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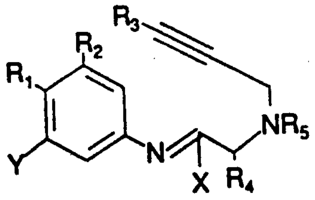

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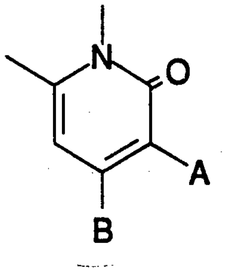

(IVa)

(57) Abstract

The present invention provides a process for preparing certain pyrrolo[3,4-*b*]quinolines, certain 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, specifically camptothecin and its analogs, and certain 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-ones, specifically mappicine ketones and mappicines, said process comprising the step of intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of formula (IV) where: X = OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H; R_1 = H, or OR, where R is an ester protecting group; R_2 = H, NO_2, or a protected amine function; R_3 = H, C_2H_5, or a trialkylsilyl; R_4 = H or CH_2COOEt; R_5 = COOMe or tosyl; or R_4 and R_5 are joined together to form a substituted pyridone (IVa): Y = H or Y,R_1 = -OCH_2O-, formula in which A = H,COOR, or a functionnality for preparation of the hydroxymethyl (C-17) portion of an E ring lactone; B = H, OH, an appropriate leaving group such as halide or O(trifluoromethanesulfonate) or a functionality for preparation of C-(18-21) of the E ring lactone portion of camptothecin, with the unactivated acetylene portion of said compound.

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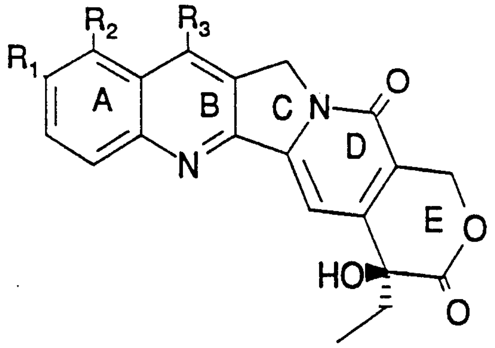
PROCESS FOR PREPARING CERTAIN PYRROLO[3,4-*b*]QUINOLINES, CERTAIN 1H-PYRANO[3',4':6,7]INDOLIZINO[1,2-*b*]QUINOLIN-3,14(4H,12H)-DIONES, AND CERTAIN 8-METHYL-7-(OXOPROPYL)-INDOLIZINO[1,2-*b*]QUINOLIN-9(11H)-ONES

FIELD OF THE INVENTION

The present invention relates to a process for preparing certain pyrrolo-[3,4-*b*]quinolines, certain 1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, specifically camptothecin and its analogs, and certain 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-ones, specifically mappicine ketones and mappicines.

BACKGROUND OF THE INVENTION

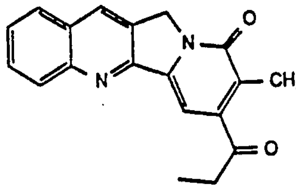
Certain 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones are known to be pharmaceutically useful. Several important examples of such compounds are shown in Formulae Ia-Ie. Referring to these formulae, note that R_3 is substituted at the 7-position, R_2 is substituted at the 9-position, and R_1 is substituted at the 10-position, and so forth. Each ring is designated by a letter A-E as shown. 4-Ethyl-4-hydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, commonly known as camptothecin (Formula Ia, below), and certain of its close congeners are known to inhibit the growth of tumor cells both *in vitro* and *in vivo*.



I

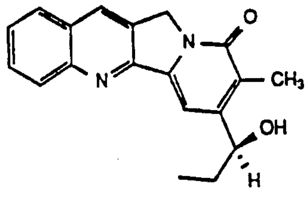
Formula No. (Compound Name)	
Ia (Camptothecin):	$R_1=R_2=R_3=H$
Ib (Topotecan):	$R_1=OH, R_2=-CH_2N(CH_3)_2, R_3=H$
Ic (irinotecan/CPT-11):	$R_1=OC(O)$-(4-piperidino)-piperidinyl, $R_2=H, R_3=C_2H_5$
Id (9-aminocamptothecin):	$R_1=H, R_2=NH_2, R_3=H$
Ie(10,11-methylenedioxy camptothecin):	$Y,R_1=-OCH_2O-, R_2=R_3=H$

While camptothecin itself is known to be cytotoxic at levels which inhibit tumor growth, certain water-soluble camptothecin analogs which exhibit little or no cytotoxicity are efficacious against solid tumor types normally refractory to known treatments. For instance, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, commonly known as topotecan (Formula Ib), which is disclosed in U.S. Pat. No. 5,004,758, issued to Boehm et al. on April 2, 1991, is particularly useful in the treatment of a variety of cancerous tumors. As further disclosed in U.S. Ser. Nos. 07/658,948, 07/658,936, and 07/658,937, filed by R. K. Johnson on February 21, 1991, and in U.S. Ser. No. 07/804,570, filed by R. K. Johnson on December 10, 1991, such tumors include, but are not limited to, ovarian, esophageal, non-small cell lung and colorectal carcinomas. As is further disclosed in U.S. Ser. No. 07/793,041, filed by R. K. Johnson on November 15,1991, topotecan is also useful for the preparation of a combination chemotherapeutic pharmaceutical composition which also comprises a platinum coordination compound, most preferably cis-platin. The 4-(piperidino)-piperidinyl carbamate analogue of 7-ethyl-10-hydroxycamptothecin, commonly known as irinotecan (or CPT-11) (Formula Ic), has also been shown to be efficacious against certain tumors. Both compounds are presently undergoing human clinical testing in refractory tumor types. Additionally, the 9-amino and 10,11-methylenedioxy analogs of camptothecin (Formula Id) have shown promising antitumor activity in preclinical testing.



mappicine ketone

IIa



mappicine

IIb

Certain other modifications of the camptothecin molecule result in compounds possessing antiviral activity while exhibiting little or no cytotoxicity. Examples of such compounds include derivatives in which the E ring lactone has been replaced by some other functionality, *i.e.*, two broad classes of compounds commonly called mappicine ketones and mappicines, of Formulas IIa and IIb respectively. These compounds, which are useful in treating infections in humans and animals caused by a variety of viruses, (for example, *Herpes simplex* virus types 1 and 2, cytomegalovirus, and *Varicella zoster* virus) are disclosed in U.S. Ser. No. 07/606,216, filed by S. Petteway et al. on October 31,1990; U.S. Ser. No. 07/783,063, filed by H. S. Alaudeen on October 25, 1991; U.S. Ser. No. 07/870,649, filed by D. Berges et al. on April 17, 1992; and U.S. Ser. No. 07/868,824, filed by D. Berges et al. on April 14, 1992.

Camptothecins have also been recently shown to possess antiretroviral activity, specifically the ability to inhibit the replication of Human Immunodeficiency Virus (HIV-1) at dosages non-cytotoxic to mammalian cells, and thus may be useful in the treatment of patients suffering from Acquired Immune Deficiency Syndrome (AIDS, see *AIDS Res. Hum. Retr.*, 1991, 7, 65).

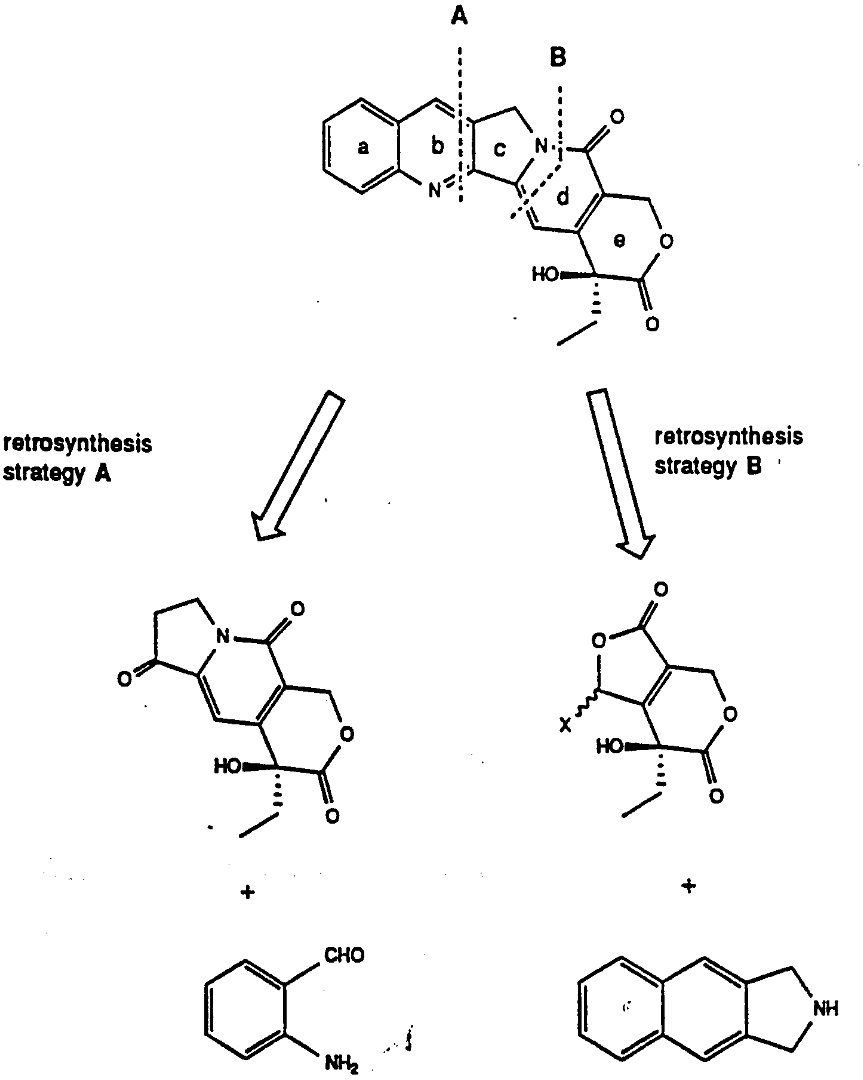
The mode of action of these compounds is grounded in the inhibition of the eukaryotic cellular enzymes topoisomerase I and II. See *Cancer Res.* 1988, *48*, 1722; *Molec. Pharmacol.* 1988, *34*, 755. In order to utilize its genetic information as a template for DNA transcription and replication, certain topological features of cellular DNA must be temporarily altered. Specifically, the supercoiled DNA helix must undergo relaxation/uncoiling, with subsequent unwinding of its helical structure, before the process of transcription and replication can proceed.

Topoisomerase I is a monomeric enzyme with a molecular weight of approximately 100,000. This enzyme undergoes covalent binding to DNA and introduces a transient single strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. There is evidence that this mechanism of action is selectively important for the replication of DNA in tumorigenic cells. Camptothecin is known to exert its antitumor activity by stabilization of the covalently bound topoisomerase I - DNA complex. As a result, progression of the DNA replication sequence proceeds only as far as induction of a single strand break. The ultimate result of this inhibition of the DNA transcription/replication process is cell death. Camptothecin and a few of its close congeners are the only agents in clinical drug development which inhibit topoisomerase I.

Topoisomerase II consists of two identical subunits of molecular weight 170,000. Topoisomerase II induces transient breaks of both strands of the DNA helix and passes another double-stranded segment through the break. Several commercially important oncolytic agents (*e.g.*, etoposide, doxorubicin and mitoxantrone) are inhibitors of topoisomerase II. Although camptothecin does not inhibit topoisomerase II, related derivatives in which the E ring lactone has been replaced by an alternate functionality, i.e,. mappicines and mappicine ketones, are known to inhibit topoisomerase II. As such these compounds are of interest both as potential antineoplastic and antiviral agents.

A number of approaches to the preparation of camptothecin and its analogs are known. These include several semisynthetic approaches for the transformation of camptothecin into various related analogs, e.g. topotecan, which rely on naturally occurring camptothecin as the starting material. For example, our U.S. Ser. No. 07/589,848, filed on September 28, 1990 and allowed according to the Notice of Allowance and Issue Fee Due dated June 17, 1992, discloses a semisynthetic method of preparing certain 8-methyl-7-(-oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones from camptothecin or derivitized camptothecins. U.S. Ser. No. 07/589,643, filed by P. Burk *et al.* on September 28, 1990, discloses a semisynthetic method of preparing certain water-soluble camptothecin analogs from camptothecin. At present, the only practical method for obtaining preparative- and commercial-scale quantities of camptothecin is by extraction of the tissues of the *Camptotheca acuminata* tree indigenous to the People's Republic of China or the *Nothapodytes foetida* shrub indigenous to India. However, as is well-known, reliance on such natural sources has certain inherent disadvantages, including very high starting material cost (about $28,000/kg) and lack of a dependable source.

Camptothecin has also been prepared from readily available materials by various totally synthetic approaches. Recently, a 4+1 radical annulation in which a radical N-propargylated intermediate is intramolecularly cyclized to form the B and C rings of what is formally a camptothecin precursor was disclosed in *J. Am. Chem. Soc.* 1992, *114*, 5863-5864. However, generally the published strategies for the total synthesis of 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, and specifically camptothecins, follow the two broad retrosynthetic outlines shown in Scheme 1.



