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(54) Title: PROCESS AND NOVEL INTERMEDIATES

(57) Abstract

This invention provides intermediates and processes useful for the preparation of crytophycin compounds.

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PROCESS AND NOVEL INTERMEDIATES

This invention relates to the fields of pharmaceutical and organic chemistry and provides novel intermediates and processes useful for the preparation of cryptophycin compounds.

Antimetabolites have been used for a number of years as chemotherapeutic agents in the treatment of cancer. A new class of antimetabolites, cryptophycin compounds are useful for disrupting the microtubule system and, thus, can be useful for the treatment of cancer. In order to produce sufficient quantities of these compounds, there is a need for efficient totally synthetic processes for their preparation.

The novel processes and intermediates of this invention are important elements in providing an efficient route for preparing other cryptophycin intermediates. A special advantage provided is that the intermediates thus prepared have only minimal residual impurities. Ultimately, these intermediates can be linked to provide a total synthesis of cryptophycin compounds.

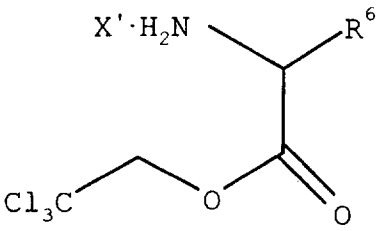
A number of problems must be resolved in order to accomplish a large scale total synthesis of a complex molecule such as the cryptophycin molecule. It is difficult to obtain intervening intermediates of sufficient purity, to be able to handle the materials easily and to obtain reliable yields when processes are carried out on the scale

needed to obtain the quantities of compounds needed for pharmaceutical purposes.

The novel intermediates and processes of this invention accomplish some of these goals. For example, one of the processes permits removal of a protecting group to provide an intermediate that can now be isolated as a convenient white solid. The new coupling process results in unexpectedly greater yields and avoids what previously was an extra step of preparing a pentafluorophenyldiphenyl-phosphinic chloride coupling reagent. A rhodium-catalyzed process prepares a novel fragment, called Fragment C', that is useful for an alternative synthesis of cryptophycin compounds. Another process that is applicable to acid-and base sensitive products minimizes recrystallization and chromatography steps.

Thus, the processes and intermediates of this invention are important advances in the synthesis of useful cryptophycin compounds. These advances include, but are not limited to, increased efficiency, decreased cost, and improved purity.

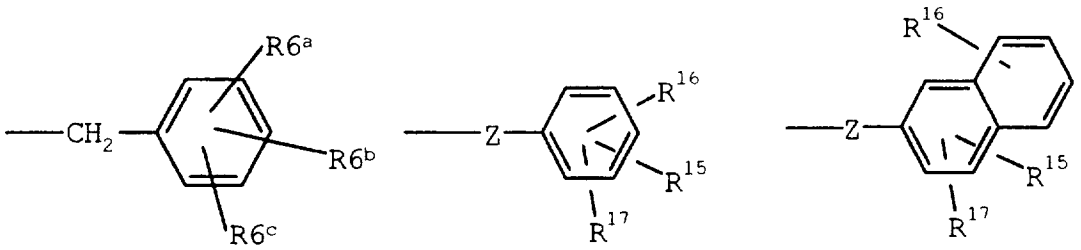
In one aspect, this invention provides a novel intermediate of Formula **XII**



XII

wherein **X'** represents a strong acid; and

R^6 is C_1-C_6 alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III'or III":



IIIa **III'** **III''**

wherein

R^{6a}, **R^{6b}**, and **R^{6c}** independently are H, halo or OR^{18};

R^{15}, **R^{16}**, and **R^{17}** independently are hydrogen, halo, (C_1-C_6)alkyl, OR^{18}, O-aryl, NH_2, $NR^{18}R^{19}$, NO_2, OPO_4H_2, (C_1-C_6 alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H, PO_3H_2, SO_2R^{23}, or Z';

R^{18} and **R^{19}** independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or (C_1-C_3)alkyl;

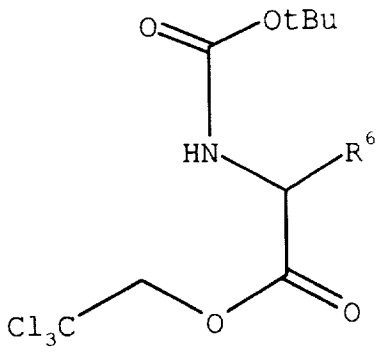
Z is $-(CH_2)_n-$ or (C_3-C_5)cycloalkyl;

n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group.

Further, this invention provides a process for preparing an intermediate of Formula **XII** as defined supra, **comprising**

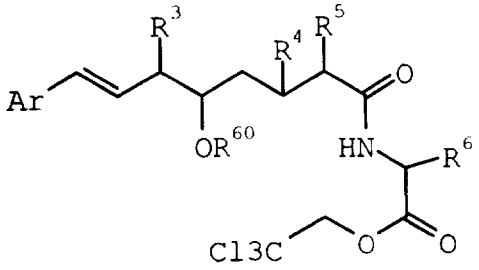
contacting a compound of the formula **XII'**



XII'

with a strong acid.

In another aspect, this invention provides a new coupling process for preparing compounds of Formula **XIII** (known as Fragment A-B of the cryptophycins):



XIII

wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

R^{60} is an alcohol protecting group;

R^3 is C_1-C_6 alkyl;

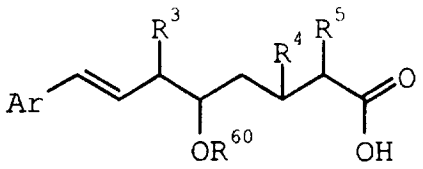
R^4 and R^5 are H; or

R^4 and R^5 together form a second bond;

R^6 is as defined supra;

comprising contacting a compound of Formula **XII** as defined supra,

with 1) a compound of Formula **XV**



XV

wherein Ar, R^3, R^4, R^5 and R^{60} are as defined supra;

2) an $(R^A)_2$phosphinic halide, wherein R^A is C_1-C_6 alkyl, C_1-C_6 aralkyl, or Ar; and 3) a base.

Furthermore, this invention provides an improved process for preparing a compound of Formula **XIII**, as defined supra,

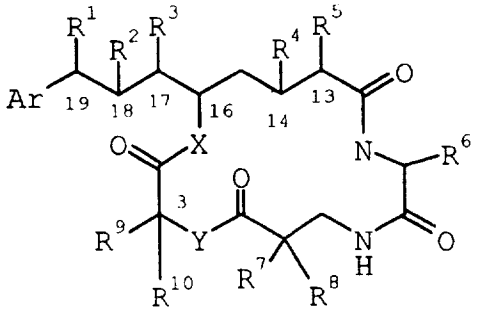
comprising

reacting a compound of Formula **XII**, as defined supra, with a compound of formula **XV** as defined supra, in the presence of 1) the coupling reagent diphenyl chlorophosphate $[(PhO)_2P(O)Cl]$;and 2) an amine.

Carboxyl activation *via* phosphorous based reagents is an often used method for the synthesis of amides and related

compounds. The particular method employed by Barrow *et al.* (J. Am. Chem. Soc. 1995, **117**, 2479-2490) for the synthesis of the formula XIII compound wherein Ar=Ph, R^3=Me, R^{60}=TBS, R^4 and R^5=a second bond; and R^6=3-chloro-4-methoxybenzyl (compound **4** *infra*) utilized pentafluorophenyl diphenylphosphinic chloride (FDPP) as the coupling reagent. That reaction only afforded compound **4** in 65% yield after silica gel chromatography. Thus, that method suffered from low yield (65%) and required FDPP preparation because it is not commercially available. The improved coupling procedure of this invention is advantageous in that it does not require preparation of the reagent [$(PhO)_2P(O)Cl$], and it gives higher yields (78%). Additionally, using $(PhO)_2P(O)Cl$ provides a significant cost advantage.

In yet another aspect, this invention provides a process for preparing a compound of Formula I



I

wherein

Ar , R^3, R^4, R^5 and R^6 are as defined supra;

$\mathbf{R^1}$ is halo, SR, OR, amino, mono or di-(C_1-C_6-alkyl)amino,

tri(C_1-C_6-alkyl)ammonium, C_1-C_6-alkylthio, di(C_1-C_6-alkyl)sulfonium, C_1-C_6-alkylsulfonyl, or C_1-C_6-alkylphosphonyl; and

R^2 is OH or SH; or

R^1 and **R^2** taken together form a second bond between C-18 and C-19 or together form an epoxide, aziridine, episulfide, or cyclopropyl ring;

R is H, C_1-C_6 alkyl, C_1-C_6 alkanoyl or Ar;

R^7 is H, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, benzyl, or benzyl substituted with up to three substituents independently selected from C_1-C_6-alkyl, halo, C_1-C_6-alkoxy, amino or $NR^{51}R^{52}$; and

R^8 is H or C_1-C_6 alkyl; or

R^7 and **R^8** together form a C_3-C_8 cycloalkyl ring;

R^{51} and **R^{52}** independently are C_1-C_3 alkyl;

R^9 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6-alkynyl or (C_1-C_6 alkyl)C_3-C_5 cycloalkyl;

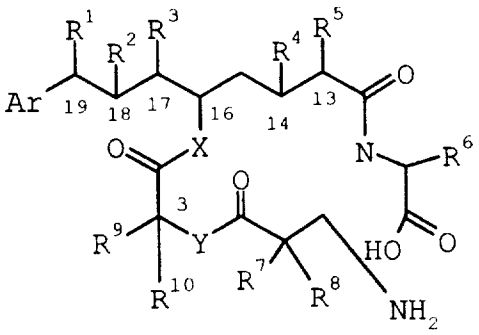
R^{10} is H or C_1-C_6 alkyl;

X is O, NH or (C_1-C_3 alkyl)N-; and

Y is C, O, NH, S, SO, SO_2 or (C_1-C_3 alkyl)N-;

comprising

contacting 1) a compound of Formula **XVI**



XVI

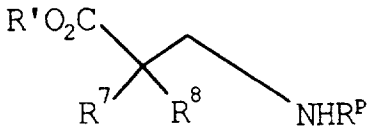
wherein Ar, X, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are as defined supra;

with 2) an $(R^A)_2$phosphinic halide,

wherein R^A is as defined supra; and

3) a base.

