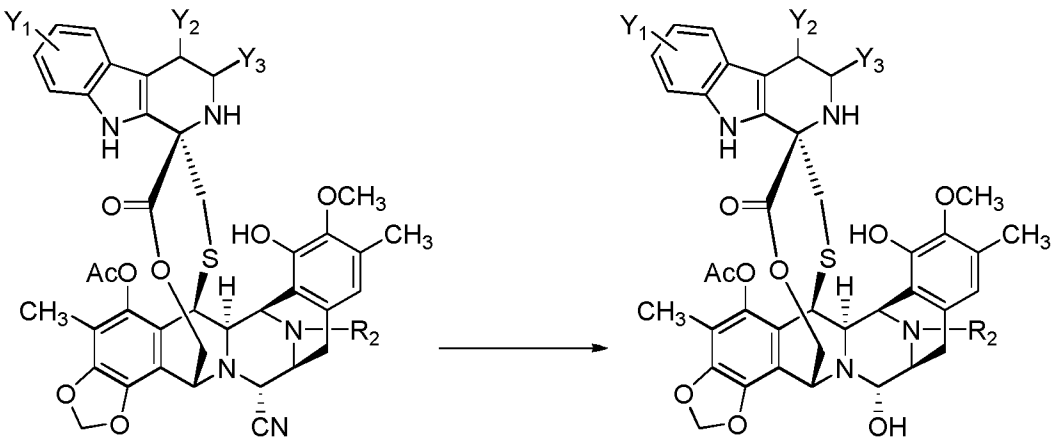
11. A process according to any of claims 1 to 7, which further comprises the step of stereospecifically forming a spirotetrahydro-*1H*-pyrido[3,4-b]indole compound of formula **Ie** from the α-ketolactone of formula **Id** by a Pictet-Spengler reaction:



wherein

R_2, Y_1, Y_2, and Y_3 are as defined in formula **I** of claim 1 and R_3 is cyano.

12. A process according to claim 11, which further comprises the step of replacement of the cyano group at R_3 in the compound of formula **Ie** by a hydroxy group:

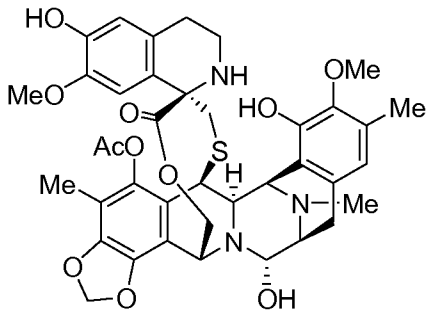


wherein R_2, Y_1, Y_2, and Y_3 are as defined in formula **I** of claim 1.

13. A process according to claim 11 or 12 wherein Y_1 is hydrogen or methoxy, and Y_2 and Y_3 are hydrogen.

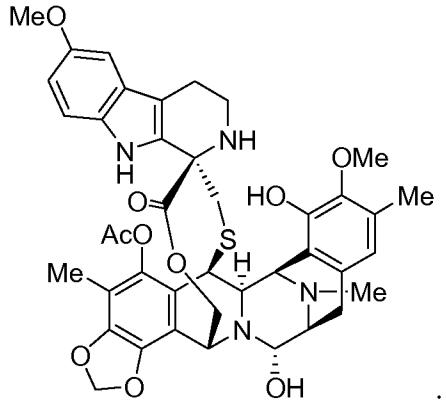
14. A process according to any preceding claim, wherein R_2 is methyl.

15. A process according to claim 9 or 10 wherein the compound of formula **If** is ET-743:



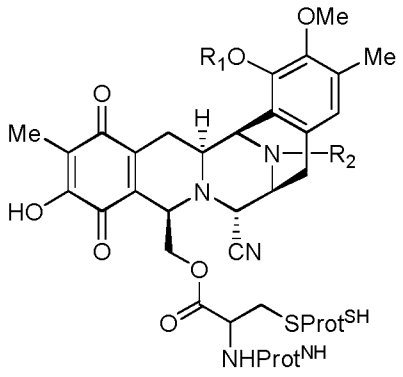
ET-743

16. A process according to any of claims 12 to 14, wherein the compound of formula **Ie** is:



.

17. A compound of formula **II**:



II

wherein

R_1 is a protecting group for OH;

R_2 is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, $C(=O)R^a$, $C(=O)OR^b$, $C(=O)NR^cR^d$, and a protecting group for amino;

R^a is selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

R^b is selected from substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group

for OH;

R^c and R^d are independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and a protecting group for amino;

$Prot^{NH}$ is a protecting group for amino; and

$Prot^{SH}$ is a protecting group for SH.