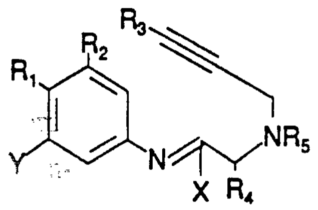
Scheme 1

In strategy A, a tricyclic CDE ring system is prepared by known methods and is coupled with *ortho*-aminobenzaldehyde via a Friedlander quinoline synthesis. As such, the critical bond disconnection strategy is shown by the dashed line labelled A. In strategy B, tricyclic ABC and bicyclic DE ring components are prepared separately by known methods and are coupled using a two-step, standard procedure to form the D ring pyridone. The critical bond disconnection strategy is shown by the dashed line labelled B. In many cases, the tricyclic ABC ring fragment for strategy B is ultimately prepared via a Friedlander quinoline synthesis requiring several steps. The Friedlander quinoline synthesis is therefore a basic component of many of the known approaches. However, such total syntheses are of limited value because they suffer from a variety of drawbacks: *ortho*-aminobenzaldehydes are difficult to prepare, are prone to polymerization, and require multi-step synthesis from commercially available starting materials for A- and B- ring analogs of camptothecin. Thus, many of these syntheses are troublesome to perform and result in very poor chemical yields of the desired analog. Other strategies which rely on multi-step elaborations of commercially available quinolines suffer from similar drawbacks.

SUMMARY OF THE INVENTION

The present invention provides an efficient general route for the facile synthesis of pyrrolo[3,4-*b*]quinolines, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, preferably camptothecin analogs.

In a first aspect, the present invention provides a process for preparing pyrrolo[3,4-*b*]quinolines, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones; and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, preferably camptothecin analogs , more preferably water-soluble camptothecin analogs, yet more preferably topotecan and irinotecan, most preferably topotecan, said process comprising the step of intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV with the unactivated acetylene portion of said compound, the compound of Formula IV being generated from compounds of Formula III (shown in Scheme 2 below and having the same substitutions as compounds of Formula IV), which are derived from generally available compounds.



IV

where:

X= OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H

R_1 = H, OH, or OR, where R is an ester protecting group;

R_2 = H, NO_2, or a protected amine function;

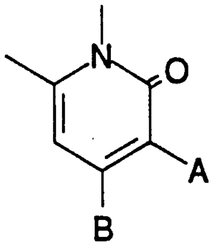
R_3 = H, C_2H_5, or a trialkylsilyl;

R_4 = H or CH_2COOEt;

R_5 = COOMe or tosyl; or

R_4 and R_5 are joined together to form a substituted pyridone IIa:

Y=H, or Y,R_1 = $-OCH_2O-$



IVa

where:

A = H, COOR, or a functionality for preparation of the hydroxymethyl (C-17) portion of an E ring lactone;

B = H, OH, an appropriate leaving group such as halide or O(trifluoromethanesulfonate) or a functionality for preparation of C-(18-21) of the E ring lactone portion of camptothecin.

In a second aspect, the present invention also provides a process for the preparation of 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-ones, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones; and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, preferably camptothecin analogs, more preferably water-soluble camptothecin analogs, yet more preferably topotecan and irinotecan, most preferably topotecan, said process comprising the step of coupling a vinyl triflate derived from a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to prepare a 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one. The resulting 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one may be conveniently elaborated into a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione or a 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-one as disclosed elsewhere in the present application.

In a third aspect, the present invention also provides a process for the preparation of pyrrolo[3,4-*b*]quinolines, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones; and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, preferably camptothecin analogs, more preferably water-soluble camptothecin analogs, yet more preferably topotecan and irinotecan, most preferably topotecan, said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV with the unactivated acetylene portion of said compound to give a pyrrolo[3,4-*b*]quinoline substituted with an acetate ester at C-2;

(b) cyclizing the 2-(acetate ester)-substituted pyrrolo[3,4-*b*]quinoline to form a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(c) coupling a 7-trifluoromethanesulfonate derivative of the 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 with an (alkyl)malonate diester; and

(d) converting the 7-(1,1-bis-alkoxycarbonyl)propyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, preferably a camptothecin analog.

In a fourth aspect, the present invention also provides a process for the preparation of camptothecin analogs which lack the lactone E ring, preferably 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-ones, most preferably mappicines and mappicine ketones, said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV with the unactivated acetylene portion of said compound to give a pyrrolo[3,4-*b*]quinoline substituted with an acetate ester at C-2;

(b) cyclizing the 2-substituted pyrrolo[3,4-*b*]quinoline to form a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(c) coupling a 7-trifluoromethanesulfonate derivative of the 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 with an (alkyl)malonate diester;

(d) converting the 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, preferably a camptothecin analog;

(e) opening the E ring of said camptothecin analog with extrusion of carbon dioxide to provide, depending upon choice of termination step, a camptothecin analog which lacks the lactone E ring, preferably a 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one, most preferably a mappicine ketone; and

(f) reduction of mappicine ketone with a hydride source such as sodium borohydride to give a mappicine.

In a fifth aspect, the present invention provides a process for the total synthesis of, depending upon choice of termination step, 4-ethyl-4-hydroxy-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H, 12H)-dione, more commonly known as 10-methoxycamptothecin, 4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, more commonly known as 10-hydroxycamptothecin, as well as of 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, more commonly known as topotecan, said process comprising the steps of:

(a) heating a compound of Formula III (e.g. VII) in a polar solvent, preferably methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone or N-methylpyrrolidinone, most preferably acetonitrile;at a temperature of about 20 - 85°C, preferably about 60 - 85°C, most preferably at about the reflux temperature of acetonitrile; in the presence of a strong alkylating agent or such agent as is capable of transforming an amide into its corresponding O-alkylimidate or imidate ester, imidoyl halide, or a strong acid (such as aluminum chloride) capable of initiating a cyclodehydration, preferably trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide, most preferably trimethyloxonium tetrafluoroborate; to yield a pyrrolo[3,4-*b*]quinoline substituted at C-2 by an acetate ester;

(b) hydrolyzing the carbamate function of the C-2 substituted pyrrolo[3,4-*b*]quinoline resulting from step (a) with acetic acid saturated with HBr to give a tricyclic amine;

(c) coupling said tricyclic amine with a monoalkyl malonyl chloride, preferably monomethyl malonyl chloride, to give the half-amide of a malonate diester;

(d) subjecting said diester to a Dieckmann condensation in the presence of base to give a a tetracyclic enol;

(e) forming a vinyl triflate of said tetracyclic enol, and coupling said triflate with a tertiary malonate anion to form a (1, 1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(f) 1,2- elimination of hydrogen at the 5,6 bond to give a 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-indolizino[1,2-*b*]quinolin-9(11H)-one;

(g) reduction of the 8-methoxycarbonyl group, followed by hydrolysis-decarboxylation of the diester group at C-7, and lactone formation to give a 1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione;

(h) forming a tertiary alcohol α to the E ring carbonyl of said product to give 10-methoxycamptothecin;

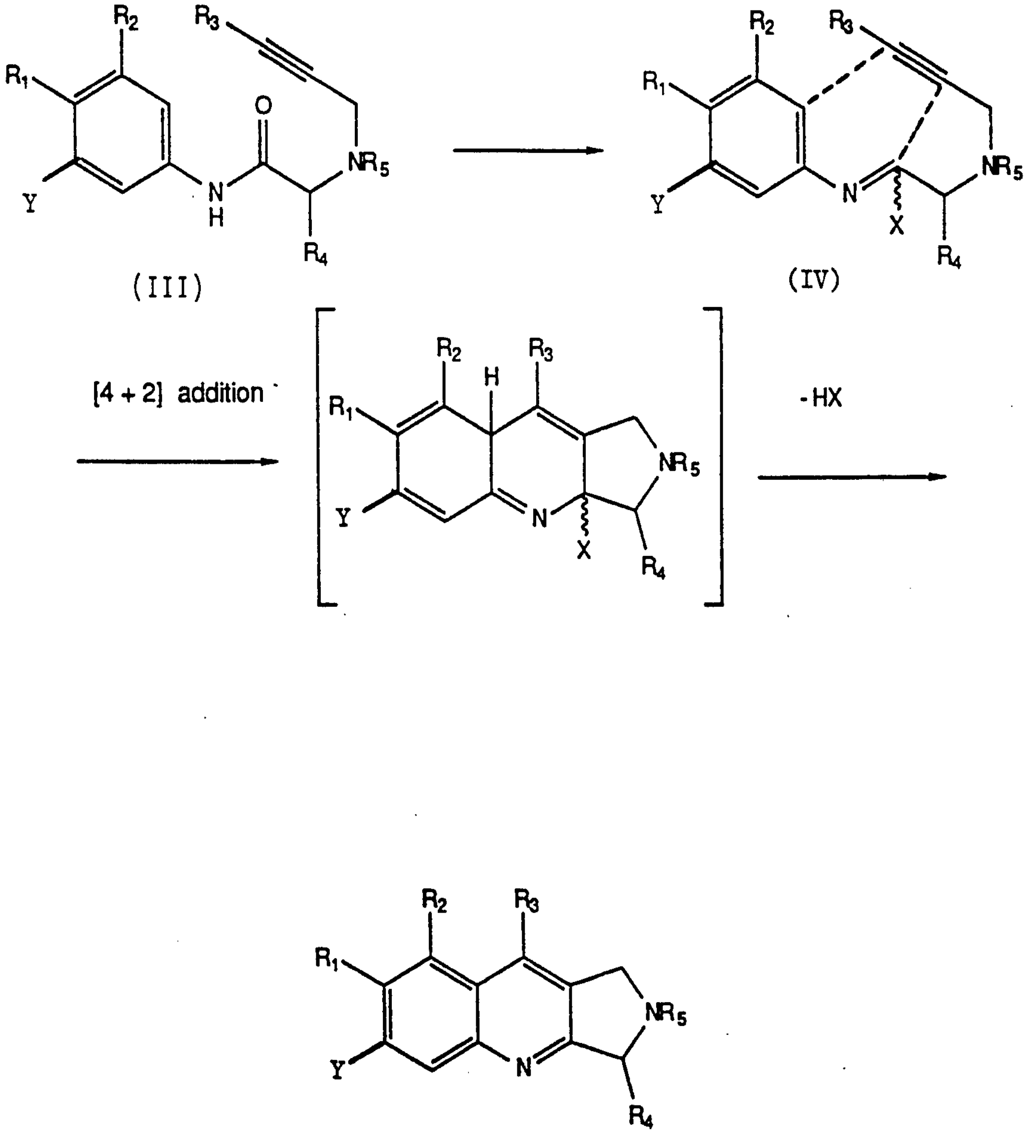
(i) cleaving the methyl ether of said 10-methoxycamptothecin to yield 10-hydroxycamptothecin; and

(j) alkylating the 9-position of said 10-hydroxycamptothecin by reaction with N,N,N',N'-tetramethyldiaminomethane (BDAM) to give topotecan.

DETAILED DESCRIPTION OF THE INVENTION

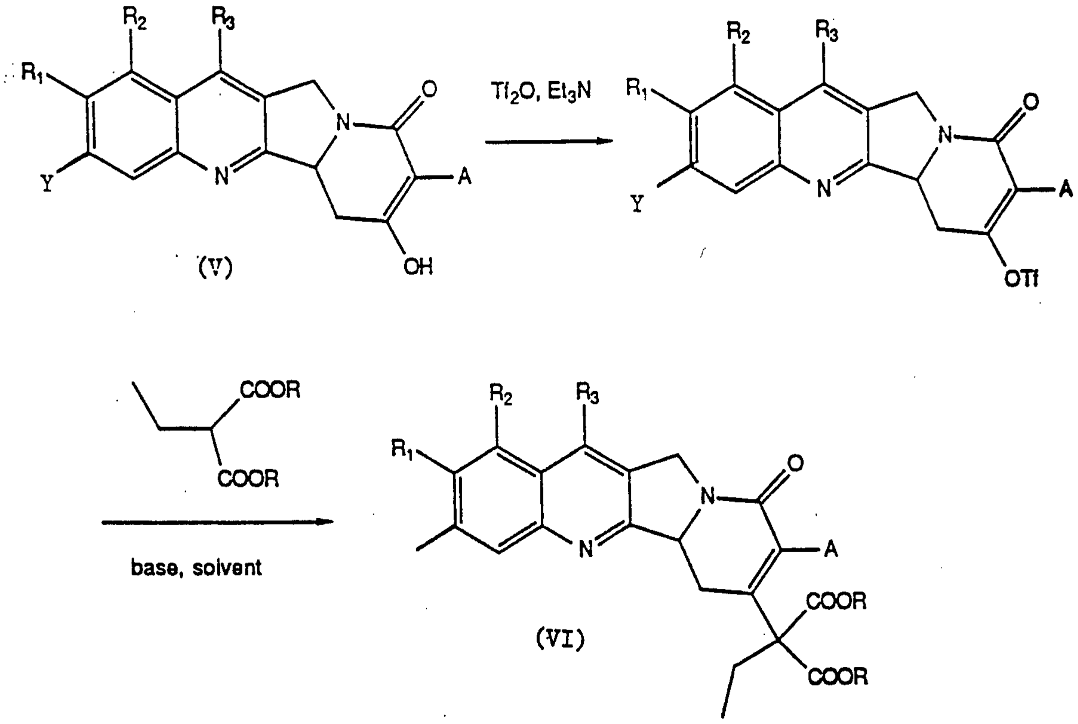
Here and throughout this application, the term "a camptothecin" includes camptothecin and and any derivative thereof the structure of which is based on the 1H-pyrano[3',4':6,7] indolizino-[1,2-*b*]quinolin-3,14(4H,12H)-dione ring system. The terms "pyrrolo[3,4-*b*]quinoline", "indolizino[1,2-*b*]quinolin-9(11H)-one" and 1H-pyrano[3',4':6,7] indolizino-[1,2-*b*]quinolin-3,14(4H,12H)-dione refer generally to compounds based on these ring systems. The term " camptothecin analog" includes camptothecins as defined above and also includes derivatives of camptothecin wherein the E ring has been replaced with another functionality. The term "ester protecting group" is defined to include C_1-C_6 alkyl groups as well as allyl, benzyl, phenyl and β,β,β-trichloroethyl. The term " amine protecting group" is defined to include alkyl and arylsulfonate esters, carbamates of common alkyl groups such as methyl, ethyl, β,β,β-trichloroethyl, allyl, *tert*-butyl and phenyl, amides such as acetamido and propionamido, as well as common alkyl groups such as methyl and benzyl. The term "trialkylsilyl" is defined to include trimethyl, triethyl, triisopropyl and tripropylsilyl, as well as phenyldimethylsilyl and *tert*-butyldimethylsilyl.