This invention also provides a process for preparing a compound of Formula **XVII**



XVII

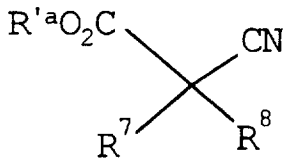
wherein R' is hydrogen or C_1-C_6 alkyl;

R^7 and R^8 are as defined supra; and

R^P is *tert*-butoxycarbonyl or benzyloxycarbonyl;

comprising

contacting a compound of Formula **XVIII**



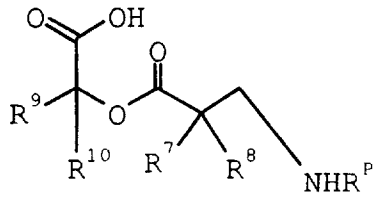
XVIII

wherein R'^a is C_1-C_6 alkyl,

with a rhodium catalyst and hydrogen gas; and optionally hydrolyzing the product to obtain the compound wherein R' is hydrogen.

Processes where R^7=R^8 are preferred embodiments of this invention.

In another aspect, this invention provides a process for preparing a compound of Formula **XIX**



XIX

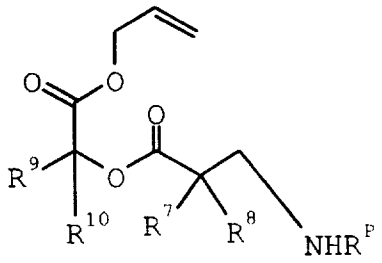
wherein

R^7, R^8, R^9 and R^{10} independently are H or C_1-C_6 alkyl;

R^P is *tert*-butoxycarbonyl (BOC) or benzyloxycarbonyl;

comprising

contacting a compound of Formula **XX**



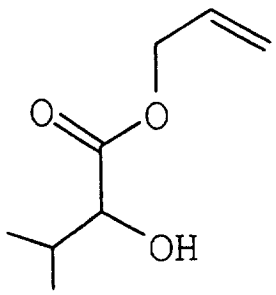
XX

in the presence of

1) a catalytic quantity of $Pd(PPh_3)_4$, wherein the catalytic quantity is less than about four (4) mole percent, and

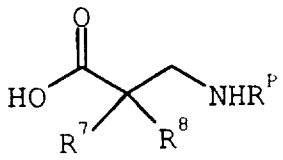
2) an allyl scavenger.

In addition, this invention provides an improvement in the process for preparing a compound of formula **XX** by coupling a Fragment **D** compound of the formula:



D

and a Fragment **C** compound of the formula:



C

wherein R^7 and R^8 are as defined supra, but provided R^7 and R^8 cannot be H, in an inert organic solvent;
the improvement **comprising** using the coupling reagent 1,1'-carbonyldiimidazole (CDI). This process provides a significant improvement in yields of Fragment **C** compound. In addition, costs are reduced, and it is easier to remove unwanted by-products.

The phrase "catalytic quantity" refers to less than a stoichiometric amount, but an amount sufficient to achieve the desired results. The term is intended to have the meaning commonly understood in the art.

The term "alkyl" refers to an alkyl group with the designated number of carbon atoms. It may be saturated or unsaturated, and branched or straight chain. "Lower alkyl" means a C_1-C_5 alkyl group. Examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, propenyl, sec-butyl, n-pentyl, isobutyl, tert-butyl, sec-butyl, methyl-substituted butyl groups, pentyl, tert-pentyl, sec-pentyl, methyl-substituted pentyl groups and the like.

"Substituted alkyl" refers to a C_1-C_6 alkyl group that may include up to three (3) substituents containing one or more heteroatoms. Examples of such substituents are OH, NH_2, $CONH_2$, CO_2H, PO_3H_2 and SO_2R^{21} wherein $\mathbf{R^{21}}$ is hydrogen, C_1-C_3 alkyl or aryl.

The term "cycloalkyl" refers to a saturated C_3-C_8 cycloalkyl group. A "substituted cycloalkyl group" refers

to a cycloalkyl group having up to three C_1-C_3 alkyl, halo, or OR^{21} substituents. The substituents may be attached at any available carbon atom. Cyclohexyl is an especially preferred cycloalkyl group.

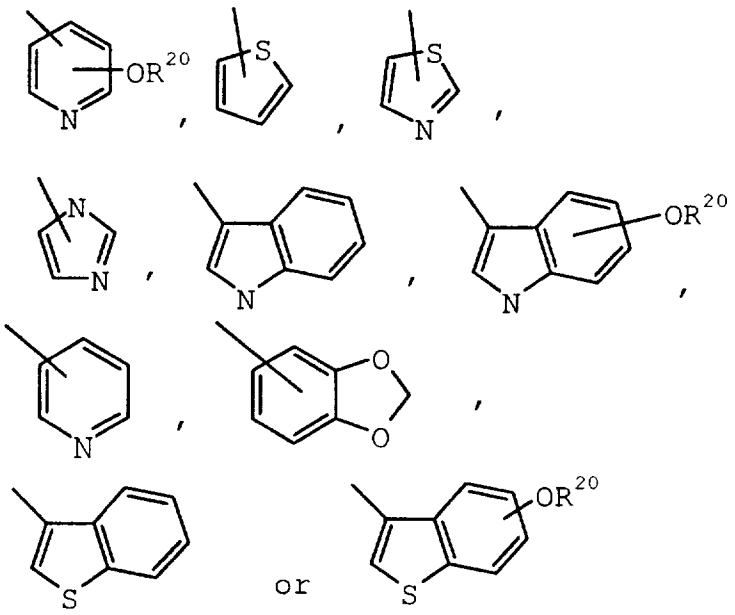
"Lower alkoxy" means a C_1-C_5 alkyl group bonded to an oxygen atom.

The term "allyl" means a 2-propenyl group. The term "allyl scavenger" is commonly understood in the art. Preferred allyl scavengers are pyrrolidine, piperidine, morpholine, and 1,3-dicarbonyl compounds. An especially preferred allyl scavenger is morpholine.

The term "halo" refers to Cl, Br, F, or I.

The terms "aromatic group" and "heteroaromatic group" refer to common aromatic rings having 4n + 2 pi electrons in a monocyclic or bicyclic conjugated system. The term "aryl" refers to an aromatic group, and the term "aralkyl" refers to an aryl(C_1-C_6-alkyl) group. Examples of aromatic groups are phenyl, benzyl and naphthyl. Heteroaromatic groups will contain one or more oxygen, nitrogen and/or sulfur atoms in the ring. Examples of heteroaromatic groups include furyl, pyrrolyl, thienyl, pyridyl and the like. When the aromatic or heteroaromatic groups are substituted, they may have from one to three independently selected C_1-C_7 alkyl, C_1-C_6-alkoxy or halo substituents. The substituents may be attached at any available carbon atom.

Especially preferred heterocyclic groups are



wherein R^{20} is hydrogen or C_1-C_6 alkyl.

The term "amino protecting group" refers to a standard amino protecting group that is either acid labile or can be removed under mildly basic to neutral conditions. Such groups are well known in the art. [See, for example, J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, (London and New York, 1973); Greene, T.W. "Protecting Groups in Organic Synthesis", Wiley (New York, 1981)]. Peferred amino protecting groups are acid labile. An especially preferred amino protecting group for compounds of Formula **XVII** is tert-butoxycarbonyl ("BOC"). When the R^6 substituent in a Formula I compound contains an amino substituent, it must be protected using an amino protecting group.

The term "alcohol protecting group" is one that is introduced during a portion of the synthetic process to protect an alcohol group that might otherwise react in the course of chemical manipulations. The group is then removed at a later stage of the synthesis. Reactions for the formation and removal of such protecting groups are described in a number of standard works, including the two references listed supra. A particularly useful alcohol protecting group is tert-butyldimethylsilyl (TBS).

The processes of this invention are preferably carried out in the presence of a solvent. Selection of an appropriate solvent is commonly understood in the art. An inert organic solvent, such as N,N-dimethylformamide (DMF), ethyl acetate, dichloromethane, toluene or acetonitrile, or a mixture thereof, is recommended.

"Epoxide ring" means a three-membered ring whose backbone consists of two carbon and one oxygen atoms. "Aziridine ring" means a three-membered ring whose backbone consists of two carbon and one nitrogen atoms. "Episulfide ring" refers to a three-membered ring whose backbone consists of two carbon and one sulfur atoms.

Examples of methods of halogenation include the addition of hydrogen halides, free radical halogenation, etc. Such methods are known in the art.

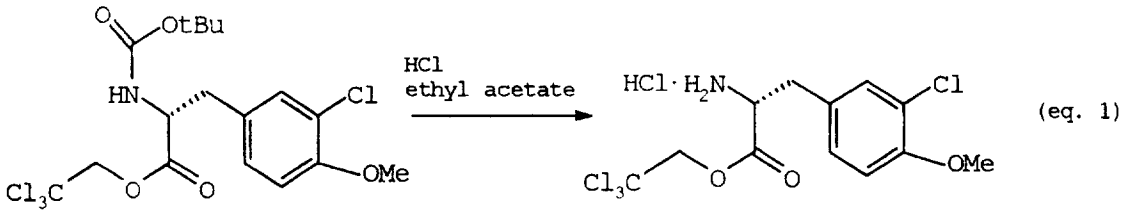
The term "strong acid" refers to an acid that has a pKa of 2 or less. A hydrohalic acid is most suitable. A

preferred hydrohalic acid is hydrochloric acid. Other mineral acids, such as phosphoric and sulfuric, and organic acids, such as tosic and acetic, may also be used.