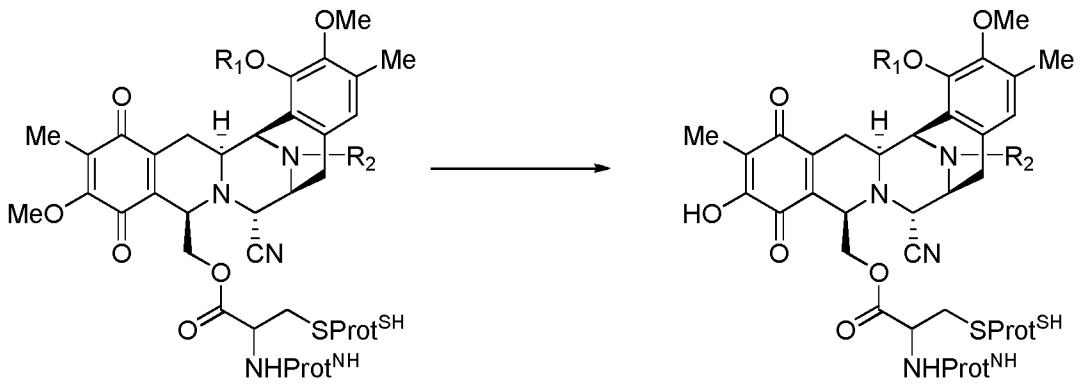
18. A compound according to claim 17, wherein R_1 is an ether protecting group for OH.

19. A compound according to claim 17 or 18, wherein R_2 is methyl.

20. A compound according to any of claims 17 to 19, wherein $Prot^{NH}$ together to the amino group to which is attached form a carbamate and $Prot^{SH}$ together to the S atom to which is attached form a thioether.

21. A compound according to claim 20, wherein $Prot^{NH}$ is t-butyloxycarbonyl and $Prot^{SH}$ is S-9-fluorenylmethyl (Fm).

22. A process for the synthesis of a compound of formula **II** which comprises a process step of demethylating a methoxyquinone of formula **IIa'**:



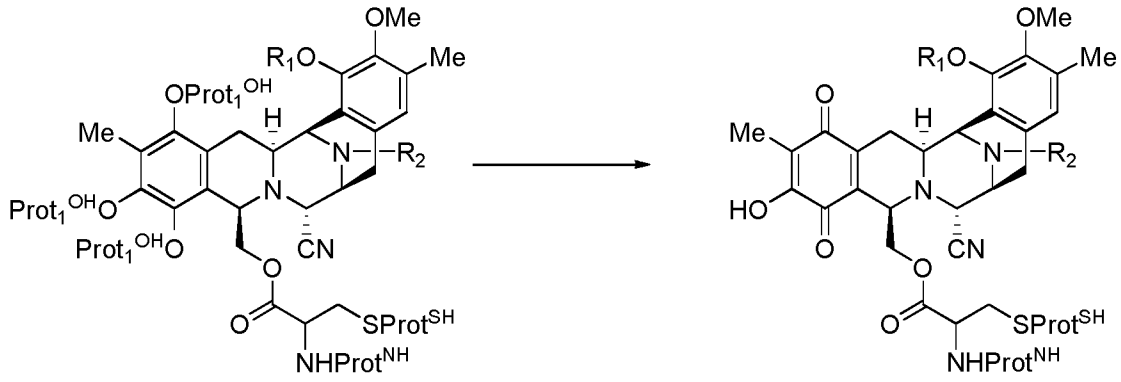
wherein:

R_1 is as defined in claim 17 or 18;

R_2 is as defined in claim 17 or 19 and

$Prot^{NH}$ and $Prot^{SH}$ are as defined in claim 17, 20, or 21.

23. A process for the synthesis of a compound of formula **II** which comprises deprotecting the $Prot_1{}^{OH}O$- groups of a compound of formula **IIa**"and oxidating the resulting hydroquinone:



wherein

R_1 and $Prot_1{}^{OH}$ are protecting groups for OH, with the proviso that R_1 is selected to be removed selectively in the presence of $Prot_1{}^{OH}$ and vice versa;

R_2 is as defined in claim 17 or 19; and

$Prot^{NH}$, and $Prot^{SH}$ are as defined in claim 17, 20, or 21.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/058466

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D515/22
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CUEVAS C ET AL: "SYNTHESIS OF ECTEINASCIDIN ET-743 AND PHTHALASCIDIN PT-650 FROM CYANOSAFRACIN B", ORGANIC LETTERS, AMERICAN CHEMICAL SOCIETY, US, vol. 2, no. 16, 1 January 2000 (2000-01-01), pages 2454-2458, XP002940454, ISSN: 1523-7060, DOI: 10.1021/OL0062502 Scheme I -----	1-23
A	EP 1 496 060 A1 (PHARMA MAR SA [ES]) 12 January 2005 (2005-01-12) cited in the application scheme II, page 32 -----	1-23

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2011	28/09/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/058466

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