The present invention provides a process for preparing pyrrolo[3,4-*b*]quinolines, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones; and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, preferably camptothecin analogs, more preferably water-soluble camptothecin analogs, yet more preferably topotecan and irinotecan, most preferably topotecan, the process comprising the step of intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV, generated from a starting material of Formula III, with the unactivated acetylene portion of said compound. Scheme 2 illustrates one embodiment of the present process wherein R_4 and R_5 of the compound of Formula IV are not joined together to form a pyridone of Formula IVa.



Scheme 2

X, R_1 - R_5, and Y are as defined for Formula IV;


R2
R3
R1
Y
O
N
N
A
OH
(V)
Tf2O, Et3N
R2
R3
R1
Y
O
N
N
A
OTf
COOR
COOR
base, solvent
R2
R3
R1
O
N
N
A
COOR
COOR
(VI)

Scheme 3

Table I illustrates representative compounds and intermediates made by the present process.

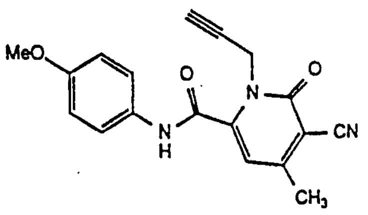
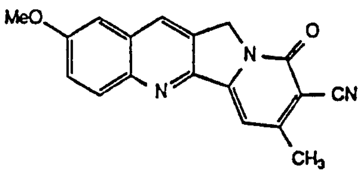
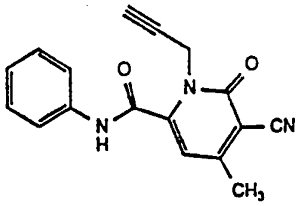
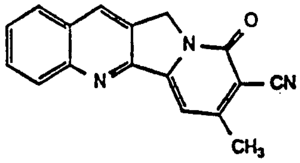
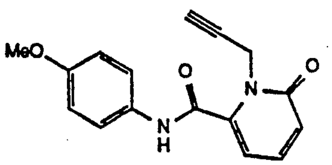
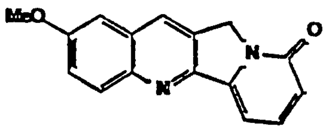
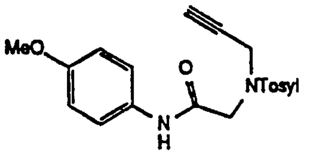
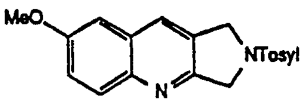
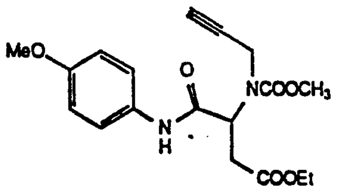
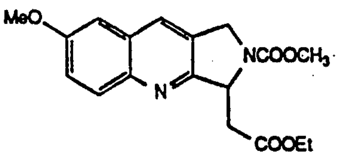
Substrate	Isolated Yield	Product
	82%	
	35%	
	65%	
	72%	
	60%	

Table I

The starting material of Formula III is heated in a polar solvent, preferably methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone or N-methylpyrrolidinone, most preferably acetonitrile; at a temperature of about 20 - 85 °C, preferably 60 - 85 °C, most preferably at the reflux temperature of acetonitrile; in the presence of a strong alkylating agent or such agent as is capable of producing either an O-alkylimidate or imidate ester, imidoyl halide, or such imide derivative as is capable of cyclodehydration, preferably trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide, most preferably trimethyloxonium tetrafluoroborate, thereby generating the compound of Formula IV which then undergoes [4 + 2] cycloaddition to yield a pyrrolo[3,4-*b*]quinoline. Compounds of Formula IV have not been isolated, but have been detected. The products of the present process are either pharmaceutically useful themselves, *e.g.* topotecan, or are intermediates, e.g. 10-methoxycamptothecin, useful for elaboration into pharmaceutically useful compounds, particularly camptothecin analogs.

The present invention also provides a process for the preparation of 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-ones, 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones; and1H-pyrano [3',4': 6,7] indolizino [1,2-*b*] quinolin - 3,14 (4H, 12H - diones, preferably camptothecin analogs, more preferably water-soluble camptothecin analogs, yet more preferably topotecan and irinotecan, yet more preferably topotecan and irinotecan, most preferably topotecan, said process, referring to Scheme 3, comprising the step of coupling a vinyl triflate dervived from a 7-hydroxy-5,6-dihydroindolizino [1,2-*b*] quinolin-9(11*M*)-one (V) with a tertiary malonate anion to prepare a 7-(1,1-*bis*)-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino [1,2-*b*] quinolin - 9(11*M*)-one (VI). The resulting 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one may be conveniently elaborated into a 1H-pyrano[3',4':6,7]indolizino-[1,2-*b*]quinolin-3,14(4H,12H)-dione or a 8-methyl-7-(oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-one as disclosed elsewhere in the present application.

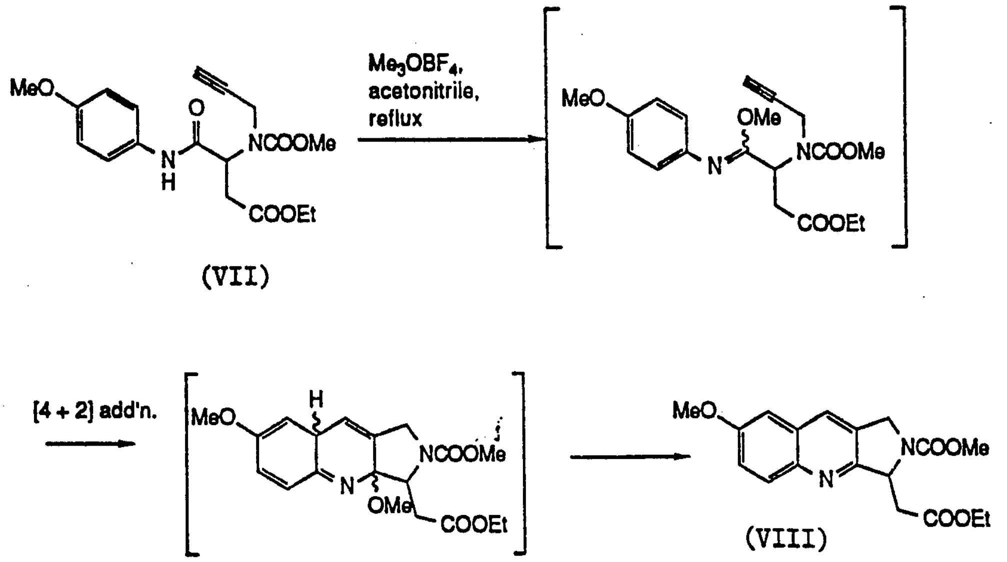
In one preferred embodiment of the present invention, an exemplary illustration of which is shown in Scheme 4, the starting material (VII) has the structure (referring to Formula III in Scheme 2) wherein: R_4 = H or CH_2COOEt; R_5 = COOMe, toluenesulfonyl, benzyl, $COCH_3$; or $COCH_2CH_3$; and Y=M. As will be readily apparent to one of ordinary skill in the art, this embodiment of the present process may be conveniently used to provide a variety of useful intermediates (pyrrolo[3,4-*b*]quinolines, indolizino[1,2-*b*]quinolin-9(11H)-ones and 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones) and products, preferably camptothecin analogs, by the selection of appropriately substituted starting materials and of the appropriate terminating step. This process comprises the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV (exemplified by Formula IV, Scheme 2) with the unactivated acetylene portion of said compound to give a pyrrolo[3,4-*b*]quinoline substituted with an acetate ester at C-2 (exemplified by Formula VIII, Scheme 4);

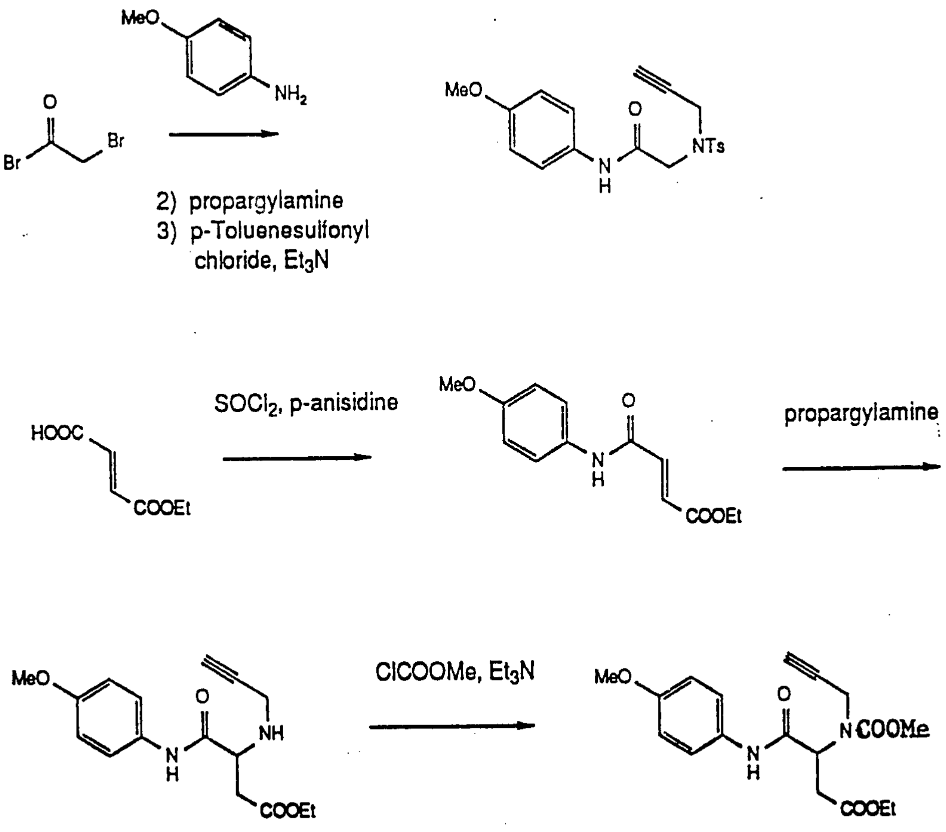
(b) cyclizing the 2-(acetate ester) substituted pyrrolo[3,4-*b*]quinoline to form a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one (e.g. XII, Scheme 7).

(c) coupling a 7-trifluoromethanesulfonate derivative of the 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 an (alkyl) malonate diester (e.g. XIII, Scheme 7); and

(d) converting the 7-(1,1-*bis*-alkoxycarbonyl) propyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, preferably a camptothecin analog (e.g. XVI, Scheme 7).



Scheme 4



Scheme 5

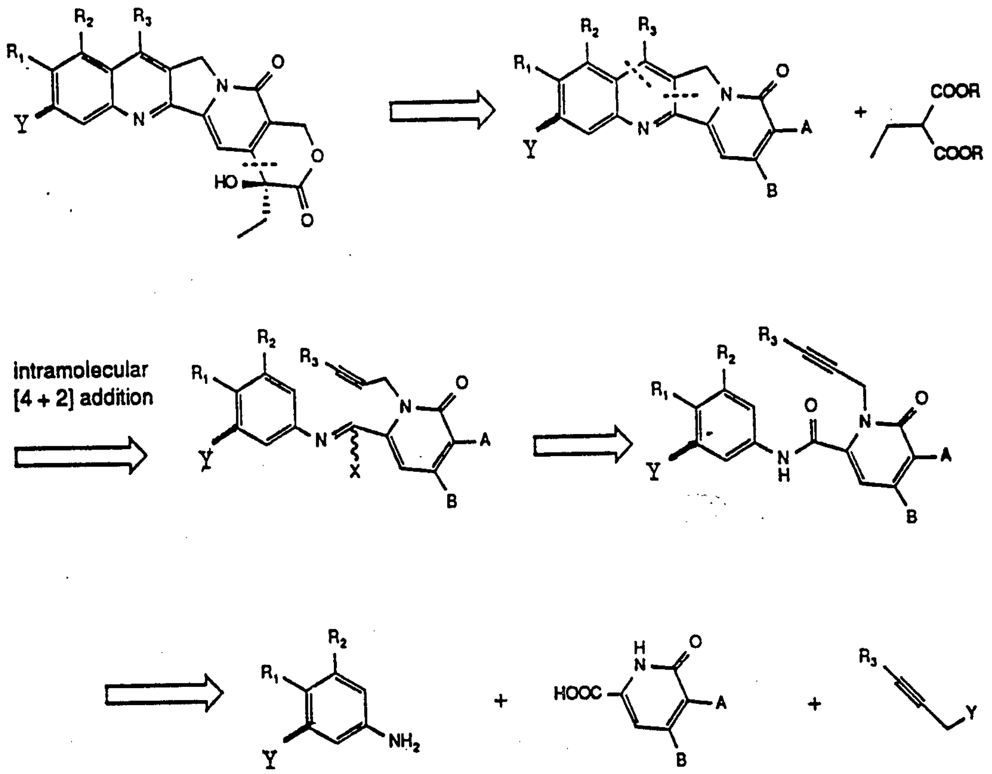
Referring to the above embodiment, the compounds of Formula IV are readily prepared by known methods, for example as shown in Scheme 5 and Steps 1-3 of Scheme 7, below, and as is exemplified in the Example (Steps 1-3). In step (a), the amide starting material of Formula IV is reacted in a polar solvent such as methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone or N-methylpyrrolidinone, but preferably acetonitrile; at a temperature of about 20 - 85 °C, preferably at 60 - 85 °C, most preferably at the reflux temperature of acetonitrile; in the presence of a strong alkylating agent or an agent capable of transforming an amide into its corresponding O-alkylimidate or imidate ester, or an imidoyl halide, e.g. trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide, preferably trimethyloxonium tetrafluoroborate, thereby generating a compound of Formula IV which then undergoes [4 + 2] cycloaddition to yield a substituted pyrrolo[3,4-*b*]quinoline. The choice of solvents, temperature ranges, and alkylating agents applies to all embodiments disclosed in the present application.