The term "base" has its accepted meaning. Thus, a base is a compound that yields hydroxyl ions in water or the negative ion of a solvent; or a base is any molecule or ion that can combine with protons or hydrogen ions, i.e. a proton acceptor. The term includes, but is not limited to, N,N-diisopropylethylamine, carbonates, and other tertiary amines.

Many of the cryptophycin compounds prepared by the processes of this invention are known. As used herein, the term refers to both known cryptophycins and to new cryptophycin compounds of Formula I, as defined supra.

The process for preparing a formula XII compound that is a hydrochloride salt is illustrated by equation 1:



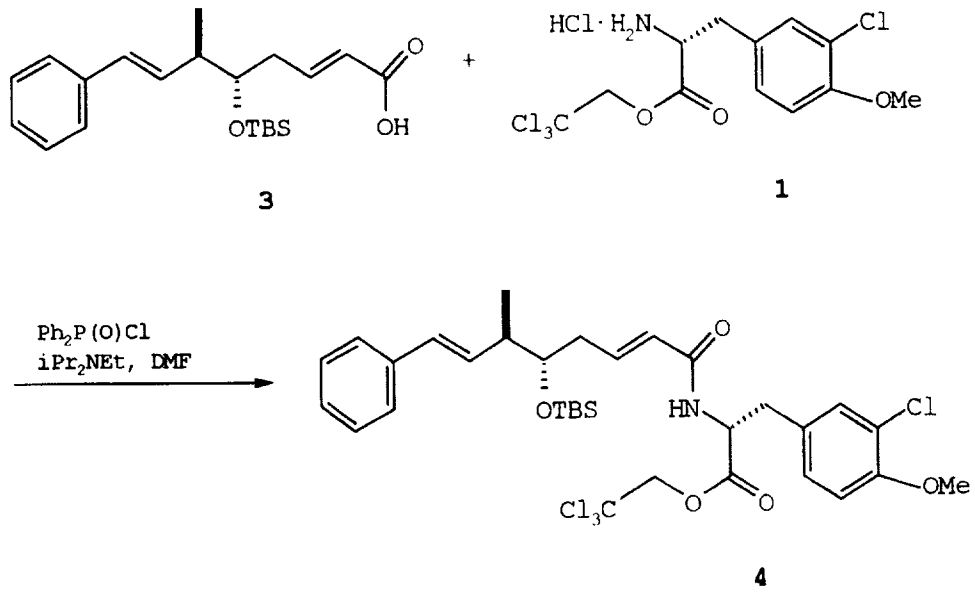
(eq. 1)

2 1

Other R^6 groups can be substituted for the chloromethoxy-benzyl group.

The first process for preparing the enamide fragment 4 is illustrated in equation 2.

(eq. 2)



In Eq. 2, TBS refers to a tert-butyldimethylsilyl group.

The improved process of preparing Fragment **4** is illustrated in Equation 3.

$$\mathbf{1} + \mathbf{3} \xrightarrow[\text{yield } 78\%]{(PhO)_2POCl,\ iPr_2NEt,\ DMF} \mathbf{4}$$

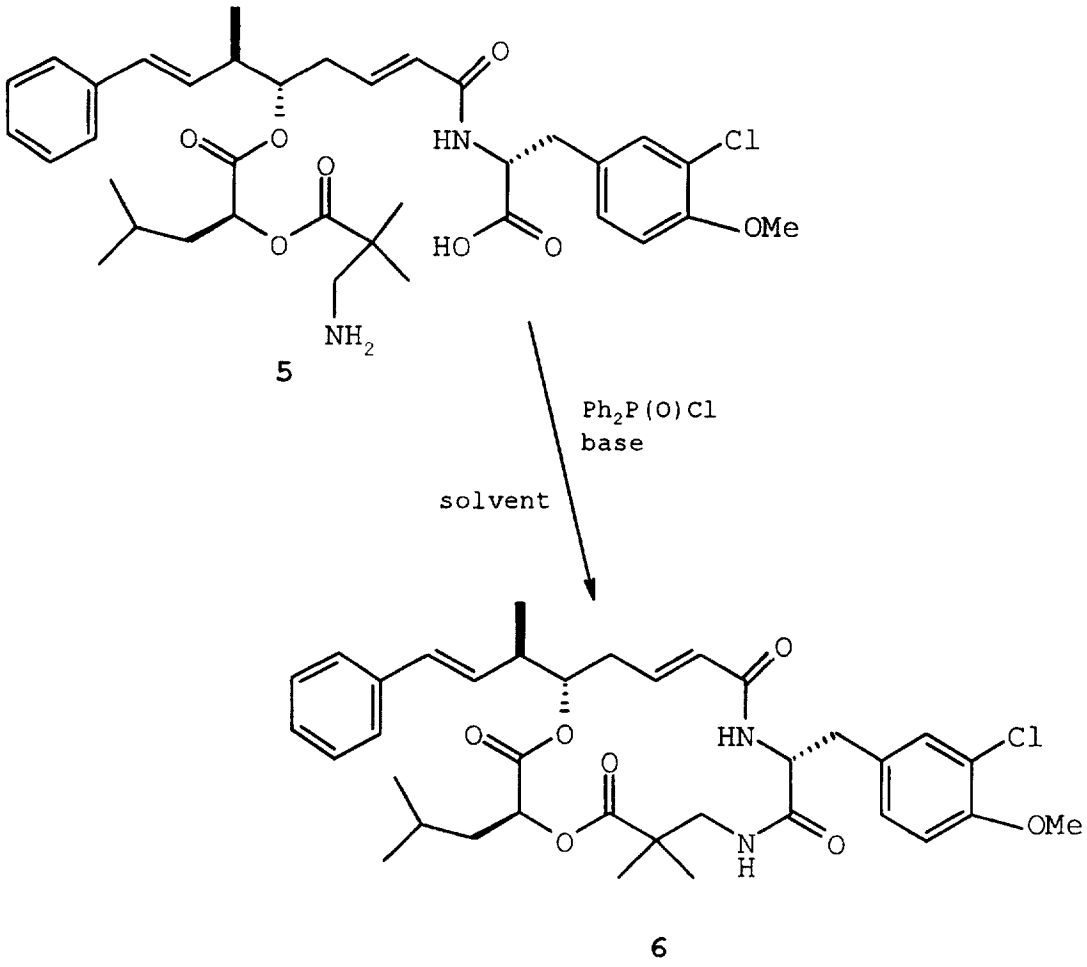
(eq. 3)

Equations **2** and **3** are applicable to corresponding intermediates having various Ar, R^{60}, and R^{6} groups.

Although DMF and N,N-diisopropylethylamine are the illustrated solvent-base used in equations **2** and **3**, and in that of equation **4** infra, any nonparticipating solvent or solvent combination-base will be appropriate for the processes. Typical solvents include ethers, halogenated hydrocarbons, and esters. Typical bases include tertiary

amines and carbonates. An especially preferred base for these processes is diisopropylethylamine.

The process for preparing an illustrative macrolactam of Formula **I** is illustrated by equation **4**:

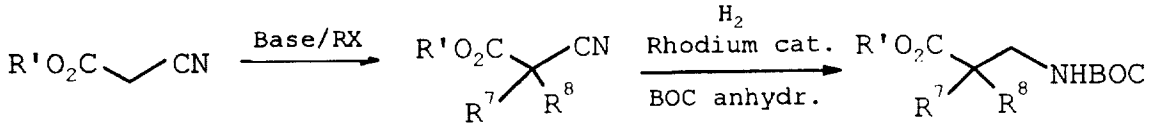


(eq. 4)

An especially preferred solvent for the process of eq. 4 is DMF. This process is especially useful because it provides improved yields. In addition, it makes it possible to use $Ph_2P(O)Cl$, which is commercially available, to complete the macrolactamization.

The process for preparing a compound of Formula

XVII wherein R^P=BOC is illustrated by Equation **5**.



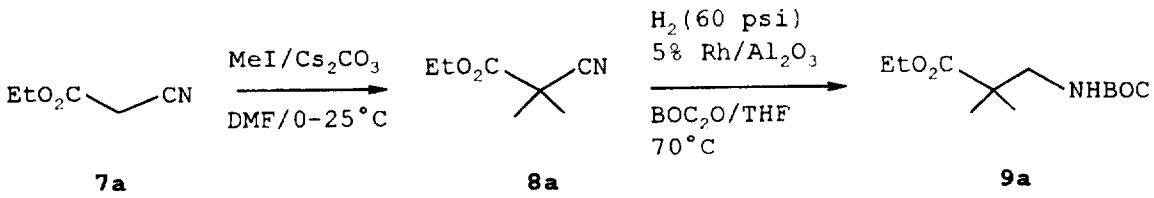
7 **8** **9**

X=Br, I, OTs

(eq. 5)

This process is especially useful because it is amenable to scale up, is cost effective, and provides good product yields.

Preparation of a specific compound of Formula **XVII** is illustrated by Equation **6**.