In step (b), the substituted pyrrolo[3,4-*b*]quinoline resulting from step (a) is cyclized to a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one as follows. The carbamate function protecting the C-ring nitrogen is hydrolytically cleaved, preferably with acetic acid saturated with HBr, to give the resulting tricyclic amine. The amine is then coupled at the C-ring nitrogen with a monoalkyl malonyl chloride, preferably monomethyl malonyl chloride, to give the resulting malonate half-amide. The D ring is formed when the malonate half-amide undergoes a Dieckmann condensation in the presence of base, preferably methoxide, to give a 7-hydroxy-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one.

When synthesis of an indolizino[1,2-*b*]quinolin-9(11H)-one is desired, the 7-hydroxy-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one is further reacted as follows. In step (c), the vinyl triflate of the 7-hydroxy-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one is coupled with a tertiary malonate anion to form a 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one. In step (d), the diester is cyclized to form the lactone E ring of an indolizino[1,2-*b*]quinolinone, preferably a camptothecin analog. More specifically, 1,2 elimination of the tertiary hydrogen α to the quinolino nitrogen by oxidation in the presence of sodium nitrite or other oxidizing agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the analogous indolizino[1,2-*b*]quinolin-9(11H)-one, followed by reduction of the carbomethoxy group at C-8 to a hydroxymethyl function and hydrolysis/decarboxylation of the malonate diester to give the resulting 4-ethyl-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione. The 4-ethyl-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione may be further reacted to form a tertiary alcohol α to the E ring carbonyl by air-oxidation, thus giving a camptothecin.

The camptothecin may be further elaborated to give a variety of camptothecin analogs. For instance, cleavage of the methoxy group of 4-ethyl-4-hydroxy-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione (10-methoxycamptothecin) with HBr yields 10-hydroxycamptothecin, which is itself pharmaceutically useful. 10-Hydroxycamptothecin may be conveniently converted to topotecan by reaction with N,N,N',N'-tetramethyldiaminomethane (BDAM). The camptothecin products of the present process may further be converted to camptothecin analogs in which the E ring has been replaced by some other functionality, *e.g.*, mappicines and mappicine ketones, for instance by the process described in our recently allowed U.S. Ser. No. 07/589,848, which discloses a semisynthetic method of preparing certain 8-methyl-7-(-oxopropyl)indolizino[1,2-*b*]quinolin-9(11H)-ones from camptothecin or derivitized camptothecins.

In another preferrred embodiment of the present invention, which is illustrated retrosynthetically in Scheme 6, the starting material is a compound of Formula III wherein R_4 and R_5 are joined together to form a substituted pyridone.



Retrosynthetic Analysis of the approach to the total synthesis of camptothecins

Scheme 6

In yet another preferred embodiment, the present invention provides a process for the preparation of camptothecin analogs which lack the lactone E ring, preferably 8-methyl-7-(oxopropyl)-indolizino [1,2-*b*]quinolin-9(11H)-ones, most preferably mappicines (IIb) and mappicine ketone (IIa), said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV with the unactivated acetylene portion of said compound to give a pyrrolo[3,4-*b*]quinoline substituted with an acetate ester at C-2;

(b) cyclizing the 2-substituted pyrrolo[3,4-*b*]quinoline to form a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(c) coupling a 7-trifluoromethanesulfonate derivative of the 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 with an (alkyl)malonate diester;

(d) converting the 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, preferably a camptothecin analog; and

(e) opening the E ring of said camptothecin analog with extrusion of, depending upon choice of termination step, carbon dioxide to provide a camptothecin analog which lacks the lactone E ring, preferably a 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one, most preferably a mappicine or mappicine ketone.

Most preferably, the present invention provides a process, as shown in Scheme 7, for the total synthesis of, depending upon choice of termination step, 4-ethyl-4-hydroxy-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H, 12H)-dione, more commonly known as 10-methoxycamptothecin, 4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, more commonly known as 10-hydroxycamptothecin, as well as of 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, more commonly known as topotecan, said process comprising the steps of:

(a) heating a compound of Formula III (e.g. VII) in a polar solvent, preferably methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone or N-methylpyrrolidinone, most preferably acetonitrile;at a temperature of about 20 - 85°C, preferably about 60 - 85°C, most preferably at about the reflux temperature of acetonitrile; in the presence of a strong alkylating agent or such agent as is capable of transforming an amide into its corresponding O-alkylimidate or imidate ester, imidoyl halide, or a strong acid (such as aluminum chloride) capable of initiating a cyclodehydration, preferably trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide, most preferably trimethyloxonium tetrafluoroborate; to generate a compound of Formula IV which undergoes [4 + 2] cycloaddition to yield a pyrrolo[3,4-*b*]quinoline substituted at C-2 by an acetate ester (VIII);

(b) hydrolyzing the carbamate function of the C-2 substituted pyrrolo[3,4-*b*]quinoline from step (a) with acetic acid saturated with HBr to give a tricyclic amine (X);

(c) coupling said tricyclic amine with a monoalkyl malonyl chloride, preferably monomethyl malonyl chloride, to give the half-amide of a malonate diester (XI);

(d) subjecting said malonate half-amide to a Dieckmann condensation in the presence of an alkoxide to give a a tetracyclic enol (XII);

(e) forming a vinyl triflate of said tetracyclic enol, and coupling said triflate with a tertiary malonate anion to form a 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one (XIII);

(f) 1,2 elimination of hydrogen at the 5,6 bond of the 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one to give a 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-indolizino[1,2-*b*]quinolin-9(11H)-one (XIV);

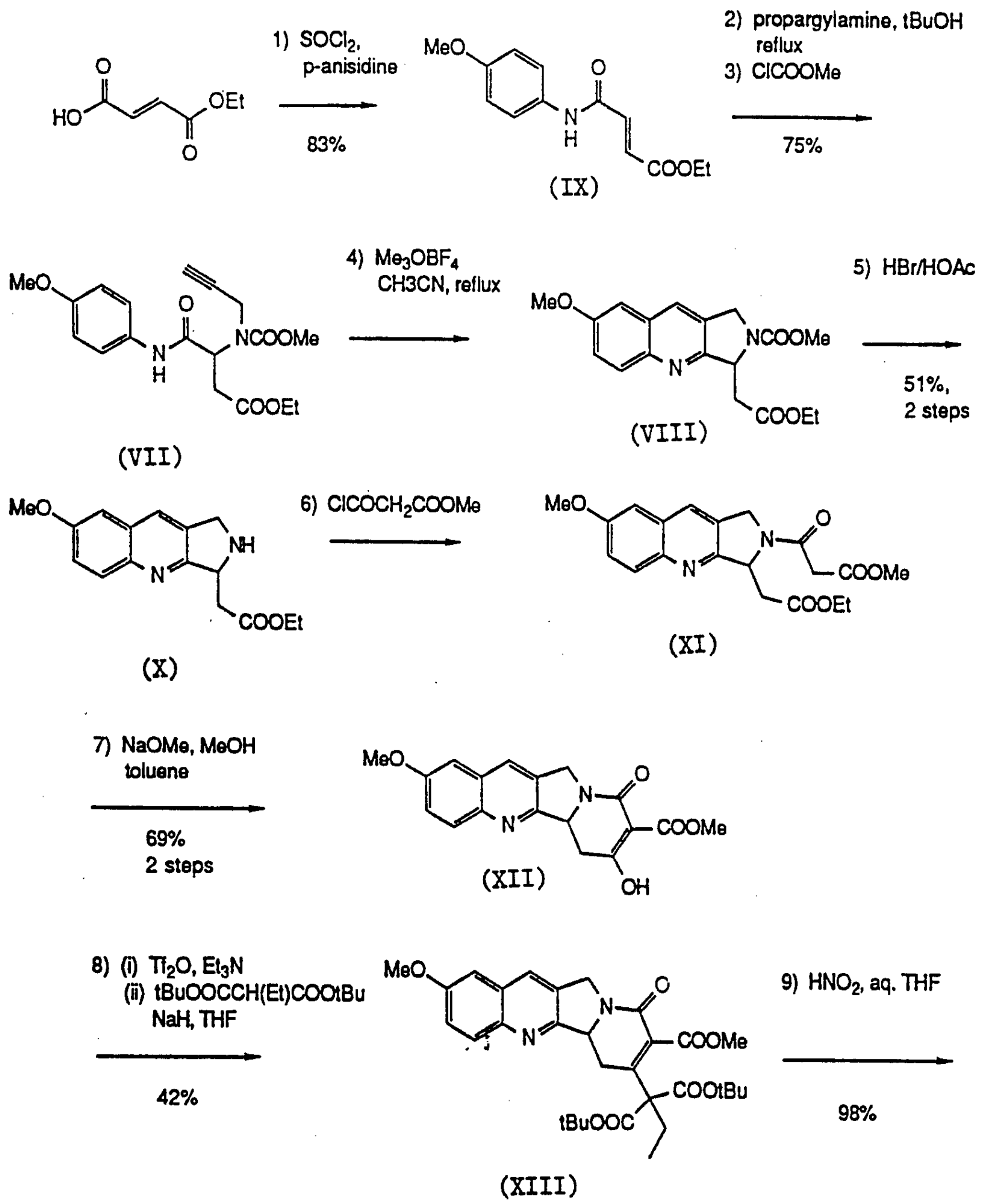
(g) reduction of the 8-methoxycarbonyl group of the 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-indolizino[1,2-*b*]quinolin-9(11H)-one, followed by hydrolysis-decarboxylation of the diester group at C-7, and lactone formation to give a 4-ethyl-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione (XV);

(h) forming a tertiary alcohol α to the E ring carbonyl of said 4-ethyl-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione to give 10-methoxycamptothecin (XVI);

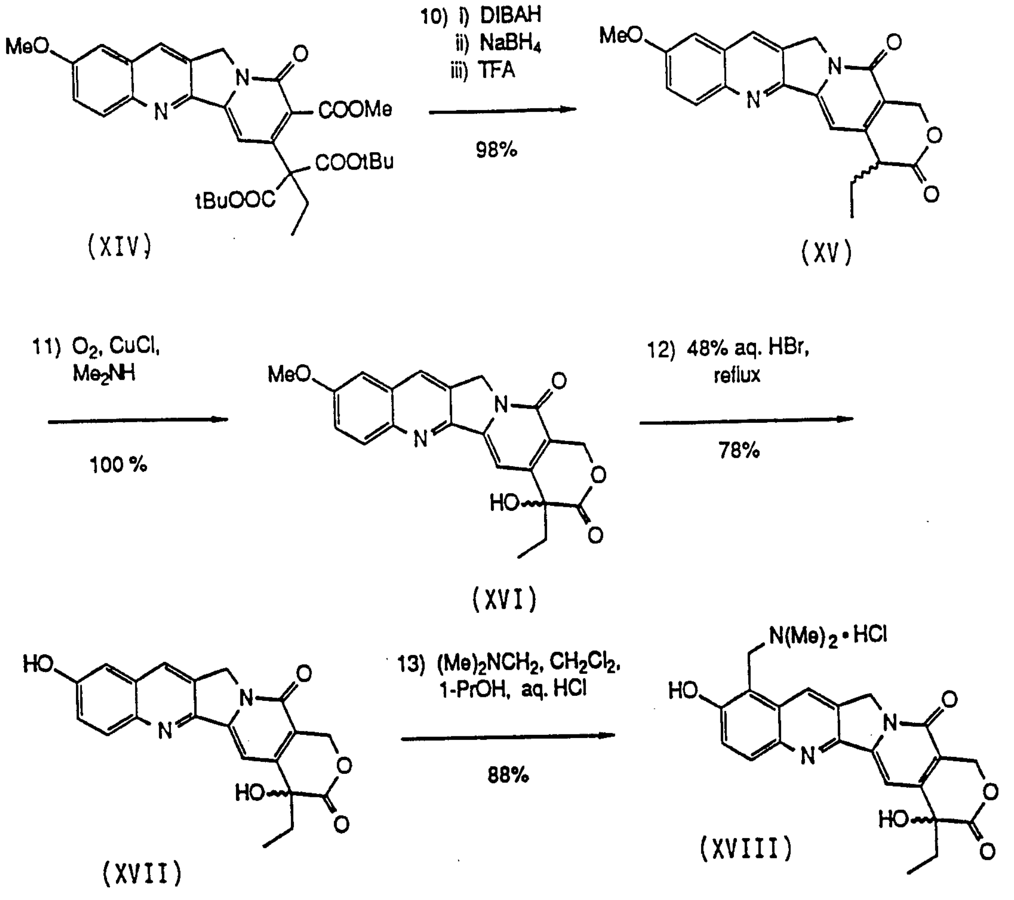
(i) cleaving the methyl ether of said 10-methoxycamptothecin to yield 10-hydroxycamptothecin (XVII); and

(j) alkylating the 9-position of said 10-hydroxycamptothecin by reaction with N,N,N',N'-tetramethyldiaminomethane (BDAM) to give topotecan (XVII).

As may be seen in both Schemes 5 and 7, the starting material of Formula III (e.g. VIII) may be prepared from a variety of readily available starting materials using well-known methods.



Scheme 7



Total synthesis of topotecan; 13 steps, overall yield 5-6%

Scheme 7 (con't)

The most preferred process of the present invention, which provides for the total synthesis of topotecan, is further described in the Example below.

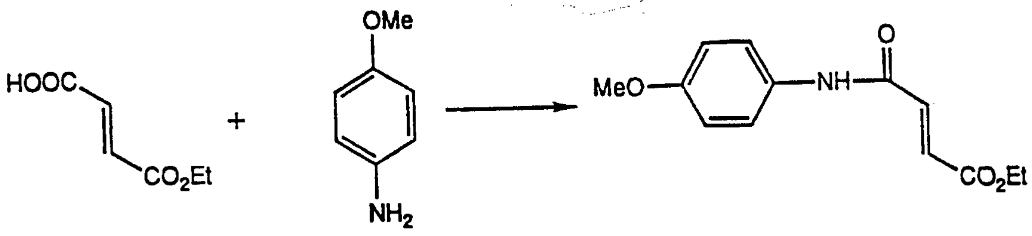
EXAMPLE

In the following synthetic Example, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. This Example is given merely to illustrate the present invention, and should not be construed as limiting the scope thereof in any way. Reference is made to the claims for what is reserved to the inventors hereunder.

The following Example describes the most preferred process of the present invention for the total synthesis of topotecan, which process is outlined in Scheme 7. The steps in the Example correspond numerically with the steps outlined in Scheme 7.

EXAMPLE 1

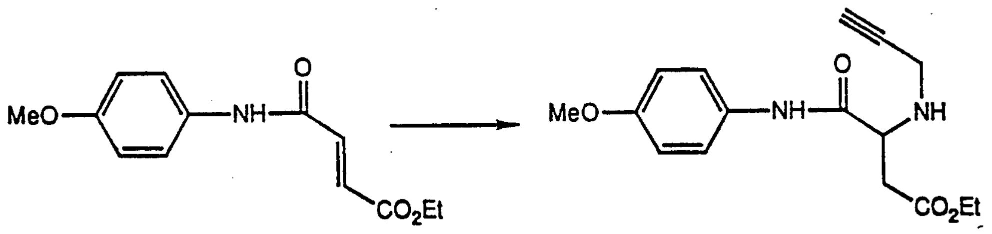
Step 1



To a stirred suspension of fumaric acid monoethyl ester (100 g, 95% purity; 0.66 mol) p-anisidine (90 g, 99% purity, 1.1 eq.) and 1-hydroxybenzotriazole (89 g, 1 eq.) in methylene chloride (3000 ml) was added dimethylaminopropyl ethyl cabodiimide (WSC, 125 g, 1eq.). The resulting mixture was stirred at 20 °C for 16 hours. Additional methylene chloride (2000 ml) was added and the mixture was successively washed with dilute, aqueous, hydrochloric acid (10%, 1500 ml) and water (2 x1500 ml). The organic layer was evaporated to give a crude, greenish-yellow solid which was triturated with 500 ml of diethyl ether and isolated by filtration to give 147 g of a yellow powder (89% yield) mp 144-145 °C.

IR (KBr) 3400-3200, 1720, 1699, 1687, 1672, 1651, 1638, 1613, 1556, 1509, 1240, 1163, 843, 830 cm^{-1};
^{1}H NMR (δ, $CDCl_3$): 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 3.77 (s, 3H, OCH_3), 4.25 (q, J = 7.1 Hz, 2H, CH_2CH_3), 6.85 (d, J = 8.8 Hz, 2H, aromatic), 6.91, 7.07 (AB, q, J = 15.3 Hz, 4H, olefin), 7.50 (d, J = 8.9 Hz, 2H, aromatic), 7.84 (br, 1H, NH); ^{1}H NMR (δ, MeOD): 1.23 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.69 (s, 3H, OCH_3), 4.16 (q, J = 7.1 Hz, 2H, CH_2CH_3), 6.71, 7.08 (AB, q, J = 15.3 Hz, 4H, olefin), 6.81 (d, J = 9.1 Hz, 2H, aromatic), 7.47 (d, J = 9.1 Hz, 2H, aromatic); MS m/z 250 (MH^+), 204, 176, 127.

Step 2



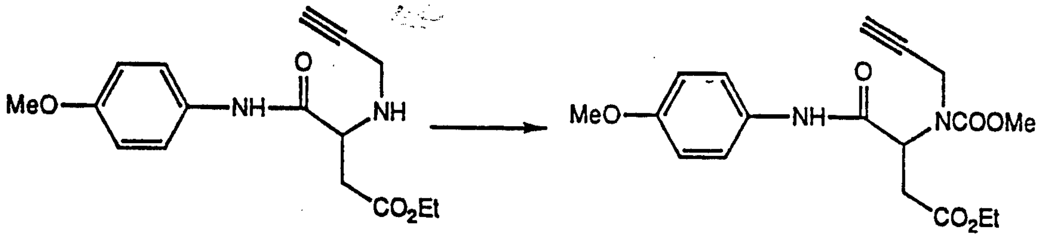
A mixture of fumaric acid mono p-methoxy phenyl amide mono ethyl ester (50g, 0.2 mol) and propargyl amine (40 ml, 3 eq.) in ^{t}BuOH (700 ml) was stirred under reflux at 100 °C for 24 h. The reaction mixture was cooled to 20 °C and solvent was removed on a rotavapor. Ethyl acetate (1500 ml) was added to the remaining thick oil. The resulting solution was washed with hydrochloric acid (10%, 3 x 500 ml). The aqueous phase was then made basic to a pH of approximately 8 by the slow addition of solid sodium bicarbonate. The resulting suspension was extracted with ethyl acetate (3 x 500 ml). The combined organic layers were washed with water (300 ml) dried and evaporated to give a black semisolid which was treated with hexane:ethyl acetate (1:1) and filtered. The filtrate was concentrated using a rotary evaporator to give a brown oil which slowly formed a solid. The solid could be crystallized by trituration with t-butyl methyl ether to give white crystals, mp 66-67 °C (52.4g, 85.9% yield).
IR (KBr) 3400-3200, 2048 1734, 1650, 1605, 1552, 1514, 1464, 1272, 1248, 1178, 1165, 833 cm^{-1};

^{1}H NMR (δ, CDCl$_3$): 1.23 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$), 2.24 (t, J = 2.4 Hz, 1H, alkyne), 2.81, (AB, q, J = 16.6, 7.3Hz, 1H, CH$_2$COO), 2.94 (AB, q, J = 16.6, 4.2 Hz, 1H, CH$_2$COO), 3.45, 3.55 (AB, d,d, J = 17.0, 2.4 Hz, 2H, CH$_2$NH), 3.65 (d,d, J = 7.3, 4.3 Hz, 1H, OCCHNH), 3.76 (s, 3H, OCH$_3$), 4.14 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 6.84 (d, J = 8.9 Hz, 2H, aromatic), 7.46 (d, J = 8.9 Hz, 2H, aromatic), 9.13 (br, 1H, NH);
MS m/z 305 (MH$^+$), 259, 217, 182, 154, 123.

The white grey solid obtained as a byproduct from the initial filtration from hexane:ethyl acetate was N-propargyl aspartic N-p-methoxy phenylamide, mp 165-166 °C.

^{1}H NMR (δ, CDCl$_3$): 2.30 (t, J = 2.4 Hz, 1H, alkyne), 2.69, (AB, q, J = 17.9, 5.3Hz, 1H, CH$_2$CO$_2$R), 3.09 (AB, q, J = 17.9, 8.3 Hz, 1H, CH$_2$CON), 3.46, 3.70 (AB, d,d, J = 17.4, 2.4 Hz, 2H, CH$_2$NH), 3.80 (s, 3H, OCH$_3$), 4.17 (d,d, J = 8.3, 5.2 Hz, 1H, OCCHNH), 6.96 (d, J = 8.9 Hz, 2H, aromatic), 7.18 (d, J = 8.9 Hz, 2H, aromatic).

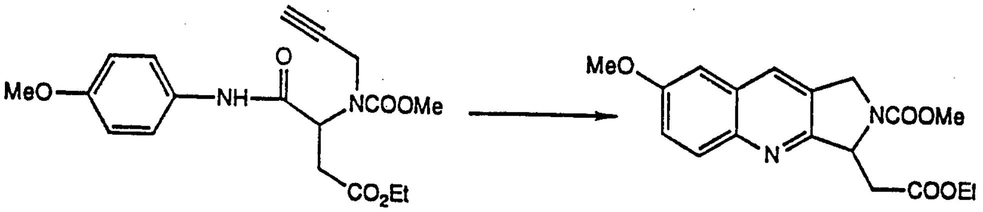
Step 3



To a solution of starting amine (44.66g, 0.146 mol) and pyridine (15.1g, 1.3 eq.) in methylene chloride (150 ml) was added neat methyl chloroformate (14.9 ml, 1.3 eq.) dropwise with the internal temperature maintained at 0 °C with cooling. The resulting mixture was stirred at 0 °C for 30 min. Additional methylene chloride (400 ml) was added to the reaction mixture. The solution was successively washed with aqueous hydrochloric acid (10%, 2 x 150 ml) and saturated sodium chloride solution (2 x 150 ml). The organic solvent was removed on a rotavapor to give a brown oil which was passed through a silica gel pad (200 g) with ether as eluent. The filtrate was concentrated on a rotavapor to give the desired product (41.46g) in 78% yield, which was used as obtained. The product could be recrystallized in approximately 95% recovery by trituration with diethyl ether to give white crystals with mp 97-98 °C.

IR (KBr) 3300, 2120, 1725, 1709, 1687, 1600, 1512, 1463, 1247, 1173, 830 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 1.25 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.30 (br, 1H, alkyne), 2.89, 3.31 (br, 2H, CH_2COO), 3.76 (s, 3H, OCH_3),4.06, 4.22 (AB, d,d, J = 18, 2.3 Hz, 2H, CH_2NH),4.56 - 4.98 (br, 1H, OCCHNH), 6.82 (d, J = 8.9 Hz, 2H, aromatic), 7.36 (d, J = 8.9 Hz, 2H, aromatic), 7.90 - 8.03 (br, 1H, NH); MS m/z 363 (MH^+), 331, 317, 240, 212, 123.

Step 4

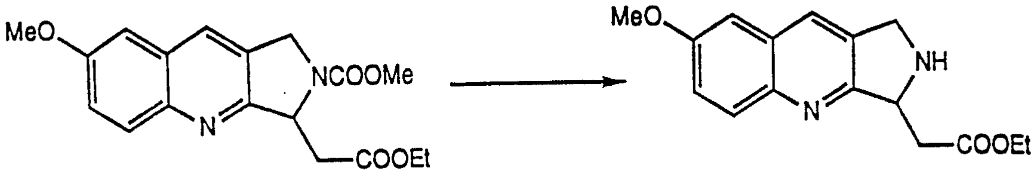


A mixture of carbamate (27.7g, 0.077 mol) and trimethyloxonium tetrafluoroborate (40g, 3.5 eq.) in acetonitrile (500 ml) was stirred under reflux for 2.5 h. After cooling to ambient temperature, saturated sodium chloride solution (200 ml) was added with continued stirring. The organic layer was separated and the aqueous phase was extracted with 3 x 300 ml of ethyl acetate. The combined organic phase was washed with saturated sodium bicarbonate solution (3 x 100 ml) and saturated sodium chloride solution (100 ml) dried, and evaporated to give a yellow semisolid which was recrystallized from methanol to give 25.4 g of yellow solid, mp 132-134 °C.

IR (KBr) 1728, 1701, 1623, 1577, 1504, 1451, 1228, 1122, 1029, 825, 769 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 1.06, 1.08 (t,t, J = 7.3 Hz, 3H, CH_2CH_3), 3.80 (br, 2H, CH_2COO), 3.78, 3.80 (s,s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.78 - 4.95 (m, 2H, CH_2NH), 5.29 (d, J = 14.1Hz, 1H, OCCHNH), 7.05 (s, 1H, aromatic), 7.31 (d,d, J = 9.2, 2.8 Hz, 1H, aromatic), 7.84, 7.88 (s, s, 1H, aromatic), 7.91 (d, J = 9.0 Hz, 1H, aromatic);

MS m/z 345 (MH^+), 317, 299, 285, 271, 257.