7a **8a** **9a**

10

(Fragment C')

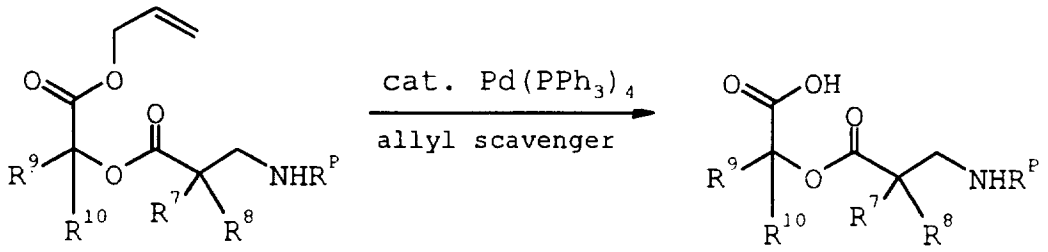
(eq. 6)

Compound **8a** is a known compound. It has been prepared by the reaction of ethyl cyanoacetate with methyl iodide in the presence of sodium ethoxide,[a,b] and sodium hydride.[c] [a) Hessler, J.C. *J. Am. Chem. Soc.* 1913, **35**, 990. b) Biechler, S.S. and Taft, R.W. *J. Am. Chem. Soc.* 1957, **79**,

4928. c) Thompson, H. W. and Swistok, J. *J. Org. Chem.* 1981, *46,* 4907].

Appropriate hydrolysis conditions for preparing Compound **10** from Compound **9a** can be readily determined. Especially preferred hydrolysis agents are LiOH and NaOH.

The new allyl ester deprotection process is illustrated by Equation 7:



11 **12**

(eq. 7)

In the compounds in Equation **7**, R^P, R^7, R^8, R^9 and R^{10} have the meanings defined supra.

As illustrated, the $Pd(PPh_3)_4$ catalyst should be present in an amount less than about four (4) mole percent. Preferably, the amount of $Pd(PPh_3)_4$ catalyst is less than two mole percent (2 %). It is especially preferred that the amount of $Pd(PPh_3)_4$ catalyst is about two tenths mole percent (0.2%) or less. In addition, using less catalyst provides a significant cost advantage.

A preferred embodiment of the Equation **7** process is when R^9 is isobutyl, and R^{10} is hydrogen. Especially

preferred are compounds **11** and **12** wherein R^P=BOC, R^9=iBu, R^{10}=H, and R^7 and R^8=Me (compounds **11a** and **12a**) or R^7 and R^8=H (compounds **11b** and **12b**).

An especially preferred allyl scavenger is morpholine.

Preferred solvents for the process of Equation 7 are tetrahydrofuran, acetone, alcohols, acetonitrile, and ethyl acetate. An especially preferred solvent is tetrahydrofuran.

The use of the allyl ester as a protecting group for carboxylic acids is well known and has been the subject of reviews. Kocienski, P. J. *Protecting Groups;* Georg Thieme Verlag: Stuttgart, 1994; pp 139-154; Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 2nd Edition; John Wiley and Sons, Inc.: New York, 1991; pp 248-9; and Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20,* 140-45. The allyl ester deprotection process in the literature uses ten (10) mole percent $Pd(PPh_3)_4$. Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117,* 2479.

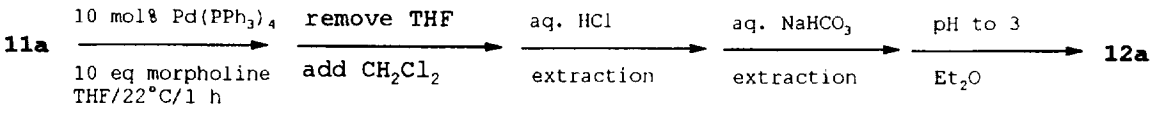
In the case of complex substrates such as **12** that are sensitive to the acidic and/or basic conditions used in subsequent isolation steps, isolation of pure product is problematic. The protecting group in **12** is generally not stable below pH 2-3, and the ester group of **12** can be

cleaved by base (hydroxide). Isolation and purification were even more significant issues for **12**, because it could not be purified easily. Thus, there was a need to streamline the work-up and avoid exposure of **12** to aqueous acids or bases.

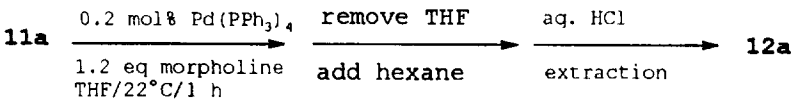
The present process provides surprisingly greater yields, fewer undesired impurities in the product, and allows isolation of acid-sensitive products without crystallization or chromatography of the product.

Procedures A and B illustrate the isolation advantage of the new process over the prior art process:

PROCEDURE A (Barrow[1]):



PROCEDURE B (new process):



[1]reference supra.

Table 1 illustrates the yield advantage provided by the new process.

Table 1. Deprotection of Allyl Ester **11a**.

Procedure	mol % $Pd(PPh_3)$	Amount of **11a (g)**	Yield of **12a (%)**	mol % $Ph_3P/Ph_3P=O$ in **12a** (NMR)
A	10	11	32	not detected
A	10	5	58	"
A	10	37	34	"
B	2	1.2	81	3
B	0.2	5	91	not detected
B	0.2	24	94	"

The product of process A was contaminated with triphenylphosphine and triphenylphosphine oxide. These contaminants could be partially removed by eluting the crude product through silica gel with organic solvents. However, the acid adheres very strongly to silica gel, and this procedure was impractical for preparing large amounts of **12a**.

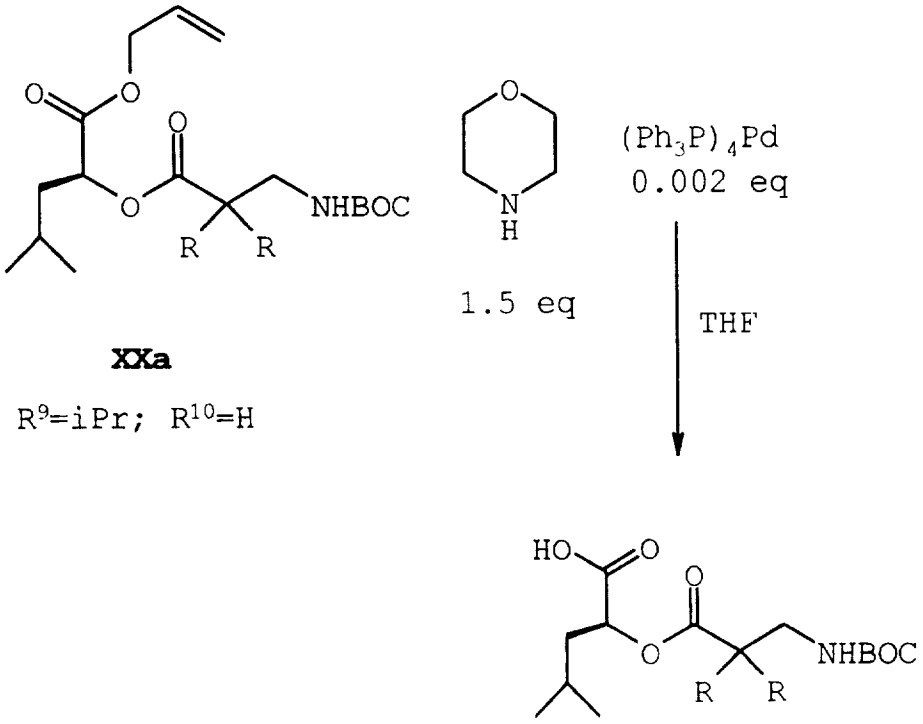
In the new process, the amount of $Pd(PPh_3)_4$

catalyst was reduced from 10 to 0.2 mole percent (50 fold reduction), and compound **12a** was obtained in greater than 90% yield. Equally important, triphenylphosphine residues in the product were non-detectable by NMR spectroscopy. Surprisingly, the reaction was complete in less than one hour, even with the lower amounts of catalyst. Thus, Procedure B is simpler, more economical, and provides product with acceptable purity in 90+% yields.

The process of Equation 7 can be run at a temperature of from about zero (0) to about seventy (70) degrees C. A preferred temperature is about 25°C.

Table 2 summarizes the preparation of a number of Formula XIX compounds using this process:

TABLE 2: Preparation of Formula XIX Compounds by Allyl Ester Deprotection



XXa

R^9=iPr; R^{10}=H

XIXa

R^9=iPr; R^{10}=H

R	% Yield
19b methyl	91
19c ethyl	99
19d spirocyclopentyl	95
19e spirocyclohexyl	99
19f benzyl	93
19g *n*-propyl	63
19h *i*-butyl	34

Some preferred embodiments are set forth in the following tabular form wherein the features may be independently selected to provide preferred embodiments of this invention. The invention is in no way limited to the features described below:

A) an intermediate of Formula **XII** wherein R^6 is halomethoxybenzyl;

B) a compound of Formula **XII** wherein X' is HCl;

C) a process wherein R^{60} in intermediate **XV** is TBS;

D) a process wherein Ar in intermediate **XV** is phenyl; and

E) a process wherein R^4 and R^5 in product **I**, together form a double bond.

Appropriate starting materials and reagents to prepare the desired substrates and reagents for the intermediates and processes can be obtained using the guidance of the previous schemes and following examples. Most of the reagents are commercially available, and those which are not can be prepared using accepted chemical methods.

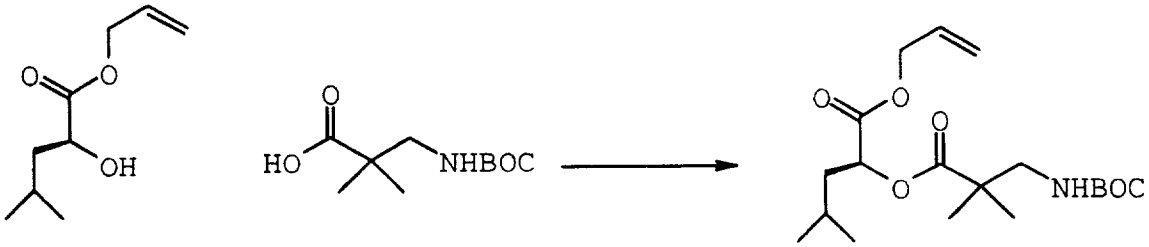
The necessary reaction time is related to the starting materials and operating temperature. The optimum reaction time for a given process is, as always, a compromise which is determined by considering the competing goals of throughput, which is favored by short reaction times, and

maximum yield, which is favored by long reaction times.