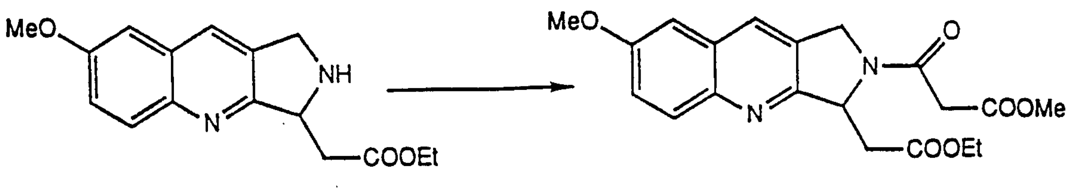
Step 5



To the tricyclic compound (25.4g) was added a solution of acetic acid saturated with hydrobromic acid (129 ml) and the mixture was stirred at ambient temperature for 24 h. The solvent was removed on a rotavapor and 300 ml of water was added to the residue. The mixture was extracted with 2 x 200 ml of ethyl acetate and the organic extracts were discarded. The aqueous phase was made alkaline with solid sodium carbonate to a pH of >10. The resulting precipitated solid was collected by filtration and dried in oven (45 °C/740 mm) to give 8.98 g of product. The aqueouse phase obtained after filtration was further extracted with 3 x 400 ml of methylene chloride. This organic phase was dried and evaporated to give a black oil to which ethyl acetate (100 ml) was added. The resulting mixture was washed with dilute, aqueous hydrochloric acid (3%, 3 x 100 ml). The aqueous phase was made basic by the addition of sodium bicarbonate to a pH > 8, then extracted with methylene chloride, dried, and evaporated to give 2.25 g of product which was combined with the first isolated fraction, giving a total yield of 11.13 g of a yellow solid, m.p. 83-86 °C (51% total yield for 2 steps from the uncyclized carbamate).

IR (KBr) 3350, 1723, 1622, 1502, 1236, 1183, 1026, 893, 842 cm^{-1};
^1H NMR (δ, $CDCl_3$): 1.24 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.63 (d,d, J = 16.5, 9.8Hz, 1H, CH_2COO), 3.26 (d, d, J = 16.5, 2.9 Hz, 1H, CH_2COO), 3.89 (s, 3H, OCH_3), 4.16 (q, d, J = 7.0, 1.3 Hz, 2H, CH_2CH_3), 4.36 (s, 2H, CH_2NH), 4.84 (d, d, J = 9.8, 2.8Hz, 1H, OCCHNH), 7.03 (d, J = 2.7Hz, 1H, aromatic), 7.29 (d,d, J = 9.2, 2.8 Hz, 1H, aromatic), 7.82 (s, 1H, aromatic), 7.91 (d, J = 9.2 Hz, 1H, aromatic);
MS m/z 287 (MH^+), 199.

Step 6

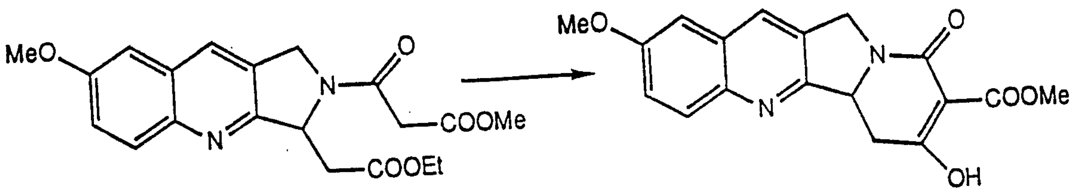


To a solution of the tricyclic amine (6.98g, 24.4 mmol) in methylene chloride (250 ml) was added pyridine (3.0g, 1.56 eqoride (2.66

ml, 95% purity, 1.3 eq.) was then added dropwise, neat, at a rate so as to maintain the internal temperature at 0 °C. The mixture was stirred at 0 °C for an additional 1 hour after addition was complete. Methylene chloride (350 ml) was added and the resulting solution was washed with hydrochloric acid (10%, 2 x 100 ml) followed by saturated, aqueous, sodium bicarbonate solution and saturated, aqueous, sodium chloride solution. The organic layer was dried and evaporated to give 10.4 g of crude product as a heavy oil which was used in the next reaction without further purification. An analytical sample was obtained by recrystallization from 1:1 ethyl acetate:hexane to give a white powder, mp 1145-116 °C.

IR (KBr) 1747, 1737, 1654, 1621, 1503, 1441, 1135, 900, 846 cm^{-1};
^{1}H NMR (δ, $CDCl_3$): 1.08 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.24 (dd, J = 17.2, 3.3 Hz, 1H, CH_2COO), 3.55, 3.57 (2 x s, 2H, $COCH_2COO$), 3.78 (s, 3H, $COCCH_3$), 3.93 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.93 (s, 3H, OCH_3), 4.98, 5.07 (AB, d, J = 13.6 Hz, 2H CH_2N), 5.47 (t, J = 3.8 Hz, 1H, CHNH), 7.07 (d, J = 2.7 Hz, 1H, aromatic), 7.35 (dd, J = 9.2, 2.8 Hz, 1H, aromatic), 7.88 (s, 1H, aromatic), 7.95 (d, J = 9.1 Hz, 1H, aromatic)
MS m/z 387 (MH$^+$), 355, 313, 299, 285, 239, 199, 101 .

Step 7



To a solution of starting material (10.4g) in mixed solvent (216 ml, methanol:toluene = 1: 5) was added sodium methoxide solution (7.4 ml of 25% solution in methanol, 1.2 eq.) dropwise at ambient temperature. The resulting mixture was stirred at 20 °C for 1 h. Water (250 ml) was added with stirring and the layers were separated. The organic layer was extracted with water. The combined aqueous phases were acidified with hydrochloric acid (10%) to a pH < 2. The precipitate was collected by filtration and washed with water until neutral as indicated by pH paper. The white solid was dried under vacuum (60 °C/ 740 mm) to give 5.73g of product, mp 219 - 220 °C (69% yield for 2 steps).

IR (KBr) 3429, 1673, 1661, 1643, 1623, 1567, 1501, 1450, 1238, 1227, 1377, 1046, 1026, 822 cm^{-1};
^{1}H NMR (δ, CDCl3): 2.86 (d,d, J = 17, 13.6Hz, 1H, CH_2COO), 3.31 (d, d, J = 17, 4.4 Hz, 1H, CH_2COO), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.75, 5.13 (AB, d, J = 17 Hz, 2H, CH_2NH), 5.14 (d, d, J = 13.5, 4.5Hz, 1H, OCCHNH), 7.07 (d, J = 2.7Hz, 1H, aromatic), 7.36 (d,d, J = 9.2, 2.8 Hz, 1H, aromatic), 7.94 (d, J = 9.3 Hz, 1H, aromatic), 7.97 (s, 1H, aromatic) 13.89 (s, 1H, OH);
MS m/z 341 (MH^+), 337, 323, 309, 283, 265.

Step 8

To a suspension of the tetracyclic enol (1g, 2.9 mmol) in methylene chloride (50 ml) was added triethylamine (0.5 ml, 1.2 eq.). The resulting brown solution was cooled to -78 °C using a dry ice-acetone bath. Trifluoromethanesulfonic anhydride (0.6 ml, 1.2 eq.) was added dropwise, neat. After the addition was complete, the dry ice-acetone bath was replaced by an ice bath and the reaction mixture was stirred at 0 °C for another hour, then poured into ice water (100 ml). The mixture was extracted with 3 x 100 ml of methylene chloride. The combined organic phases were washed with water (100 ml) dried, and evaporated to give a brown solid which was used directly in the next reaction.

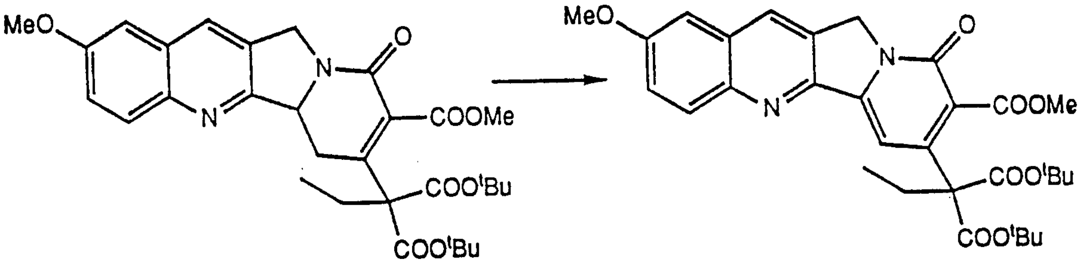
^{1}H NMR (δ, $CDCl_3$): 2.75, 3.12 (AB, d,d, J = 15.9, 13.8Hz, 1H, CH_2COO), 3.25, 3.48 (AB, d, d, J = 17.3, 5.3 Hz, 1H, CH_2COO), 3.82, 3.92 (s, s, 3H, OCH_3), 3.95, 3.96 (s, s, 3H, OCH_3), 4.80, 5.14 (AB, d, J = 17.8 Hz, 2H, CH_2NH), 5.39 (d, d, J = 15.0, 4.5Hz, 1H, OCCHNH), 7.11 (d, J = 2.7Hz, 1H, aromatic), 7.42 (d,d, d, J = 9.4, 2.9, 2.9 Hz, 1H, aromatic), 7.99 (d, J = 9.2 Hz, 1H, aromatic), 8.03, 8.04 (s, s, 1H, aromatic).

To a suspension of sodium hydride (132 mg, 80% in mineral oil, 1.3 eq.) in THF (10 ml) was added a solution of ethyl, di-*tert*-butyl malonate (1.43g, 2eq.) in THF (10 ml) dropwise. The resulting mixture was stirred at 20 °C for 15 min. The mixture became a clear solution, to which the triflate obtained above in THF (50 ml) was added dropwise. The resulting dark green mixture was stirred at 20 °C for 1 h and poured into 150 ml of ice-cold water containing 2 ml of acetic acid. The mixture was extracted with 3 x 150 ml of methylene chloride. The combined organic layers were dried over magnesium sulfate and evaporated to give a black semisolid which was purified by flash chromatography (2 :1 hexane:ethyl acetate as eluant) to give the desired product (680 mg) in 41% yield. The product was isolated as fluffy, tan crystals, mp 88-91 °C.

IR (KBr) 1736, 1665, 1623, 1504, 1368, 1130, 1158, 1231, 1253, 832, 726 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$): 1.03 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.48, 1.51 (s, s, 9H, CCH_3), 2.05, 2.19 (q, d, J = 14.2, 7.3Hz, 2H, CH_2CH_3), 2.65 (d, d, J = 14.2, 14.2 Hz, 1H, CH_2COO), 3.21 (d, d, J = 16.4, 4.1 Hz, 1H, CH_2COO), 3.80 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.76, 5.14 (AB, d, J = 16.4 Hz, 2H, CH_2NH), 5.13 (d, d, J = 13.9, 4.0Hz, 1H, OCCHNH), 7.07 (d, J = 2.5Hz, 1H, aromatic), 7.33 (d,d, J = 9.2, 2.6 Hz, 1H, aromatic), 7.94 (d, J = 9.2 Hz, 1H, aromatic), 7.95 (s, 1H, aromatic);

MS m/z 567 (MH+), 511, 479, 467, 411, 379, 323.

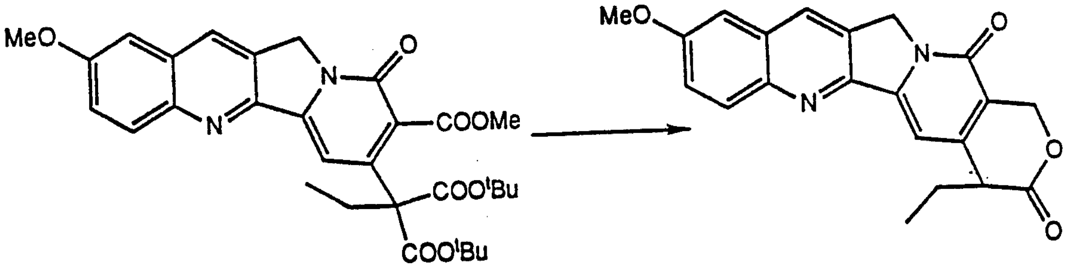
Step 9



A mixture of the starting material (1.84g, 3.25 mmol) and sodium nitrite (1.15g, 95% purity, 5 eq.) in 39 ml of 10:3 acetic acid:water was stirred at 65 °C 8 h. The reaction mixture was cooled to ambient temperature and poured into 300 ml of ice-water. The mixture was extracted with 3 x 200 ml of methylene chloride and the organic layers were dried over magnesium sulfate. The organic layer was concentrated on a rotavapor to give 1.8 g of yellow solid (98% crude yield) which was pure enough to carry directly on to the next reaction. An analytical sample was obtained by recrystallization from methylene chloride:hexane, mp 198-200 °C.

IR (KBr) 1742, 1730, 1649, 1623, 1605, 1510, 1370, 1254, 844, 834 cm^{-1};
^1H NMR (δ, $CDCl_3$): 1.00 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.50 (s, 9H, CCH_3), 2.38 (q, J = 7.4Hz, 2H, CH_2CH_3), 3.89 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.27(s, 2H, CH_2NH), 7.15 (d, J = 2.7Hz, 1H, aromatic), 7.25 (s, 1H, aromatic), 7.45 (d,d, J = 9.3, 2.8 Hz, 1H, aromatic), 8.09 (d, J = 9.4 Hz, 1H, aromatic), 8.24 (s, 1H, aromatic);
MS m/z 565 (MH+), 509, 493, 477, 465, 453, 409, 393, 377, 365, 333.