To further illustrate the intermediates and processes of this invention, the following non-limiting examples are provided.

Example 1

a) Allyl (2*S*)-2-[[3-[*tert*-Butoxycarbonyl)amino]-2'-dimethylpropanoyl]oxy]-4-methylpentanoate (**11a**).



Fragment D **13** **11a**

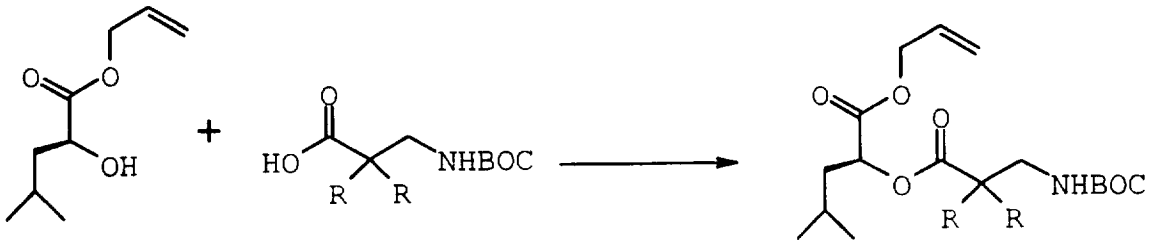
To a solution of 1,1'-carbonyldiimidazole ("CDI", 1346 g, 8.30 mol) in 3 L of THF was added a solution of compound **13** (1803 g, 8.3 mol) in 4 L of THF over 30 min. The reaction was stirred for 2 h at which time NMR analysis showed complete reaction of compound **13**. Fragment **D** (1450 g, 7.54 mol) was added as a solid, and the reaction mixture was heated to approximately 70 °C for 16 h. The reaction mixture was cooled to 25 °C and concentrated *in vacuo* to give a suspension. Heptane (4 L) was added, and the mixture was extracted with 0.2 N HCl solution (6 L) to remove imidazole. The aqueous layer was extracted with 2 L of heptane. The combined organic layers were extracted successively with 0.2 N HCl solution (3 L), deionized water (3 L), and brine (3 L). The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to give 2984 g of

compound **11a** as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (d, 3H, J = 8.4 Hz), 0.98 (d, 3H, J = 8.4 Hz), 1.27 (d, 6H, J = 5 Hz), 1.45 (s, 9H), 1.71 (m, 3H), 3.31 (m, 2H), 4.66 (m, 2H), 5.1 (m, 1H), 5.3 (m, 3H), 5.9 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.4, 170.7, 156.4, 131.5, 119.1, 78.9, 70.9, 66.0, 48.7, 44.0, 39.6, 28.4, 24.9, 23.1, 23.0, 22.3, 21.6. IR ($CHCl_3$) 3398, 2964, 1739, 1720, 1511, 1472, 1366, 1266, 1252 cm^{-1}. MS {FD^+} m/z (relative intensity) 371 (100).

b) **Preparation of 12a**

To a solution of the **11a**, obtained supra, in 8 L of THF was added $Pd(PPh_3)_4$ (3.0 g, 2.6 mmol). Morpholine (800 mL, 9.15 mol) was then added dropwise over 30 min at 15-25 °C, and the reaction was then stirred at that temperature for 1.5 h. The reaction mixture was concentrated *in vacuo* to an oil, which was dissolved in 6 L of heptane. The heptane solution was extracted with 1 N HCl (9.8 L). The aqueous layer was back-extracted with 2 L of heptane. The combined organic layers were washed with 3 L of brine, dried (sodium sulfate), and filtered. The filtrate was stirred at room temperature and seeded with 200 mg of compound **12a**. The product crystallized, and the slurry was stirred for 64 h (4 h is sufficient). The slurry was cooled to 0-10 °C for 3.5 h and filtered. The filter cake was washed with cold heptane (2 x 500 mL) and vacuum dried at 45-50 °C to give 2324 g (93% overall yield from Fragment **D**) of compound **12a** as a white solid, mp 70-73 °C.

TABLE 3: Preparation of Formula XX Intermediates



R	Conditions	% Yield
methyl	CDI, 0.1N THF, 17h reflux	94
ethyl	CDI, 1N THF, 72h reflux	78
spirocyclopentyl	CDI, 0.1N THF, 17h reflux	55
spirocyclohexyl	CDI, 0.1N THF, 17h reflux	19
benzyl	CDI, 0.1N THF, 17h reflux	21
n-propyl	CDI, 0.1N THF, 17h reflux	0
n-propyl	CDI, 0.4N PhMe, 17h reflux	59*
i-butyl	CDI, 0.4N PhMe, 17h reflux	52*

* About 50%/wt unknown impurities

Example 2 (See Eq. 1)

Preparation of 3-(3-Chloro-4-methoxyphenyl)-D-alanine 2,2,2-trichloroethyl ester hydrochloride salt (1). To a 1000-mL 3-necked flask fitted with a calcium chloride drying tube and a mechanical stirrer and containing a solution of **2** (46.2 g, 100 mmol) in 370 mL of ethyl acetate was added a solution of hydrochloric acid in ethyl acetate (*ca.* 4.5 M, 800 mmol). After stirring for 19 h at room temperature, the

resulting thick white reaction was cooled to 0 °C and filtered. The collected solid was washed with cold ethyl acetate (1 x 90 mL) followed by drying *in vacuo* at 40 °C to provide 36.9 g (93%) of compound **1** as a white powder: mp 217-219 °C; [a]+3.1° (c 1.21, MeOH); IR (KBr) 2830 (m), 1755 (s), 1502 (s), 1282 (s), 1258 (s), 1229 (s), 814 (s) cm^{-1}; 500 MHz ^1H NMR (DMSO-d_6) δ 8.88 (br s, 3H), 7.45 (d, 1H, J = 2.0 Hz), 7.28 (dd, 1H, J = 8.5, 2.0 Hz), 7.11 (d, 1H, J = 8.5 Hz), 5.01 and 4.96 (AB quartet, 2H, J = 12.2 Hz), 4.48 (t, 1H, J = 6.6 Hz), 3.84 (s, 3H), 3.23 (dd, 1H, J = 14.4, 5.9 Hz), 3.17 (dd, 1H, J = 14.4, 7.3 Hz); 125 MHz ^{13}C NMR (DMSO-d_6) d 168.8, 154.7, 131.8, 130.3, 128.4, 121.9, 113.8, 95.2, 75.1, 57.0, 53.8, 35.3. Anal. calcd. for $C_{12}H_{14}Cl_5NO_3$: C, 36.26; H, 3.55; N, 3.52. Found: C, 36.24; H, 3.59; N, 3.44.

Example 3 (See Eq. 2)

Preparation of Ene-amide 4. A solution of acid **3** (551 mg, 1.53 mmol) in 3.1 mL of DMF was treated with N,N-diisopropylethylamine (799 mL, 4.58 mmol). Upon cooling to 0 °C, the mixture was treated with diphenylphosphinic chloride (306 mL, 1.60 mmol). After the reaction was stirred at 0 °C for 5 min and at room temperature for 30 min, hydrochloride salt **1** (668 mg as a solid, 1.68 mmol) was added over *ca.* 3 min. The mixture was allowed to stir for 1 h 15 min at which time the reaction was poured onto 20 mL of

water and washed with diethyl ether (2 x 20 mL). The combined organic extracts were washed with 1N hydrochloric acid (1 x 10 mL). The acid wash was extracted with diethyl ether (1 x 10 mL); and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a yellow oil. Chromatography on 55 g of flash silica gel, eluting with ethyl acetate:hexanes (1:4), afforded 903 mg (84%) of compound **4** as a faint yellow foam.

Example 4 (see Eq. 4)

Preparation of Cryptophycin 51 (compound 6).

To a solution of cryptophycin seco-acid **5** (671 mg, 0.963 mmol) in 10 mL of DMF was added N,N-diisopropylethylamine (503 mL, 2.89 mmol), followed by diphenylphosphinic chloride (202 mL, 1.06 mmol). After being stirred at room temperature for 3 h, the reaction was diluted with ethyl acetate (50 mL) and washed successively with water (1 x 25 mL), 1 N HCl (1 x 25 mL), saturated aqueous $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL). Each aqueous layer was washed with ethyl acetate (1 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a crude solid residue which was diluted with ethyl acetate. After standing at room temperature overnight, the mixture was filtered to provide 188 mg (30%) of **6** as a white solid. The filtrate was chromatographed over flash silica gel, eluting with ethyl acetate:hexanes (2:1 followed by 3:1) to afford another 304 mg (48%) of compound **6**.