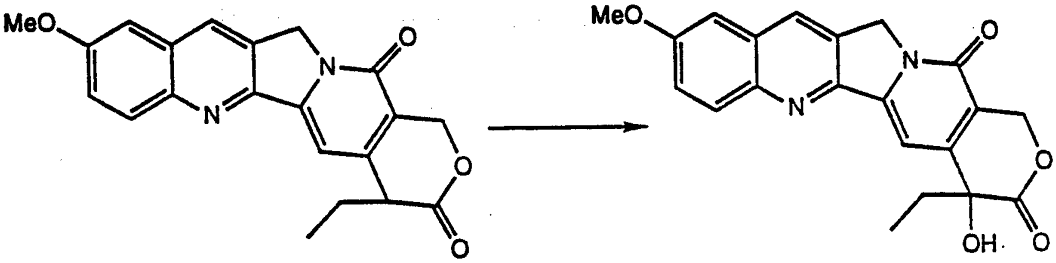
Step 10



To a solution of starting material (1.24g, 2.2 mmol) in dimethoxyethane (50 ml) was added DIBAL (11 ml, 1.0M in hexane, 5 eq.) dropwise at 0 °C. The colour turned from yellow to blue and finally to dark brown. After the addition was complete, the mixture was stirred at 0 °C for 1h and poured into a ice water (300 ml). The mixture was extracted with 3 x 250 ml of methylene chloride. The organic layers were dried and evaporated to give 1.18 g of yellow solid, to which was added a 50 ml of 3:2 methanol:hydrochloric acid. Soduim borohydride (200 mg, 3 eq.) was added in small portions to this stirred solution and the resulting mixture was stirred for 15 minutes after addition was complete. The solvent was removed on a rotavapor and dilute hydrochloric acid (50 ml of 0.4% solution) was added to the residue. The mixture was extracted with 3 x 100 ml of methylene chloride. The combined organic layers were dried over magnesium sulfate and concentrated to give a dark solid to which trifluoroacetic acid (20 ml) was added. The mixture was stirred at ambient temperature for 1 h. Trifluoroacetic acid was removed on a rotavapor and water (50 ml) was added to the residue. The mixture was extracted with 3 x 100 ml of methylene chloride.The combined organic layers were dried over magnesium sulfate and concentrated to give 774 mg of crude product (98% yield) which was carried directly on to the next reaction. An analytical sample was obtained by recrystallization from methylene chloride:hexane, mp 259-261 °C.

IR (KBr) 1735, 1657, 1604, 1506, 1243, 825cm^{-1};
^{1}H NMR (δ, CDCl3): 1.09 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.09 (m, 2H, CH_2CH_3), 3.61 (t, J = 6.5 Hz, 1H, CHCOO), 3.98 (s, 3H, OCH_3), 5.27 (s, 2H, CH_2NH), 5.39, 5.56 (AB, d, J = 16.0 Hz, 2H, CH_2OCO), 7.13 (s, 1H, aromatic), 7.16 (d, J = 2.7 Hz, 1H, aromatic), 7.47 (d, d, J = 19.3, 2.7Hz, 1H, aromatic), 8.10 (d, J = 9.3 Hz, 1H, aromatic), 8.25 (s, 1H, aromatic);
MS m/z 363 (MH$^+$), 333, 319.

Step 11

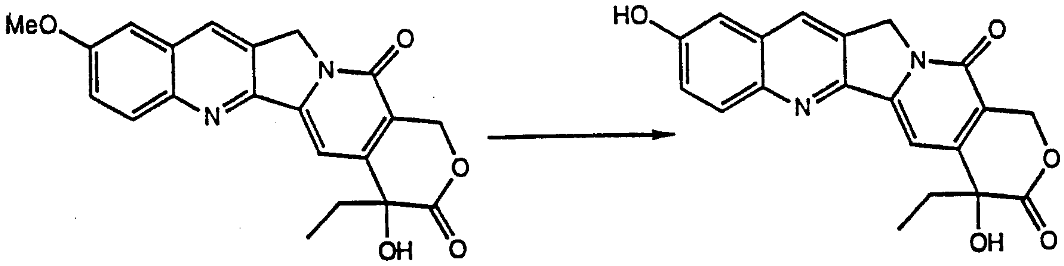


To a solution of starting material (665 mg, 1.84 mmol) in 60 ml of N,N-dimethylformamide was added piperidine (3.2 ml) and oxgen gas was bubbled through the solution for 6 h with stirring. DMF was removed on a rotavapor to give 680 mg of brown solid, mp 278 -280 °C (100%). The crude product showed >95%

total area response for the desired product as indicated by HPLC, and was carried on as obtained.

IR (KBr) 3400, 1738, 1656, 1600, 1512, 1267, 1165, 1156, 1105, 825cm^{-1};
^{1}H NMR (δ, $CDCl_3$): 1.05 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.91 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.70 (s, 1H, OH), 3.99 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2NH), 5.32, 5.76 (AB, d, J = 15.8 Hz, 2H, CH_2OCO), 7.17 (s, 1H, aromatic), 7.48 (d, J = 10.0 Hz, 1H, aromatic), 7.62 (s, 1H, aromatic), 8.13 (d, J = 9.3 Hz, 1H, aromatic), 8.27 (s, 1H, aromatic);
MS m/z 379 (MH^+), 335, 333.

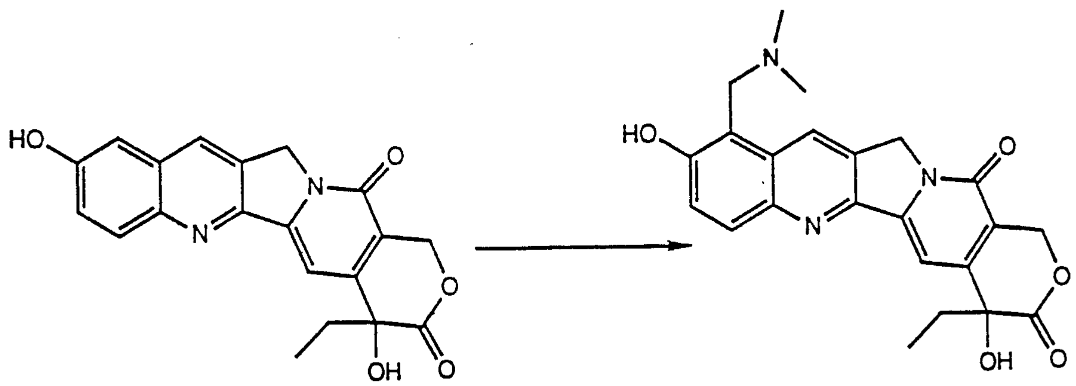
Step 12



A mixture of starting material (60 mg, 0.16 mmol) and HBr (48% solution, 3 ml) was refluxed at 155 °C for 2 h. The reaction mixture was cooled to ambient temperature. Water (50 ml) was added and the mixture was extracted with methylene chloride:methanol. The organic layers were dried over magnesium sulfate and concentrated to give crude product which was purified by silica gel chromatography using a chromatotron to give the desired product (42 mg, 72% yield) with mp 269 - 272 °C which was spectroscopically and chromatographically identical to a sample prepared independently by semisynthesis from naturally-occurring camptothecin.

^{1}H NMR (δ, DMSO-d_6): 0.87 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.85 (hept, J = 7.3 Hz, 2H, CH_2CH_3), 5.22 (s, 2H, CH_2N), 5.40 (s, 2H, CH_2OCO), 7.25 (s, 1H, aromatic), 7.28 (s, 1H, aromatic), 7.41 (d, J = 9.1 Hz, 1H, aromatic), 8.01 (d, J = 9.1 Hz, 1H, aromatic), 8.45 (s, 1H, aromatic);

Step 13



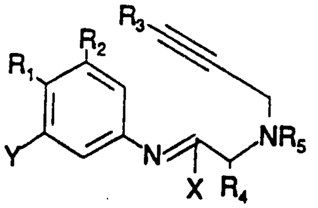
To a solution of starting material (20 mg, 0.05 mmol) in 3 ml of 2:1 methylene chloride:1-propanol was added 0.05 ml (1.5 eq) of N,N,N',N'-tetramethyldiaminomethane (BDAM) and the mixture was stirred at ambient temperature for 16 h. Hydrochloric acid (1 ml of 37% aqueous in 5 ml of 1-PrOH) was slowly added and the mixture was stirred at ambient temperature for another 5h. The solvent was removed *in vacuo* to give a hygroscopic, brown semisolid which was purified by reverse-phase HPLC (acetonitrile:water:trifluoroacetic acid; 16 : 84 : 1.5) to give racemic SK&F 104864 in approximately 88% yield from 10-hydroxycamptothecin. The identity of the product was confirmed by comparison of NMR and Mass spectra as well as chromatographic behavior with an authentic sample of the desired product.

^{1}H NMR (δ, DMSO-d_6): 0.87 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.86 (hept, J = 7.0 Hz, 2H, CH_2CH_3), 2.84 (s, 6 H, NCH_3), 4.72 [s, 2H, $CH_2N(CH_3)_2$], 5.28 (s, 2H, CH_2N), 5.41 (s, 2H, CH_2OCO), 6.50 (s, 1H, OH), 7.28 (s, 1H, aromatic), 7.64 (d, J = 9.2 Hz, 1H, aromatic), 8.18 (d, J = 9.2 Hz, 1H, aromatic), 8.91 (s, 1H, aromatic); MS m/z 422 (MH^+), 377, 307, 289, 220, 154, 136, 107, 77.

The overall yield of topotecan for the total synthesis in 13 steps was about 5-6%.

We claim:

1. A process for preparing a compound selected from the group consisting essentially of pyrrolo[3,4-*b*]quinolines, 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-diones, and 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-ones, said process comprising the step of intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV:



IV

where:

X=OH, OAlCl$_2$, Cl, Br, I, F, OR, OSO$_2$CF$_3$ or any good leaving group or H

R_1 = H, OH, or OR, where R is an ester protecting group;

R_2 = H, NO$_2$, or a protected amine function;

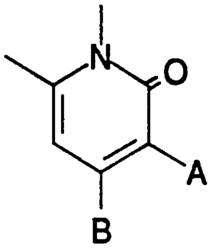
R_3 = H, C$_2$H$_5$, or a trialkylsilyl;

R_4 = H or CH$_2$COOEt;

R_5 = COOMe or tosyl; or

R_4 and R_5 are joined together to form a substituted pyridone IVa:

Y=H or Y,R_1 = -OCH$_2$O-



IVa

where:

A = H, COOR, or a functionality for preparation of the hydroxymethyl (C-17) portion of an E ring lactone;

B = H, OH, an appropriate leaving group such as halide or O(trifluoromethanesulfonate) or a functionality for preparation of C-(18-21) of the E ring lactone portion of camptothecin.

with the unactivated acetylene portion of said compound.

2. A process according to Claim 1 wherein said step further comprises heating said compound of Formula IV, a compound Formula III, corresponding to in a polar solvent at a temperature of about 20-85°C in the presence of an agent selected from the group consisting essentially of a strong alkylating agent, such agent as is capable of producing either an O-alkylimidate or imidate ester, imidoyl halide, and such imide derivative as is capable of cyclodehydration.

3. A process according to Claim 2 wherein said polar solvent is selected from a group consisting essentially of methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone and N-methylpyrrolidinone.

4. A process according to Claim 3 wherein said polar solvent is acetonitrile.

5. A process according to Claim 2 wherein said temperature is about 60-85°C.

6. A process according to Claim 5 wherein said temperature is about the reflux temperature of acetonitrile.

7. A process according to Claim 2 wherein said strong alkylating agent or such agent as is capable of producing either an O-alkylimidate or imidate ester, imidoyl halide, or such imide derivative as is capable of cyclodehydration, is selected from a group consisting essentially of trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide

8. A process according to Claim 7 wherein said agent is trimethyloxonium tetrafluoroborate.

9. A process according to Claim 1 wherein said compound is a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione.

10. A process according to Claim 9 wherein said 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione is a camptothecin analog.

11. A process according to Claim 10 wherein said camptothecin analog is a water-soluble camptothecin analog.

12. A process according to Claim11 wherein said water-soluble camptothecin analog is selected from the group consisting essentially of topotecan and irinotecan.

13. A process according to Claim12 wherein said water-soluble camptothecin analog is topotecan.

14. A process according to Claim 1 wherein said compound is a 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one.

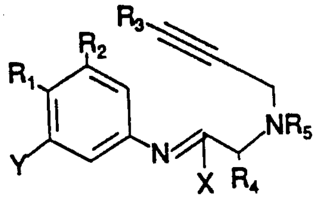
15. A process according to Claim 14 wherein said 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one is a mappicine.

16. A process according to Claim 14 wherein said 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one is a mappicine ketone.

17. A process for preparing a 7-(1,1-*bis*-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one, said process comprising the step of coupling a vinyl triflate derived from a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion.

18. A process for preparing a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV:



IV

where:

X=OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H

R_1 = H, OH, or OR, where R is an ester protecting group;

R_2 = H, NO_2, or a protected amine function;

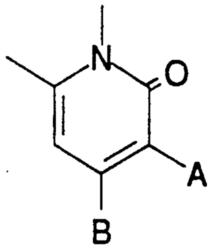
R_3 = H, C_2H_5, or a trialkylsilyl;

R_4 = H or CH_2COOEt;

R_5 = COOMe or tosyl; or

R_4 and R_5 are joined together to form a substituted pyridone IV:

Y=OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H



IVa

where:

A = H, COOR, or a functionality for preparation of the hydroxymethyl (C-17) portion of an E ring lactone;

B = H, OH, an appropriate leaving group such as halide or O(trifluoromethanesulfonate) or a functionality for preparation of C-(18-21) of the E ring lactone portion of camptothecin.

with the unactivated acetylene portion of said compound to form a 2-(acetate ester) substituted pyrrolo [3,4-*b*]quinoline;

(b) cyclizing said 2-(acetate ester) substituted pyrrolo[3,4-*b*]quinoline to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 with an (alkyl malonate) diester;

(c) coupling a 7-substituted vinyl triflate of said 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 an (alkyl malonate) diester; and

(d) converting said 7-(1,1-*bis*-alkoxycarbonyl)propyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione.