Example 5 **(See Eq. 6)**

a) **Preparation of Ethyl 2-cyano-2-methylpropanoate (8a).** Cesium carbonate (4324 g, 13.27 mol) and DMF (2.25 L) were added to a 22 L flask with an overhead stirrer. Methyl iodide (2828 g, 19.9 mol), was added and the mixture was cooled to -10 °C under nitrogen. Ethyl cyanoacetate (750 g, 6.63 mol) was added over 30 min, keeping the reaction temperature below 30 °C. The cooling bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was then filtered, and the salt cake was washed with 6 L of methyl tert-butylether (MTBE). The filtrate was combined with 3 L of 0.1N HCl and the layers were separated. The aqueous layer was extracted with 3 L of MTBE. The combined organic layers were washed with 5% LiCl solution (2 x 3 L), dried with sodium sulfate, and concentrated *via* distillation at atmospheric pressure to give compound **8a** as a light yellow oil. The oil was vacuum distilled at 50-60 °C, 10 mm Hg to give 882 g (94% yield) of **2** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.32 (t, 3H), 1.60 (s, 6H), 4.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ169.8, 120.9, 62.9, 38.7, 31.7, 24.9, 14.1. IR ($CHCl_3$) 3021, 2994, 2944, 2909, 2877, 2247, 1743, 1469, 1388, 1369, 1266, 1156 cm^{-1}. MS {FD$^+$} m/z (relative intensity): 142.1 (100). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 58.90;

H, 7.39; N, 10.00.

b) **Preparation of Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2,2-dimethylpropanoate (9a).**

To a 500 mL stainless steel autoclave were charged 5% rhodium on alumina (2.5 g), BOC anhydride (8.4 g, 38.5 mmol), compound **8a** (5.0 g, 35.4 mmol) and THF (140 mL). The stirred mixture was placed under 60 psi hydrogen at 70 °C. After 16 h, an NMR spectrum of the reaction mixture showed the reaction was complete. The reaction mixture was allowed to cool to 25 °C, vented, and purged with nitrogen. The mixture was then filtered through a Celite pad and concentrated *in vacuo* to give 8.64 g (99% crude yield) of compound **9a** as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 6H), 1.15 (t, 3H), 1.32 (s, 9H), 3.1 (d, 2H), 4.05 (m, 2H), 5.0 (bs, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 177.3, 156.3, 79.2, 60.8, 48.4, 43.7, 28.5, 23.1, 14.3. IR ($CHCl_3$) 3691, 3457, 2983, 2936, 2875, 1714, 1602, 1509, 1473, 1367, 1312, 1240, 1155 cm^{-1}. MS (FD$^+$) m/z (relative intensity) 245.2 (100). Anal. Calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.40; H, 8.95; N, 5.65.

c) Compound **10**

To Compound **9a** (164.2 g, approximately 670 mmol) was added 1.4 L of 5N NaOH, and the mixture was stirred under a

nitrogen atmosphere until homogeneous (48 h). CH_2Cl_2 (1.3 L) was added, and the mixture was cooled to 10 °C. The pH of the aqueous layer was adjusted to 3 by adding (dropwise) 1L of 6N HCl followed by 400 mL of 1N HCl. The temperature was maintained below 20 °C. The mixture stirred for 20 min, and the layers were separated. The aqueous layer was extracted with 1 L of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give 116.8 g of a crude yellow solid. The solid was stirred in 400 mL of hexane for 4 h. The slurry was filtered and the solid dried to give 114.7 g (78% yield) of compound **10** as a white solid, mp 115-16 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 6H), 1.48 (s, 9H), 3.26 (bs, 2H), 5.09 (bs, 0.7 H), 6.41 (bs, 0.3 H), 11.68 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.3, 181.7, 158.5, 156.4, 81.6, 79.6, 49.7, 48.1, 44.1, 43.7, 28.5, 23.0. IR ($CHCl_3$) 3315, 3004, 2542, 1895, 1700, 1648, 1414, 1367, 1350, 1278, 1157. MS {FD^+} m/z (relative intensity) 173 (19), 218 (100). Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.33; H, 8.59; N, 6.33.

Example 6 **(See Eq. 6)**

Large Scale Preparation.

a) Compound **9a**

To a 10 gallon stainless steel autoclave were charged 5% rhodium on alumina (390 g), BOC anhydride (1363 g, 6.25 mol), compound **8a** (prepared as described by Example **4**) (779 g, 5.52 mol), and THF (20 L). The stirred mixture was placed under 60 psi hydrogen at 70 °C. After 22 h, an NMR spectrum of the reaction mixture showed 83% conversion to **9a**. Additional 5% rhodium on alumina catalyst (195 g) was added. The hydrogenation was continued for another 4 h, at which time NMR assay of the reaction mixture showed 98% conversion. The reaction mixture was allowed to cool to 25 °Ç, vented, and purged with nitrogen. The mixture was then filtered through a multi-plate filter and concentrated *in vacuo* to give 1173 g (87% yield) of compound **9a** as an oil, which was used directly in the next step.

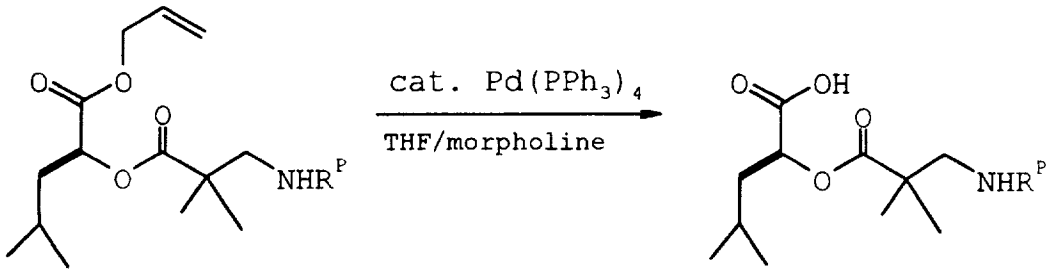
b) **Preparation of 3-[(*tert*-Butoxycarbonyl)amino]-2,2-dimethylpropanoic acid (10).**

Two 22 L flasks were each charged with compound **9a** (583 g, 2.38 mol), $LiOH \cdot H_2O$ (204.5 g, 4.87 mol), THF (5.7 L), and water (4.75 L). The reaction mixtures were heated to 64 °C for 19 h. The mixtures were then cooled to 10 °C with an ice bath. Approximately 1 L of 6N HCl was added to each

reaction mixture to bring the pH to 3-3.5. Each mixture was combined with 2.9 L of CH_2Cl_2, and the aqueous layers were separated. The aqueous layers were extracted with another 1.5 L portion of CH_2Cl_2. The combined organic layers were dried with sodium sulfate and concentrated *in vacuo* to give a white solid. The solid was slurried in 5 L of heptane for 1 h, filtered, and vacuum dried to give 830 g (80% yield) of compound **10** as a white solid, mp 114-116 °C. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.55; H, 8.77; N, 6.56.

Example 7

(2*S*)-2-[[3'-[(*tert*-Butoxycarbonyl)amino]-2',2'-dimethylpropanoyl]oxy]-4-methylpentanoic Acid (12a).



11a **12a**

(R^P=BOC)

A three-neck flask with an overhead stirrer was charged with compound **11a** (23.92 g, 64.5 mmol), $Pd(PPh_3)_4$ (149 mg, 0.13 mmol), and dry THF (100 mL). The mixture was cooled to 8 °C under nitrogen. Morpholine (6.8 mL, 77.4 mmol) in 10 mL of THF was add dropwise over 10 min. No exotherm was observed.

The cooling bath was removed, and the solution was stirred for 1 h. The solvent was then removed from the reaction mixture under vacuum. The resulting viscous oil was dissolved in 250 mL of hexane, and 70 mL of 0.01N HCl was added. Then, 1N HCl (77 mL) was added dropwise over 5 min. A small amount of yellow precipitate formed at the interface. The layers were separated, and the aqueous layer was extracted with 100 mL of hexane. The combined hexane layers were filtered to remove residual palladium complexes, dried with sodium sulfate, and concentrated *in vacuo* to obtain 21.3 g of **12a** as a very viscous oil. (The NMR spectrum showed 6% (by weight) hexane in the oil; corrected yield of **12a** = 94%.) $[\alpha]_D$ = -34.2° (c 0.032, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (d, J = 6.3, 3H), 0.99 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 9.0 Hz, 6H), 1.43 (s, 9H), 1.75 (m, 3H), 3.31 (m, 2H), 5.09 (dd, J = 9.7, 3.4 Hz, 1H), 5.5 (bs, 0.7H), 6.16 (bs, 0.3H), 10.5 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.6, 175.6, 156.8, 79.4, 70.6, 48.6, 44.0, 39.6, 28.4, 24.9, 23.1, 22.2, 21.5. IR ($CHCl_3$) 3691, 2963, 1710, 1512, 1151 cm^{-1}. MS {FD$^+$} m/z (relative intensity) 332 (100). Anal. Calcd. for $C_{16}H_{29}NO_6$: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.05; H, 8.72; N, 4.13.

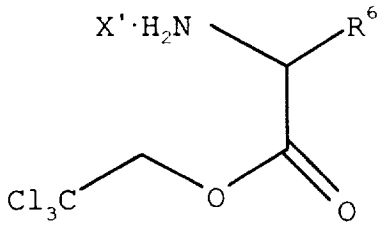
Example 8

Preparation of [5S-(2E,5R*,6S*,7E)]-3-chloro-N-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-methyl-1-oxo-8-phenyl-2,7-octadienyl]-O-methyl-2,2,2-trichloroethyl ester D-Tyrosine (4).

A solution of acid **3** (130 mg, 0.361 mmol) in 720 µL of DMF was treated with N,N-diisopropylethylamine (188 µL 1,08 mmol), followed by diphenyl chlorophosphate (82 µL , 0.396 mmol). After the mixture had stirred for 1 h, hydrochloride salt **1** (157 mg, 0.395 mmol) was added as a solid. The mixture was allowed to stir for 2 h 45 min at which time the reaction was diluted with diethyl ether (15 ml) and washed with 1N hydrochloric acid (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a yellow oil. Chromatography on 15 g of flash silica gel, eluting with ethyl acetate:hexanes (1:2), afforded 199 mg (78%) of compound **4** as a faint yellow oil.

Claims

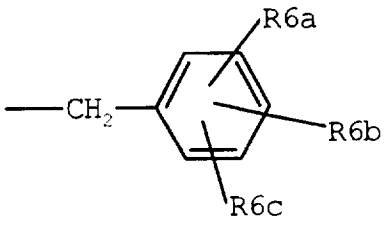
1. A compound of Formula **XII**



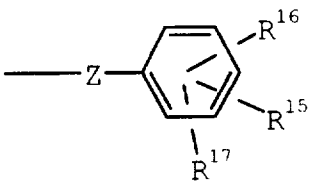
XII

wherein **X'** represents a strong acid; and

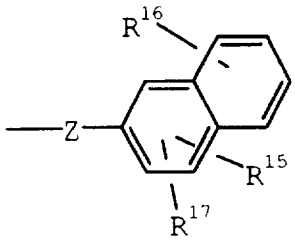
R^6 is C_1-C_6alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III'or III":



IIIa



III'



III''

wherein

R^{6a}, R^{6b}, and R^{6c} independently are H, halo or OR^{18};

R^{15}, R^{16}, and R^{17} independently are hydrogen, halo, (C_1-C_6)alkyl, OR^{18}, O-aryl, NH_2, $NR^{18}R^{19}$, NO_2, OPO_4H_2, (C_1-C_6 alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H, PO_3H_2, SO_2R^{23}, or Z';

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or (C_1-C_3)alkyl;

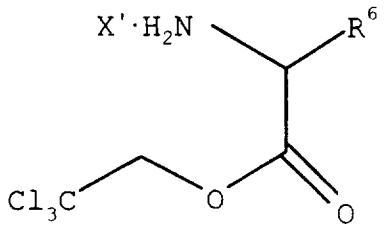
Z is $-(CH_2)_n-$ or (C_3-C_5)cycloalkyl;

n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group.

2. A compound of **Claim 1** wherein R^6 is halomethoxybenzyl.

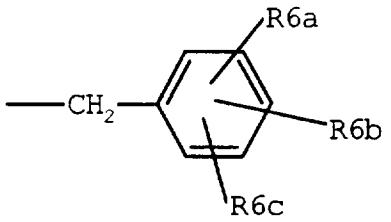
3. A process for preparing a compound of Formula **XII**



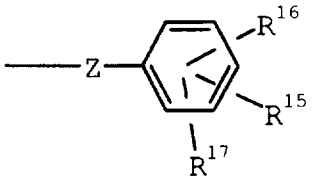
XII

wherein **X'** represents a strong acid; and

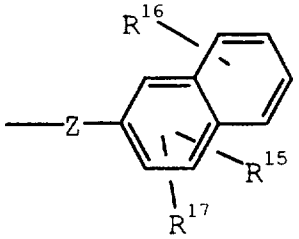
$\mathbf{R^6}$ is C_1-C_6alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III'or III":



IIIa



III'



III''

wherein

$\mathbf{R^{6a}}$, $\mathbf{R^{6b}}$, and $\mathbf{R^{6c}}$ independently are H, halo or OR^{18};

$\mathbf{R^{15}}$, $\mathbf{R^{16}}$, and $\mathbf{R^{17}}$ independently are hydrogen, halo, $(C_1-$

C_6)alkyl, OR^{18}, O-aryl, NH_2, $NR^{18}R^{19}$, NO_2, OPO_4H_2, (C_1-C_6 alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H, PO_3H_2, SO_2R^{23}, or Z';

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or (C_1-C_3)alkyl;

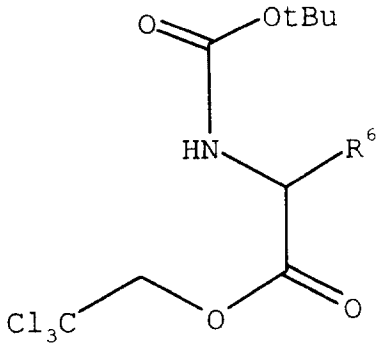
Z is $-(CH_2)_n-$ or (C_3-C_5)cycloalkyl;

n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group;

comprising

contacting a compound of formula **XII'**



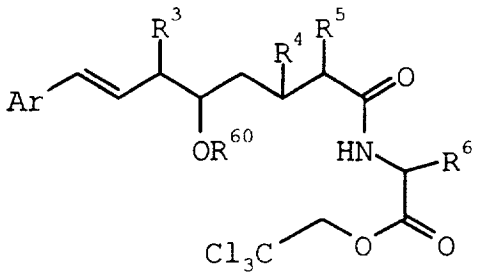
XII'

with a strong acid.

4. A process of **Claim 3** wherein R^6 is halomethoxybenzyl.

5. A process of **Claim 3** wherein the acid is hydrochloric acid.

6. A process for preparing a compound of Formula **XIII**



XIII

wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

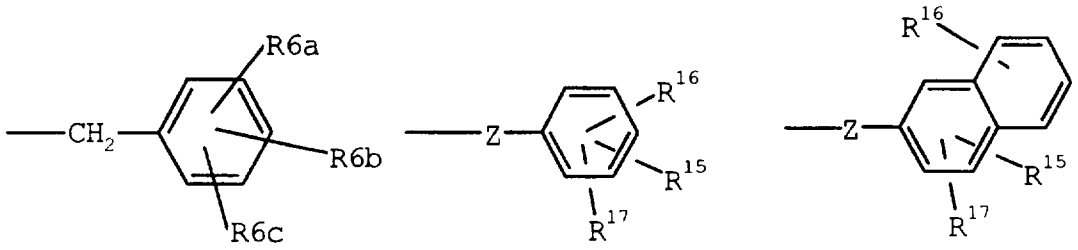
R^{60} is an alcohol protecting group;

R^3 is C_1-C_6 alkyl;

R^4 and R^5 are H; or

R^4 and R^5 together form a second bond;

R^6 is C_1-C_6alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III'or III":



IIIa **III'** **III''**

wherein

R^{6a}, R^{6b}, and R^{6c} independently are H, halo or OR^{18};

R^{15}, R^{16}, and R^{17} independently are hydrogen, halo, (C_1-C_6)alkyl, OR^{18}, O-aryl, NH_2, $NR^{18}R^{19}$, NO_2, OPO_4H_2, (C_1-C_6 alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H, PO_3H_2, SO_2R^{23}, or Z';

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or (C_1-C_3)alkyl;

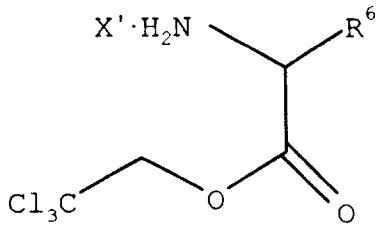
Z is $-(CH_2)_n-$ or (C_3-C_5)cycloalkyl;

n is 0, 1 or 2; and

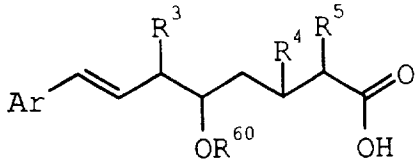
Z' is an aromatic or substituted aromatic group;

comprising

contacting 1) a compound of the Formula **XII**



wherein X' represents a strong acid; with 2) a compound of the Formula **XV**



XV

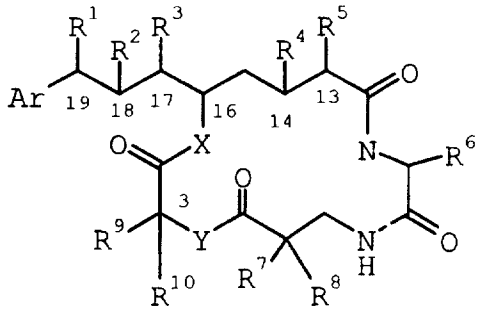
3) an $(R^A)_2$ phosphinic halide, wherein R^A is C_1-C_6 alkyl, C_1-C_6 aralkyl or Ar; and 4) a base.

7. A process of **Claim 6** wherein X' is HCl.

8. A process of **Claim 6** wherein R^{60} is TBS.

9. A process of **Claim 7** wherein the base is N,N-diisopropylethylamine.

10. A process for preparing a compound of Formula **I**



I

wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

R^1 is halo, SR, OR, amino, mono or di-(C_1-C_6-alkyl)amino, tri(C_1-C_6-alkyl)ammonium, C_1-C_6-alkylthio, di(C_1-C_6-alkyl)sulfonium, C_1-C_6-alkylsulfonyl, or C_1-C_6-alkylphosphonyl; and

R^2 is OH or SH; or

R^1 and R^2 taken together form a second bond between C-18 and C-19 or together form an epoxide, aziridine, episulfide, or cyclopropyl ring;

R is H, C_1-C_6 alkyl, C_1-C_6 alkanoyl or Ar;

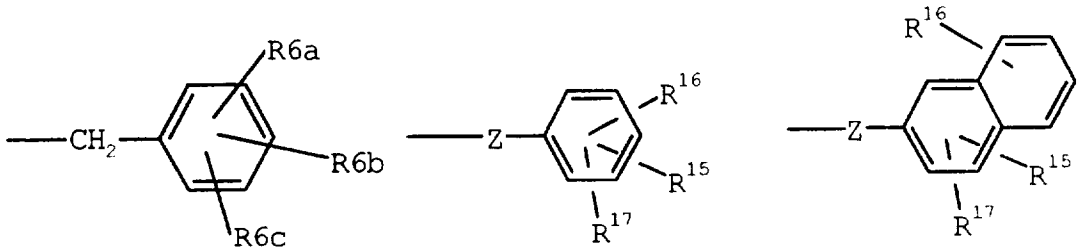
R^3 is C_1-C_6 alkyl;

R^4 and R^5 are H; or

R^4 and R^5 together form a second bond;

R^6 is C_1-C_6alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula

IIIa, III'or III":



IIIa **III'** **III''**

wherein

R^{6a}, R^{6b}, and R^{6c} independently are H, halo or OR^{18};

R^7 is H, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, benzyl, or benzyl substituted with up to three substituents independently selected from C_1-C_6-alkyl, halo, C_1-C_6-alkoxy, amino or $NR^{51}R^{52}$; and