19. A process according to Claim 18 wherein said step (a) further comprises heating a compound of Formula III, corresponding to said compound of Formula IV, in a polar solvent at a temperature of about 20-85°C in the presence of an agent selected from the group consisting essentially of a strong alkylating agent; such agent as is capable of producing either an O-alkylimidate or imidate ester; imidoyl halide; and such imide derivative as is capable of cyclodehydration.

20. A process according to Claim 19 wherein said polar solvent is selected from a group consisting essentially of methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone and N-methylpyrrolidinone.

21. A process according to Claim 20 wherein said polar solvent is acetonitrile.

22. A process according to Claim 19 wherein said temperature is about 60-85°C.

23. A process according to Claim 22 wherein said temperature is about the reflux temperature of acetonitrile.

24. A process according to Claim 19 wherein said strong alkylating agent or such agent as is capable of producing either an O-alkylimidate or imidate ester, imidoyl halide, or such imide derivative as is capable of cyclodehydration, is selected from a group consisting essentially of trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide.

25. A process according to Claim 19 wherein said agent is trimethyloxonium tetrafluoroborate.

26. A process according to Claim 18 wherein said compound is a camptothecin analog.

27. A process according to Claim 26 wherein said camptothecin analog is a water-soluble camptothecin analog.

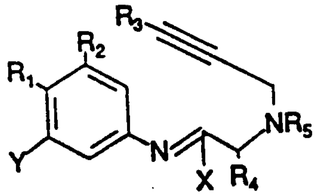
28. A process according to Claim 27 wherein said water-soluble camptothecin analog is selected from the group consisting essentially of topotecan and irinotecan.

29. A process according to Claim 28 wherein said water-soluble camptothecin analog is topotecan.

30. A process according to Claim 1 wherein R_4 and R_5 of said compound of Formula IV are joined together to form a substituted pyridone.

31. A process for the total synthesis of topotecan,, said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV:



IV

where:

X=OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H

R_1 = OMe;
R_2 = H;
R_3 = H;
R_4 = CH_2COOEt; and
R_5 = COOMe;
Y=H or Y,R_1 = $-OCH_2O-$

with the unactivated acetylene portion of said compound by heating a compound of Formula III, corresponding to compound of Formula IV, in a polar solvent at a temperature of about 20-85 °C in the presence of a strong alkylating agent or such agent as is capable of transforming an amide into its corresponding O-alkylimidate or imidate ester, imidoyl halide, or a strong acid (such as aluminum chloride) capable of initiating a cyclodehydretion to yield a pyrrolo[3,4-*b*]quinoline substituted at C-2 by an acetate ester;

(b) hydrolyzing the carbamate function of the C-2 substituted pyrrolo[3,4-*b*]quinoline from step (a) with acetic acid saturated with HBr to give a tricyclic amine;

(c) coupling said tricyclic amine with a monoalkyl malonyl chloride, preferably monomethyl malonyl chloride, to give the half-amide of a malinate diester;

(d) subjecting said malonate half-amide to a Dieckmann condensation in the presence of an alkoxide to give a a tetracyclic enol;

(e) forming a vinyl triflate of said tetracyclic enol, and coupling said triflate with a tertiary malonate anion to form a 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(f) 1,2 elimination of hydrogen at the 5,6 bond to give 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-indolizino[1,2-*b*]quinolin-9(11H)-one;

(g) reduction of the 8-methoxycarbonyl group of the 7-(1,1-di-*tert*-butoxycarbonyl)propyl-8-methoxycarbonyl-indolizino[1,2-*b*]quinolin-9(11H)-one, followed by hydrolysis-decarboxylation of the diester group at C-7, and lactone formation to give a 4-ethyl-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione;

(h) forming a tertiary alcohol α to the E ring carbonyl of said 4-ethyl-9-methoxy-1H-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione to give 10-methoxycamptothecin;

(i) cleaving the methyl ether of said 10-methoxycamptothecin to yield 10-hydroxycamptothecin; and

(j) alkylating the 9-position of said 10-hydroxycamptothecin by reaction with N,N,N',N'-tetramethyldiaminomethane (BDAM) to give topotecan.

32. A process according to Claim 31 wherein said polar solvent is selected from a group consisting essentially of methylene chloride, 1,2-dichloroethane, 1,2-dimethoxyethane tetrahydrofuran, N,N-dimethylformamide, acetonitrile, acetone and N-methylpyrrolidinone.

33. A process according to Claim 32 wherein said polar solvent is acetonitrile.

34. A process according to Claim 19 wherein said temperature is about 60-85°C.

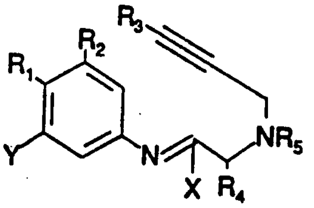
35. A process according to Claim 34 wherein said temperature is about the reflux temperature of acetonitrile.

36. A process according to Claim 31 wherein said strong alkylating agent or such agent as is capable of producing either an O-alkylimidate or imidate ester, imidoyl halide, or such imide derivative as is capable of cyclodehydration, is selected from a group consisting essentially of trifluoromethanesulfonic anhydride, dimethylsulfate, alkyloxonium tetrafluoroborates, aluminum chloride, O-benzyltrichloroacetimidate, triphenylphosine/carbon tetrachloride, or triphenylphosphine/carbon tetrabromide

37. A process according to Claim 32 wherein said agent is trimethyloxonium tetrafluoroborate.

38. A process for the preparation of a camptothecin analog which lacks the lactone E ring, said process comprising the steps of:

(a) intramolecular [4+2] cycloaddition of the N-arylimidate portion of a compound of Formula IV:



IV

where:

X=OH, $OAlCl_2$, Cl, Br, I, F, OR, OSO_2CF_3 or any good leaving group or H

R_1 = H, OH, or OR, where R is an ester protecting group;

R_2 = H, NO_2, or a protected amine function;

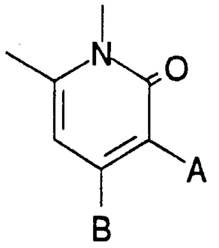
R_3 = H, C_2H_5, or a trialkylsilyl;

R_4 = H or CH_2COOEt;

R_5 = COOMe or tosyl; or

R_4 and R_5 are joined together to form a substituted pyridone IV:

Y=H or Y,R_1= $-OCH_2O-$



IVa

where:

A = H, COOR, or a functionality for preparation of the hydroxymethyl (C-17) portion of an E ring lactone;

B = H, OH, an appropriate leaving group such as halide or O(trifluoromethanesulfonate) or a functionality for preparation of C-(18-21) of the E ring lactone portion of camptothecin;

with the unactivated acetylene portion of said compound to give a pyrrolo[3,4-*b*]quinoline substituted with an acetate ester at C-2;

(b) cyclizing the 2-substituted pyrrolo[3,4-*b*]quinoline to form a 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one;

(c) coupling a 7-trifluoromethanesulfonate derivative of the 7-hydroxy-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one with a tertiary malonate anion to form a 5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one substituted at C-7 with an (alkyl)malonate diester;

(d) converting the 7-(1,1-bis-alkoxycarbonyl)propyl-8-methoxycarbonyl-5,6-dihydroindolizino[1,2-*b*]quinolin-9(11H)-one into the lactone E ring of a 1H-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4H,12H)-dione, preferably a camptothecin analog; and

(e) opening the E ring of said camptothecin analog with extrusion of, depending upon choice of termination step, carbon dioxide to provide a camptothecin analog which lacks the lactone E ring, preferably a mappicine or mappicine ketone.

39. A process according to Claim 38 wherein said camptothecin analog which lacks the lactone E ring is an 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one.

40. A process according to Claim 39 wherein said 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one is a mappicine.

41. A process according to Claim 39 wherein said 8-methyl-7-(oxopropyl)-indolizino[1,2-*b*]quinolin-9(11H)-one is a mappicine ketone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08434

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 491/14, 401/02
US CL :546/70, 85, 48, 41, 14
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)

U.S. : 546/70, 85, 48, 41, 14; 514/283, 279

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 practicable, search terms used)

CAS Reacts, CAFile "Intramolecular [4+2] cycloaddition" and CAS Online Sructure Search of Scheme 4 formula VIII

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Tetrahedron letters, Vol. 27, No. 40, issued 1986, K.J. Shea et al. "The Intramolecular Diels-Alder Cycloaddition of N Dienoyl Acrylimidates. New Methodology for the Construction of Nitrogen Heterocycles" pages 4837-40, see Scheme 1, page 4839.	1, 9-16, 30
A	Tetrahedron, Vol. 44, No. 13, issued 1985 C. Clarke et al., "An Approach to the Synthesis of Gelsemine: The Intramolecular Reaction of an Allylsilane with an acyliminium Ion for the Synthesis of the Quaternary Centres" pages 3931-44.	1

☒ 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 part of particular relevance

"E" earlier document 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 05 November 1993	Date of mailing of the international search report 30 NOV 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer D.G. DAUS Della Collins for
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 00-017,499 (Nippon Chemifar) 09 February 1977.	15,16
A	JP, A, 49-117,491 (Shionogi) 09 November 1974.	1
A,P	US, A, 5,155,225, (Fortunak et al.) 13 October 1992.	14
Y	Tetrahedron Letters, Vol. 32, No. 52, issued 1991 D.L. Boger et al. "Studies on the Synthesis of Rubrolone; 4π Participation of O-Alkylα, β, Unsaturated Oximesin Intramolecular [4+2] cycloaddition reactions", pages 7643-46, see page 7643 Scheme 1 and page 7645.	1, 9-16, 30
Y	JP, A, 03-083,986 (Nagao et al) 09 April 1991, see page 3, Structure VII.	9-16
A	JP, A, 4,702,598 (Tanaka et al) 19 October 1972, see entire document.	1
Y	Jour. Am. Chem. Soc., Vol. 114, issued July 1992, Curran et al. "New 4+1 Radical Annulations. A formal total synthesis of ($\pm$) camptothecin" pages 5863-4. See entire document.	30
A	Jour. Am. Chem. Soc., Vol. 111, issued 1989, Hayakawa et al. "Competitive Intramolecular [4+2] cycloaddition and Tandem [2+2] cycloaddition [3,3]-sigma-tropic rearrangement sequence of Allenyl^3-vinyl-2-cyclohexene ethers: Evidence for switching of the reactive pathway by the substituent effects. See pages 5312-20.	1
A	DE, A, 2534601 (BASF) 17 February 1977. See entire document.	1
A	US, A, 4,914,205 (Sawada et al.) 03 April 1990.	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08434

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(Telephone Practice)
Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 9-16, 30

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

In the examination of international applications filed under the Patent Cooperation Treaty, PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventios so linked as to form "single general inventive concept".

Additionally, current United States Patent and Trademar Office practice permits the following combinations of the claimed invention:

(1) a product, and a process specifically adapted for the manufacture of said product, and
(2) a product, and a use of the said product, as where said use as claimed cannot be practiced with another materially different product.

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1 (part) 9-16 and 30 (part), drawn to process step (a), intramolecular (4+2) cyclo addition, classified in Class 546, subclasses 14, 70, 85 and others.

Group II, claims 1 (part), 2-8 and 30 (part), drawn to process step (A^1) alkylation of step (A) product, classified in Class 546, subclasses 14, 85 and others.

Group III, claim 17, drawn to coupling process step (c), classified in Class 546, subclass 62.

Group IV, claim 18 (part) and 26-29, drawn to four step (a)(b)(c)(d) process, classified in Class 546, subclasses various.

Group V, claims 1 (part) and 19-25, drawn to four step process where A <u>also</u> alkylates, classified in Class 546, subclass various.

Group VI, claims 31-37, drawn to process for topotecans, steps (a) to (j), step (c)(d) being different than V, classified in Class 546, subclass 52.

Group VII, claims 38-41, drawn to process for camptothecin analogs steps (a) to (e), where steps (d) and (e) are different than in VI, classified in Class 546, subclasses 48, 52 and others.

The inventions listed as Groups I to VII do not meet the requirements for Unity of Invention for the following reasons:

There is no common special technical feature shared by all groups. Process steps (a), Group I is independently used in combinations IV, VI and VII, with <u>differing</u> steps (c), (d) and (e). Where there are multiple uses of I, as here, a finding of a lack of unity authorized. Groups IV, VI, VII evidence I and II are independent of any one of IV, V, VII. The Group II alkylation step (A^1) isn't used in all of, say, IV, only Group V part of claim 18. The coupling step (c), group III isn't used in all the other groups, being independent of many, Eg. of I and II.

The groups are independent of each other.

Different issues of novelty and inventive step arise. Art anticipatory of Group I wouldn't even be pertinent to III and vice versa. Different reference and combinations of references would be applicable to the different step series of IV to VII.

The groups I to VII are distinct. Because the inventions as grouped are both distinct and independent, and there is no common special technical feature a finding of a lack of unity proper.