R^8 is H or C_1-C_6 alkyl; or

R^7 and R^8 together form a C_3-C_8 cycloalkyl ring;

R^{51} and R^{52} independently are C_1-C_3 alkyl;

R^9 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6-alkynyl or (C_1-C_6 alkyl)C_3-C_5 cycloalkyl;

R^{10} is H or C_1-C_6 alkyl;

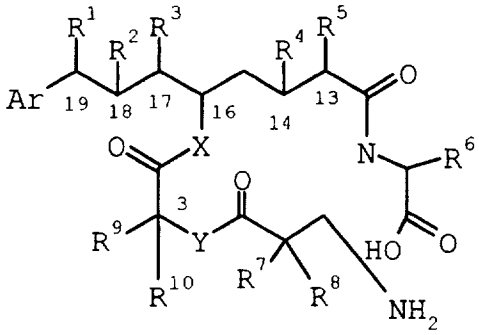
X is O, NH or (C_1-C_3 alkyl)N-; and

Y is C, O, NH, S, SO, SO_2 or (C_1-C_3 alkyl)N-;

comprising

contacting

1) a compound of Formula **XVI**



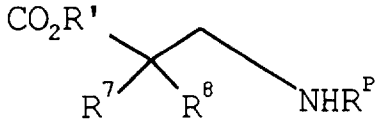
XVI

with 2) an $(R^A)_2$ phosphinic halide, wherein R^A is C_1-C_6 alkyl; and 3) a base.

11. A process of **Claim 10** wherein the base is N,N-diisopropylethylamine.

12. A process of **Claim 11** wherein R^6 is halomethoxybenzyl.

13. A process for preparing a compound of Formula **XVII**



XVII

wherein R' is hydrogen or C_1-C_6 alkyl;

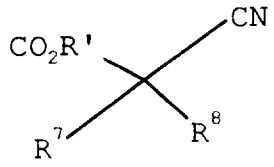
R^7 is H, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, benzyl, or benzyl substituted with up to three substituents independently selected from C_1-C_6-alkyl, halo, C_1-C_6-alkoxy, amino or $NR^{51}R^{52}$; and

R^8 is H or C_1-C_6 alkyl; or

R^7 and **R^8** together form a C_3-C_8 cycloalkyl ring; and

R^P is *tert*-butoxycarbonyl or benzyloxycarbonyl;

comprising contacting a compound of the Formula **XVIII**

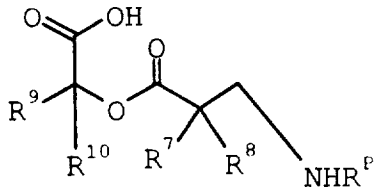


XVIII

with a rhodium catalyst.

14. A process of **Claim 13** wherein the rhodium catalyst is rhodium on alumina.

15. A process for preparing a compound of Formula **XIX**



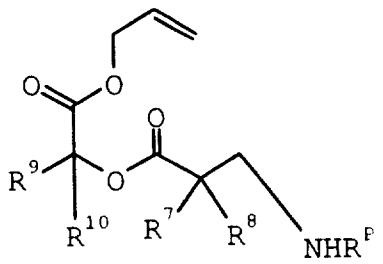
XIX

wherein

R^7, R^8, R^9 and R^{10} independently are H or C_1-C_6 alkyl; and

R^P is *tert*-butoxycarbonyl or benzyloxycarbonyl;

comprising contacting a compound of Formula **XX**



XX

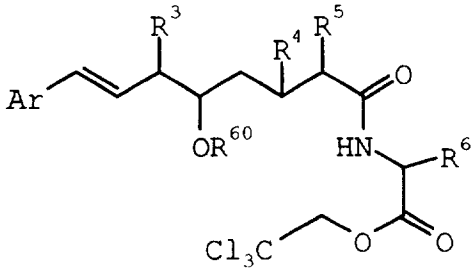
in the presence of 1) a catalytic quantity of less than about four (4) mole percent of $Pd(PPh_3)_4$ and 2) an allyl scavenger.

16. A process of **Claim 15** wherein the catalytic quantity is less than about two (2) mole percent.

17. A process of **Claim 16** wherein the catalytic quantity is about two tenths mole percent (0.2%).

18. A process of **Claim 16** wherein the allyl scavenger is morpholine.

19. In the process for preparing a compound of formula XIII



XIII

wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

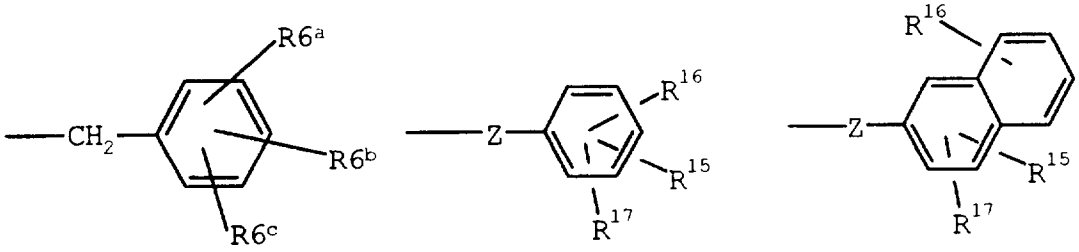
$\mathbf{R^{60}}$ is an alcohol protecting group;

$\mathbf{R^3}$ is C_1-C_6 alkyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are H; or

$\mathbf{R^4}$ and $\mathbf{R^5}$ together form a second bond;

$\mathbf{R^6}$ is C_1-C_6alkyl, substituted (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III'or III":



IIIa III' III''

wherein

R^{6a}, R^{6b}, and R^{6c} independently are H, halo or OR^{18};

R^{15}, R^{16}, and R^{17} independently are hydrogen, halo, $(C_1$-$C_6)$alkyl, OR^{18}, O-aryl, NH_2, $NR^{18}R^{19}$, NO_2, OPO_4H_2, $(C_1$-C_6 alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H, PO_3H_2, SO_2R^{23}, or Z';

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or $(C_1$-$C_3)$alkyl;

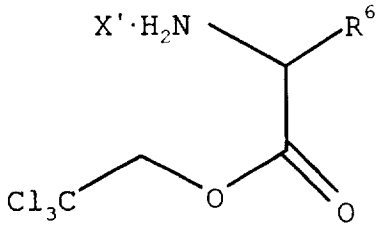
Z is $-(CH_2)_n-$ or $(C_3$-$C_5)$cycloalkyl;

n is 0, 1 or 2; and

Z' is an aromatic or substituted aromatic group;

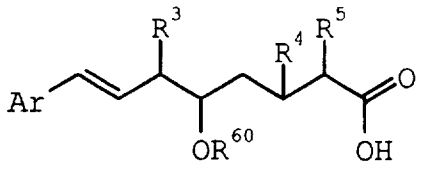
comprising

by reacting 1) a compound of formula **XII**



XII

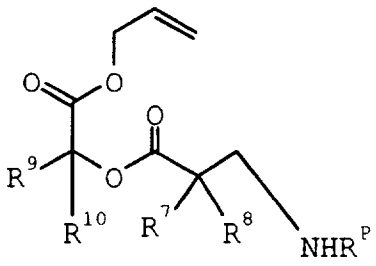
wherein X' represents a strong acid; and 2) a compound of formula **XV**



XV

2) with a coupling reagent and 3) an amine, the improvement which comprises using diphenyl chlorophosphate as the coupling agent.

20. In the process for preparing a compound of formula **XX**



XX

wherein R^7 is H, C_1-C_6 alkyl, C_1-C_6-alkenyl, C_2-C_6-alkynyl, benzyl, or benzyl substituted with up to three substituents independently selected from C_1-C_6-alkyl, halo, C_1-C_6-alkoxy, amino or $NR^{51}R^{52}$; and

R^8 is H or C_1-C_6 alkyl; or

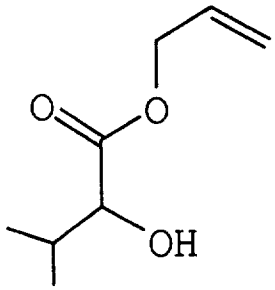
R^7 and R^8 together form a C_3-C_8 cycloalkyl ring;

R^9 is is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6-alkynyl or (C_1-C_6 alkyl)C_3-C_5 cycloalkyl;

R^{10} is H or C_1-C_6 alkyl; and

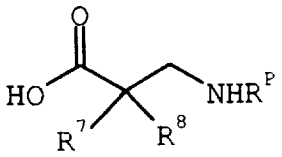
R^P is tert-butoxycarbonyl or benzyloxycarbonyl;

by coupling a Fragment **D** compound of the formula:



D

and a Fragment **C** compound of the formula:



C

provided that R^7 and R^8 cannot be H; in an inert organic solvent;

the improvement comprising using the coupling reagent 1,1'-carbonyldiimidazole.

21. An improvmment of **Claim 21** wherein R^7 and R^8 are methyl.

22. An improvement of **Claim 21** wherein R^P is BOC.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15703

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
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. : 540/454, 460; 560/38, 39, 41, 58, 121, 122, 123, 124, 125, 155, 171; 562/454, 460

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,567,834 A (GRANATEK ET AL.) 02 March 1971 (02/03/71).	1-22
A	WO 95/17093 A1 (UNIVERSITY OF HAWAII) 29 June 1995 (29/06/95).	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 06 NOVEMBER 1997	Date of mailing of the international search report 15 DEC 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT T. BOND aco Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15703

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 291/02, 285/00, 273/00; C07C 229/12, 227/18, 231/02, 235/26, 227/06, 227/16

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

540/454, 460; 560/38, 39, 41, 58, 121, 122, 123, 124, 125, 155, 171; 562/454, 460